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Influenza epidemiology and vaccine effectiveness following the 2009 pandemic

by

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A thesis submitted for the degree of

Doctor of Philosophy

of The Australian National University

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In memory of Geoff Mercer

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Declaration

Candidate

I declare that the work contained in this thesis is the result of original research and has not been submitted to any other University or Institution.

This thesis by compilation is based on the following eleven papers in which I made a significant contribution:

1. Grant KA, **Fielding JE**, Mercer GN, Carcione D, Lopez L, Smith D, Huang QS, Kelly HA. Comparison of the pandemic H1N1 2009 experience in the southern hemisphere with pandemic expectations. *Australian and New Zealand Journal of Public Health* 2012; 36: 364-368.
2. **Fielding JE**, Bergeri I, Higgins N, Kelly HA, Meagher J, McBryde ES, Moran R, Hellard ME, Lester RA. The spread of influenza A(H1N1)pdm09 in Victorian school children in 2009: implications for revised pandemic planning. *PLoS One* 2013; 8: e57265.
3. **Fielding JE**, Kelly HA, Mercer GN, Glass K. Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity but not age. *Influenza and Other Respiratory Viruses* 2014; 8: 142-150.
4. **Fielding JE**, Glass K, Kelly HA, Mercer GN. Transmission of the first influenza A(H1N1)pdm09 pandemic wave in Australia was driven by undetected infections: pandemic response implications.
5. Grant KA, Franklin LJ, Kaczmarek M, Hurt AC, Kostecki R, Kelly HA, **Fielding JE**. Continued dominance of pandemic A(H1N1) 2009 influenza in Victoria, Australia in 2010. *Western Pacific Surveillance and Response Journal* 2011; 2(3): 10-18.
6. Grant KA, Franklin LJ, Hurt AC, Garcia KT, **Fielding JE**. Higher proportion of older influenza A(H1N1)pdm09 cases in Victoria, 2011. *Victorian Infectious Diseases Bulletin* 2012; 15: 49-55.
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10. **Fielding JE**, Grant KA, Garcia K, Kelly HA. Seasonal influenza vaccine effectiveness against medically-attended pandemic influenza A (H1N1) 2009 in Victoria, Australia, 2010. *Emerging Infectious Diseases* 2011; 17: 1181-1187.
11. **Fielding JE**, Grant KA, Tran T, Kelly HA. Moderate influenza vaccine effectiveness in Victoria, Australia, 2011. *Eurosurveillance* 2012; 17: pii=20115.

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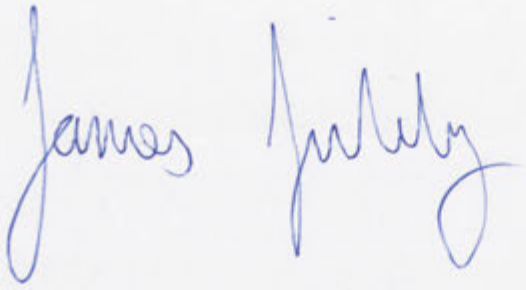
Signature: 

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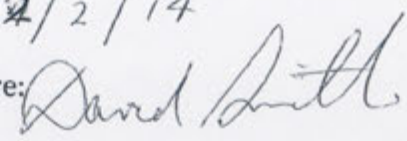
Signature: 

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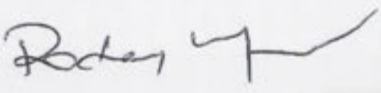
Signature: 

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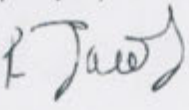
Signature: 

Table. Estimated contribution of James Edward Fielding to each publication included in this thesis.

Chapter	Title	Journal	Status	Author position	Percentage contribution		
					Conception & design	Analysis & interpretation	Drafting & revising
4	Comparison of the pandemic H1N1 2009 experience in the southern hemisphere with pandemic expectations	*Australian and New Zealand Journal of Public Health*	Published June 2012	2nd* of 8	50	30	50
	The spread of influenza A(H1N1)pdm09 in Victorian school children in 2009: implications for revised pandemic planning	*PLoS One*	Published March 2013	1st of 9	90	90	90
5	Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity, but not age	*Influenza and Other Respiratory Viruses*	Published March 2014	1st of 4	80	70	90
	Transmission of the first influenza A(H1N1)pdm09 pandemic wave in Australia was driven by undetected infections: pandemic response implications	Not applicable	Not submitted	1st of 4	50	80	90

*First and second authors made an equal contribution to the paper

Chapter	Title	Journal	Status	Author position	Percentage contribution		
					Conception & design	Analysis & interpretation	Drafting & revising
6	Continued dominance of pandemic A(H1N1) 2009 influenza in Victoria, Australia in 2010	*Western Pacific Surveillance and Response Journal*	Published August 2011	7th of 7	90	70	60
	Higher proportion of older influenza A(H1N1)pdm09 cases in Victoria, 2011	*Victorian Infectious Diseases Bulletin*	Published June 2012	5th of 5	90	70	60
	Epidemiology of the 2012 influenza season in Victoria, Australia	*Western Pacific Surveillance and Response Journal*	Published August 2013	1st of 7	90	90	90
7	Estimation of type- and subtype-specific influenza vaccine effectiveness in Victoria, Australia using a test negative case control method, 2007–2008	*BMC Infectious Diseases*	Published June 2011	1st of 4	50	90	90
	Pandemic influenza H1N1 2009 infection in Victoria, Australia: No evidence for harm or benefit following receipt of seasonal influenza vaccine in 2009	*Vaccine*	Published April 2011	3rd of 7	10	80	20
	Seasonal influenza vaccine effectiveness against medically-attended pandemic influenza A (H1N1) 2009 in Victoria, Australia, 2010	*Emerging Infectious Diseases*	Published July 2011	1st of 4	60	90	90
	Moderate influenza vaccine effectiveness in Victoria, Australia, 2011	*Eurosurveillance*	Published March 2012	1st of 4	50	90	90

Acknowledgements

Undertaking a PhD is something that I have wanted to do for many years and as my career as an applied infectious diseases epidemiologist progressed it is something I came to regard as inevitable. Initially, influenza was not high on my list of preferred subject areas but my central involvement in the Victorian public health response to the 2009 influenza pandemic provided the interest, opportunity and foundations for this PhD. It has been a sometimes challenging but enjoyable journey that has significantly advanced my skill set and experience, particularly with respect to epidemiological study design, systematic review of the literature and mathematical modelling of infectious diseases. There are a number of important people who helped me get to this point.

First and foremost I thank my supervisors Geoff Mercer, Heath Kelly and Katie Glass for their encouragement and support along my PhD journey, for answering my multitude of questions and challenging my thinking. Despite being an external candidate, Geoff and Katie were always there when I needed them (and to prod me along when I didn't) and never felt far away at all. I especially thank Heath who has been my most important mentor for many years now, and after taking a chance by giving me my first job as an epidemiologist over a decade ago, it is very satisfying that he has been an integral part of this milestone.

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Operation of the Victorian influenza surveillance system is dependent on good communication and cooperation among the participating partners. Nearly half the studies undertaken for this thesis utilised Victorian influenza surveillance system data, and I am extremely grateful for the involvement and support of all institutions involved, with special thanks to Lucinda Franklin, Rosemary Lester

and Nicola Stephens from the Victorian Government Department of Health, and Ian Barr and Sheena Sullivan from the World Health Organization Collaborating Centre for Reference and Research on Influenza.

Being an external candidate necessitated a number of trips to the ANU campus where I was well looked after by my Canberra support crew. Barbara Bowen and Greg Rathbone sorted out all my administrative needs, and Bridget O'Connor and Cameron Moffatt generously put me up (and put up with me).

During my candidature I was fortunate enough to attend the 'Introduction to Mathematical Models of the Epidemiology & Control of Infectious Diseases' course at Imperial College in London, which was partly funded by an ANU Vice-Chancellor's Higher Degree Research Travel Grant and VIDRL. I also presented at the Communicable Disease Control Conferences in Canberra in 2011 and 2013 and the 13th National Immunisation Conference in Darwin in 2012, with my attendance primarily funded by VIDRL.

Lastly I give a big shout out to my family and friends. It is their support, counsel and comradeship that has kept me steady and sound, not just through this degree but over the years in my metamorphosis from bartender to molecular biologist and finally epidemiologist.

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Abstract

Influenza A(H1N1)pdm09 was identified in April 2009 and spread rapidly around the globe. The public health response in Victoria was undertaken in accordance with the *Australian Health Management Plan for Pandemic Influenza* (AHMPPI) and included intensive case follow up, school closure, antiviral distribution and a vaccination program. However, evidence soon emerged that most cases were relatively mild compared to previous pandemics.

This thesis sought to assess how the epidemiology of influenza A(H1N1)pdm09 differed from expectations in pandemic planning and how the control measures of school closure and antiviral distribution within the AHMPPI were applied and performed, and to investigate the role of infection severity in driving the initial spread of influenza A(H1N1)pdm09. It also sought to examine how the epidemiology of seasonal influenza in Victoria changed following the emergence of influenza A(H1N1)pdm09, and measure the effectiveness of influenza vaccine in prevention of laboratory confirmed influenza infection prior to, during and following the emergence of influenza A(H1N1)pdm09.

Investigation of these questions utilised a variety of methodological approaches, including: analysis of influenza-like illness (ILI) and laboratory confirmed influenza surveillance datasets in general practice, locum service, hospital, notifiable disease and reference laboratory settings; systematic review of the literature on influenza A(H1N1)pdm09 viral shedding; deterministic mathematical modelling; and application of sentinel surveillance influenza laboratory testing data to a novel variant of the traditional case control study design to measure vaccine effectiveness.

Although it spread rapidly and primarily affected younger age groups, influenza A(H1N1)pdm09 morbidity and mortality were mild compared with previous pandemics. However, the intensity of the public health response was not commensurate with the severity and magnitude of the disease. Transmission of influenza A(H1N1)pdm09 was largely driven by those effectively invisible to the health system and the virus was therefore well-established by the time it was detected. The delay in detection and high proportion of relatively mild infections

meant that school closures and antiviral distribution to notified cases and their contacts were ineffective. Pandemic plans need to be revised to accommodate such a scenario and ensure trust from public and professionals in future pandemic responses.

Influenza A(H1N1)pdm09 replaced the previously circulating seasonal A(H1N1) and remained dominant in Victoria in 2010. Higher proportions of A(H3N2) and type B influenza were observed in 2011 before dominance of A(H3N2) in 2012, accompanied by an increase in severe infections in older people especially. Whilst ILI surveillance suggested influenza seasons of moderate magnitude from 2010-2012, notifiable disease surveillance indicated a considerable increase in influenza testing by medical practitioners.

Influenza vaccine effectiveness (VE) in Victoria varied considerably in the years preceding, during and following the 2009 pandemic. With the exceptions of high influenza A(H1N1)pdm09-specific seasonal VE in 2010 and 2011, and no protective effect of seasonal vaccine against influenza A(H1N1)pdm09 in 2009, type and subtype-specific VE were inconsistent across seasons, and had little correlation with the percentage match between circulating and vaccine strains. Further investigation of the role of previous immunity and antigenic similarity by phylogenetic analysis is needed to better understand the determinants of influenza VE.

Glossary of acronyms

AHMPPI	Australian Health Management Plan for Pandemic Influenza
CFR	Case fatality risk
CI	Confidence interval
DH	Department of Health
ED	Emergency department
FluCAN	Influenza Complications Alert Network
GP	General practitioner
GPSS	General practitioner sentinel surveillance
HI	Haemagglutinin inhibition
ICU	Intensive care unit
ILI	Influenza-like illness
IQR	Interquartile range
LAIV	Live-attenuated influenza vaccine
MMDS	Melbourne Medical Deputising Service
NIDS	Notifiable infectious diseases surveillance
NCIT	Non-contact infrared thermometer
NI	Neuraminidase inhibitor
NPA	Nasopharyngeal aspirate
NPS	Nasopharyngeal swab
NS	Nasal swab

NTS	Nose and throat swab
NZ	New Zealand
OPS	Oropharyngeal swab
PCR	Polymerase chain reaction
PRCC	Partial rank correlation coefficient
PS	Pharyngeal swab
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SIR	Susceptible-infected-recovered
TIV	Trivalent influenza vaccine
TS	Throat swab
UK	United Kingdom
US/USA	United States of America
VE	Vaccine effectiveness
VIDRL	Victorian Infectious Diseases Reference Laboratory
WA	Western Australia
WHO	World Health Organization
WHOCCRRI	World Health Organization Collaborating Centre for Reference and Research on Influenza

Chapter 1

Introduction

Despite it being one of the most studied infectious diseases, the epidemiology of influenza remains largely unpredictable with the timing, magnitude and circulating strain profile of seasonal epidemics varying considerably from one year to the next. However, even accounting for these uncertainties, the onset of a pandemic presents a multitude of new challenges, and in the first decade of the 20th century both public and private institutions around the world invested much effort in development of plans for the management of pandemic influenza [1, 2].

Emergence of the 2009 influenza pandemic

Influenza A(H1N1)pdm09 was identified in Mexico and the United States in April 2009 and spread rapidly around the globe [3, 4]. Although Australia's first case was reported in Queensland on 9 May, the second reported case in Victoria 11 days later was followed by a rapid increase in notified cases that was not observed in other states or territories [5, 6]. The Victorian Government's response to influenza A(H1N1)pdm09 was undertaken in accordance with the phases described in the *Australian Health Management Plan for Pandemic Influenza* [1], which included follow up of all notified cases, closure of classrooms and schools with reported cases and distribution of antiviral medication for treatment of cases and prophylaxis of contacts.

As the pandemic response progressed it became evident that despite the large number of notified cases a high proportion had relatively mild symptoms and much lower case fatality risk compared to previous pandemics [7]. Influenza-like illness (ILI) activity and proportion of influenza tests positive as measured by other surveillance systems was also moderate compared to other influenza seasons [8, 9]. Furthermore, evidence emerged that suggested community transmission of influenza A(H1N1)pdm09 in Victoria was well established before cases were identified [10], raising the suggestion that spread of the virus was being driven by those with asymptomatic or clinically mild infections. Although the intensity of the initial response was curtailed after several weeks [6], the experience raised questions about conventional notions and definitions of what epidemiological characteristics constitute a pandemic [11] and the flexibility of plans to scale back in the event of a milder scenario. However, it also provided an

opportunity to evaluate how pandemic plans operated in practice and observe the effect of influenza A(H1N1)pdm09 on seasonal influenza epidemiology following its emergence.

A central element of pandemic response plans is the rapid development and rollout of a pandemic vaccination program which, for influenza A(H1N1)pdm09, commenced in Australia in September 2009 [2, 5]. Victoria has had a publicly funded seasonal influenza vaccination program since 1997 [12] but influenza vaccine effectiveness (VE) estimates were not being regularly published at the time of the pandemic. However, using limited sentinel surveillance data from 2003-2007, proof of concept had been established for the application of a novel variant of a traditional case control study design to measure influenza VE in Victoria [13, 14]. The availability of more complete data from 2007 provided an opportunity to estimate and compare effectiveness of seasonal trivalent and pandemic monovalent influenza vaccines.

These uncertainties regarding influenza epidemiology during and following the 2009 pandemic, as well as seasonal and pandemic influenza VE during this period, are addressed by the research studies included in this thesis.

Aim and scope of thesis

The aims of this thesis were to examine the epidemiology of influenza during the first wave of the 2009 pandemic and the following influenza seasons, and to estimate the effectiveness of trivalent seasonal and monovalent influenza vaccines prior to, during and following the pandemic.

Several methods were employed to examine the epidemiology of influenza. Laboratory confirmed influenza and ILI surveillance datasets from a range of surveillance systems were descriptively analysed to compare the epidemiology and control strategies of influenza A(H1N1)pdm09 against pandemic planning expectations, and characterise the epidemiology of subsequent influenza seasons. A systematic review of the literature and mathematical modelling were undertaken to investigate the role different levels of disease severity had in driving pandemic influenza transmission. Influenza VE was measured by applying

influenza laboratory testing data collected in the Victorian general practitioner sentinel surveillance program to a novel variant of the traditional case control study design.

These aims were addressed by four research questions that utilised four broad research methods and are described in Chapter 3 'Research design'.

Thesis structure

This thesis is presented as a compilation of published studies that address research questions related to influenza epidemiology and vaccine effectiveness following the 2009 pandemic. The thesis is structured such that each research question and its associated studies comprises its own chapter, accompanied by a context statement for the thesis as a whole.

The context statement

The context statement consists of: this introductory chapter; background about influenza virology, clinical features, epidemiology and control (Chapter 2); description of the research questions and an overview of the methods used to address them (Chapter 3); and discussion and conclusions arising from the studies published in the thesis (Chapter 8).

The studies

In Chapter 4, titled 'Pandemic planning in practice', two studies compare the observed epidemiology and interventions implemented during the 2009 pandemic with conventional expectations about how an influenza pandemic influenza would evolve. This comparison was used to assess the performance of pandemic planning in practice. Chapter 5, titled 'Role of severity in pandemic spread', contains a systematic review of the literature to determine viral shedding duration of influenza A(H1N1)pdm09 that informed the mathematical model used in the subsequent study to determine whether transmission of influenza A(H1N1)pdm09 was driven by those with asymptomatic or very mild infections. Chapter 6, titled 'Post-pandemic influenza epidemiology', includes three papers that describe the epidemiology of laboratory confirmed influenza and ILI for the three Victorian influenza seasons following the pandemic from 2010 to 2012 inclusive. Four

studies comprise Chapter 7, titled 'Influenza vaccine effectiveness', which calculated the effectiveness for annual seasonal trivalent influenza vaccines from 2007 to 2011 inclusive and monovalent pandemic (H1N1) vaccine in 2010.

During my doctoral candidature I also made minor contributions to five other studies: intra-household transmission of influenza A(H1N1)pdm09; seasonal trivalent influenza vaccine effectiveness over five years; and the understanding, compliance with and impact of social restrictions implemented during the public health response to pandemic influenza. These papers are included in the Appendix.

Contribution to manuscripts

Guidelines produced by the *British Medical Journal* were used to estimate my contribution to the conception and design, analysis and interpretation, and drafting and revising of each paper [15] and shown in the table in the declaration. I was lead or senior (last) author and guarantor for nine of the 11 studies and took responsibility for overall management of the drafting process, the conduct of the study and controlled the decision to publish. I was joint first author on a study in Chapter 4 for which I was also corresponding author, but contributions to the paper were shared with two other authors. In one paper in Chapter 7 I was third author given my contribution was mostly restricted to analysis & interpretation of the study.

All of the papers have been reproduced with the permission of the publishing company and co-authors. All papers included in this thesis were prepared during my doctoral candidature.

Funding sources

The study examining influenza A(H1N1)pdm09 transmission among school children and the distribution of oseltamivir treatment and prophylaxis (chapter 5) was partly funded by an Australian Government National Health and Medical Research Council grant (application ID 603753) for research on H1N1 influenza 09 to inform public policy. Work conducted in all other studies in the body of this thesis was covered by institutional staff salaries.

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Chapter 2

Influenza background

Influenza viruses cause a highly contagious respiratory disease and result in localised seasonal epidemics and global pandemics. Influenza virus infection has a broad spectrum of clinical manifestations, affects all age groups and can recur in any individual. Understanding the burden and epidemiology of influenza, and thus the development of effective prevention and control strategies, is challenging because of low case ascertainment and complex interactions between numerous factors. This chapter describes these characteristics of influenza and provides the context for the thesis.

Virology

The family of *Orthomyxoviridae* is defined by viruses that have a segmented genome of negative sense single-stranded RNA. It is comprised of five genera, of which three are influenza viruses: Influenzavirus A, Influenzavirus B and Influenzavirus C. Influenza viruses are also characterised by the presence of a host-derived lipid envelope containing glycoproteins that project from the surface of the virus. In type A and B influenza viruses, haemagglutinin facilitates entry of virus into host cells by binding to sialic acid receptors whilst neuraminidase cleaves glycosidic linkages to sialic acid to release virion progeny from infected cells. The major glycoprotein of influenza C virus is HEF (haemagglutinin-esterase-fusion) which combines the functions of haemagglutinin and neuraminidase. The matrix protein 2 (M2), found only in influenza A viruses, has proton channel activity and helps mediate the uncoating of the virus in endosomes. Other influenza virus proteins include polymerases and a nucleoprotein for viral replication, and matrix and non-structural nuclear export proteins [1].

Haemagglutinin and neuraminidase are the major antigenic determinants of influenza virus. Type A influenza virus is further subtyped based on antigenic differences in these glycoproteins. Eighteen different haemagglutinin subtypes (designated H1-H18) have been identified, the two most recent of which (H17 and H18) were discovered in bats in Central America in 2012 [2] and South America in 2013 [3]. Nine neuraminidase subtypes (designated N1-N9) have been identified. With the exception of H17 and H18, all haemagglutinin and neuraminidase subtypes have been identified in aquatic birds and they are therefore considered

the natural reservoir of influenza A viruses. Influenza viruses are usually benign in aquatic birds and exist in an evolutionary stasis but evolve rapidly when introduced into land-based poultry or mammalian species which include humans, swine, horses, dogs, cats, whales and seals. Highly pathogenic H5N1 influenza A virus has also been isolated from a tiger and a leopard [4]. It is suggested that swine in particular may serve as 'mixing vessels' for the generation of human-avian influenza A virus reassortants, given that cell surface receptors for both human and avian influenza viruses have been identified in the pig trachea and that humans have been shown to be infected with avian-human reassortant virus from pigs [5, 6]. Only haemagglutinin subtypes 1, 2 and 3 and neuraminidase subtypes 1 and 2 have established stable lineages in humans. Type B influenza virus, for which only one haemagglutinin and one neuraminidase have been identified, was thought to be restricted to human populations until its isolation from a seal in 1999 [7].

The epidemiology of influenza in humans is dependent on two types of antigenic variation in the haemagglutinin and neuraminidase proteins. Antigenic drift arises from accumulated point mutations and results in evolution of new strains of the virus. These new strains are antigenically related to those circulating in previous epidemics but sufficiently different to evade immune recognition, leading to repeated (seasonal) outbreaks over time. Antigenic shift is the emergence of an antigenically distinct type A virus that contains a novel haemagglutinin or neuraminidase subtype. An antigenic shift is caused by reassortment (rearrangement of viral gene segments), typically between human and avian and/or swine viruses. Antigenic shift may also occur by direct transmission of avian or swine influenza virus to humans which then becomes established in the human population. The introduction of an antigenically distinct virus with a novel haemagglutinin alone or with a novel neuraminidase in an immunologically naïve population results in high infection rates and can lead to a pandemic. The emergence of reassortant viruses has been sudden and unpredictable, occurring at irregular intervals, and is described further below [8].

An international standard convention for influenza virus nomenclature was recommended by the WHO in 1980. The nomenclature consists of: the antigenic type; host of origin (if non-human); geographical origin; strain number; year of isolation; and, for type A viruses, haemagglutinin and neuraminidase antigen description in parentheses [9]. For example: A/Swine/Minnesota/00194/2003 (H1N2) designates a virus of swine origin and B/Perth/165/2007 represents a virus of human origin.

Clinical features

Infection with seasonal influenza virus manifests over a wide spectrum of clinical presentations, from asymptomatic to various respiratory syndromes and primary viral and secondary bacterial pneumonia. A meta-analysis of volunteer challenge studies estimated that 30-40% of infections are asymptomatic [10], but this may not be representative of community-acquired influenza, and infection most commonly manifests as an uncomplicated, acute self-limited febrile illness with myalgia and cough. Conventional descriptions of influenza illness generally indicate an abrupt onset with systemic systems (usually fever, headache, myalgia, malaise and anorexia) that generally persist for about three days, but may be as long as eight days. Although they may also be present at the onset of illness, respiratory symptoms (particularly a dry cough, pharyngeal pain and nasal obstruction and discharge) become more prominent as the disease progresses and persist for 3-4 days after the fever subsides [11].

Primary influenza viral pneumonia and secondary bacterial pneumonia are the most well recognised pulmonary complications of influenza. Primary viral influenza pneumonia is particularly common among those with cardiovascular disease and has a high mortality risk. Secondary bacterial pneumonia (most often caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*) is more common in older adults and those with chronic pulmonary, cardiac, metabolic or other disease. Other pulmonary complications include croup in children and exacerbation of chronic pulmonary disease. Non-pulmonary complications of influenza virus infection include myositis, cardiac complications, toxic shock syndrome and Reye's syndrome [11].

Immune response

Infection with influenza virus evokes innate and adaptive immune responses in humans. The innate response aims to prevent infection of the respiratory epithelial cells, whilst the second line of defence comprises humoral immunity (mediated by virus-specific antibodies) and cellular immunity (mediated by T cells).

The most important antibodies induced by infection are those specific for the haemagglutinin and neuraminidase glycoproteins. Binding of haemagglutinin-specific antibody to any of the five antibody recognition sites that surround the receptor binding site of the haemagglutinin surface neutralises the virus by preventing attachment and entry to host cells [12]. Broadly neutralising antibodies to the conserved stem region of the haemagglutinin molecule have been observed in naturally infected individuals and this observation has raised prospects for the development of a universal influenza vaccine [13]. However, more research is required because frequency of stem-specific neutralizing antibody is very low and producing a properly folded recombinant haemagglutinin stem region is difficult without co-expression of the haemagglutinin head region [14, 15]. This is problematic if the stem region is poorly immunogenic, as the head region is highly immunogenic.

Neuraminidase-specific antibody does not neutralise the virus but limits its spread by inhibiting the enzymatic cleavage of virion progeny from infected cells. Immune pressure mediated by antibody production gives rise to escape variants, especially haemagglutinin in which mutations in all five antigenic sites occur, with positive selection driving antigenic drift [16, 17].

The cellular immune response to influenza infection comprises induction of CD4+ T cells, CD8+ T cells and regulatory T cells that mediate a number of important functions including: the elimination of virus-infected cells; promotion of B cell responses; regulation of the cellular immune response; and immunological memory. T cells are also thought to play an important role in heterosubtypic immunity to influenza virus A infection; they generally recognise conserved viral proteins and cross-protective immunity has been observed in the absence of strain-specific antibodies prior to infection [16, 18]. T cell responses to influenza

infection are also significantly correlated with low virus shedding and reduced disease severity in the absence of detectable antibody response [15].

Transmission

Person-to-person transmission of influenza virus primarily occurs through respiratory droplets expelled during coughing and sneezing, particularly in enclosed spaces, and the virus can remain viable for hours in conditions of low temperature and humidity. Transmission may also occur through direct contact or from fomites. Occasionally transmission to humans may occur from birds and swine [19, 20].

The incubation period of influenza is estimated to range from 1-3 days, and up to four days for type B influenza viruses [8, 11, 19]. The period of communicability is generally equated to the detection of virus from clinical specimens, with the duration and viral titre dependent on several factors including age, clinical illness, treatment with antiviral agents and virus detection method [10, 21]. Among adults with uncomplicated infection, virus can usually be detected within about 24 hours prior to symptom onset, with the titre rising rapidly to a peak, staying elevated for 24-48 hours and decreasing to undetectable levels after 5-10 days of shedding [11]. Duration of seasonal influenza virus shedding has been found to be longer in children [22-24], and is a widely accepted assumption in text books [8, 11] and pandemic planning documents [25].

Laboratory diagnosis

Common symptoms of influenza are shared with several other pathogens and clinical criteria are often not reliable indicators of infection. A study in two Australian states over two influenza seasons found combinations of the symptoms of cough and fever with or without fatigue and/or myalgia yielded sensitivities of 44-75% and specificities 47-80%; positive predictive values ranged from 23-60% [26]. Laboratory testing is therefore required for a definitive diagnosis.

With higher sensitivity and shorter turnaround times compared to viral culture, reverse transcription polymerase chain reaction (PCR) has become the most common diagnostic method for influenza virus detection. Whilst viral culture is

still important for antigenic characterisation of circulating and novel influenza viruses, antiviral susceptibility testing using neuraminidase inhibitor assays and vaccine production, PCR assays are also able to test for several targets concurrently (such as influenza types/subtypes and other respiratory viruses), can be adapted rapidly for the detection of novel targets and are highly automated with high throughput capacity [27].

A range of serological tests are available for influenza diagnosis, including haemagglutinin inhibition assay, complement fixation test and enzyme immunoassay. They are generally not practical in the clinical setting because antibodies to influenza virus do not appear until approximately two weeks after infection, and a four-fold or greater increase in antibody titre from paired acute- and convalescent-phase sera is required for diagnosis. Furthermore, increases in antibody titres are more difficult to detect in those who have received inactivated influenza vaccine [28]. However, serological testing is useful for retrospective diagnosis (such as identification of asymptomatic and resolved infections where the patient is no longer shedding virus) and seroepidemiological studies (such as determining the cumulative incidence of infection or levels of cross-protective immunity prior to a pandemic in a given population). Caution is required when interpreting the results of seroepidemiological studies as correlates of protection are not well defined and the titre cut-off level may under- or over-estimate the extent of infection [27].

Rapid antigen tests can be conducted at the point-of-care, are technically simple and low cost thus expediting clinical decision-making and appropriate allocation of limited supplies (such as antivirals in the early stages of a pandemic). Whilst the tests generally have high specificities and positive predictive values during periods of high prevalence, reported sensitivities vary widely from 20-90% [27].

Epidemiology

Only influenza virus types A and B cause seasonal epidemics, which tend to occur during the winter or early spring months each year in temperate climates. Epidemics in tropical and subtropical climates tend to coincide with the onset of the rainy season [19]. The overall attack proportion during a typical epidemic

season is estimated to be 5-20% [29, 30] from which the World Health Organization estimates there are 3-5 million cases of severe illness and 250,000-500,000 deaths worldwide each year [31]. In Australia it is estimated that an annual average of 18,400 hospitalisations are attributable to influenza [32]. There are no recent estimates of overall excess seasonal influenza mortality in Australia, but modelling has indicated that over 3,000 deaths per annum among those aged 50 years or older are attributable to influenza [33]. Whilst these estimates were derived from national databases of mortality, hospital morbidity, laboratory virology and serology reporting and a study of GP activity, their accuracy remains unclear. Limitations of the data and their analysis include misclassification bias arising from differential diagnostic coding practices, the inability to account for changes in testing practices over time, disregarding other causes of respiratory infection and uncertainty in the estimation of undiagnosed cases.

Younger age groups (particularly school children) are most susceptible to seasonal influenza infection with infection risk of up to 40-50% observed, whilst excess mortality occurs primarily in the elderly [29, 30]. The highest risk of complications occurs in children aged less than two years, those aged 65 years or older, pregnant women and those with certain medical conditions which include chronic heart, lung, kidney, liver, neurological, blood or metabolic diseases, and those with immunocompromising conditions [31].

Accurately assessing the burden of influenza is complicated by relatively poor case ascertainment: those with asymptomatic or milder infections will not present to health services; not all symptomatic cases are tested; and some hospitalised and fatal influenza cases may be coded to pneumonia or other causes [34]. During each influenza season there is usually an increase in all-cause deaths above those coded to influenza and/or pneumonia. Therefore, a common approach to assess the mortality impact of influenza has been to calculate the excess deaths that occur during periods of influenza activity over those occurring in baseline periods when influenza is not circulating, controlling for other seasonally variable causes of disease [35]. However, such estimates are imprecise because influenza contributes

only marginally to total mortality; sensitivity is maximised at the expense of specificity [36].

Imprecision in estimation of influenza morbidity and mortality is also compounded by variation over population and geography and between seasonal epidemics due to complex interactions between the circulating influenza type(s)/subtype(s), viral antigenic variation, immunity from previous exposures and vaccination, age susceptibility, climate, ethnicity and social wellbeing [29, 34, 37, 38]. Variability between seasonal influenza epidemics is also shown by a study which estimated the reproduction number (the number of secondary cases generated by a primary case) in a partially immune population at the beginning of seasonal epidemics over three decades in the United States, France and Australia. The reproduction number varied within a range of 0.9-2.1 year-to-year, with high prevalence of influenza A(H3N2) viruses associated with high transmission seasons [39]. Influenza A(H3N2) viruses have also been noted to evolve more rapidly than A(H1N1) and type B viruses and cause more influenza-related deaths [35, 40].

Surveillance of influenza is needed to guide prevention, control and mitigation policies but is challenging to undertake and interpret because of the wide and non-specific clinical spectrum and under-ascertainment of influenza infections. Multi-component surveillance systems are therefore used to assess the epidemiology of both laboratory confirmed influenza and syndromic proxy markers of influenza activity, such as influenza-like illness (ILI) [41].

Influenza and ILI activity in Australia is measured using community-based notifiable disease and laboratory surveillance, and sentinel and absenteeism surveillance in workplaces, general practices, hospital emergency departments and amongst admitted patients. The broad objectives of influenza and ILI surveillance are to: monitor the epidemiology of laboratory confirmed influenza; identify the onset, duration and relative severity of annual influenza seasons; provide samples for the characterisation of circulating influenza strains in the community to assist in evaluation of the current seasonal vaccine and formulation of the following season's vaccine; and provide potential for early recognition of new influenza viruses and new or emerging respiratory diseases [42, 43].

Pandemic influenza

Since 2003, documents produced by the World Health Organization (WHO) stated an influenza pandemic occurs "when a new influenza virus appears against which the human population has no immunity, resulting in several, simultaneous epidemics worldwide with enormous numbers of deaths and illness" [44]. However, following the emergence of influenza A(H1N1)pdm09 this description became controversial and was amended as evidence indicated the majority of cases had a generally mild clinical course and the presence of protective immunity in the elderly, and questions were raised as to whether influenza A(H1N1)pdm09 constituted a pandemic at all [45]. The updated WHO website states that "an influenza pandemic occurs when a new influenza virus emerges and spreads around the world, and most people do not have immunity" [46].

Three pandemics of influenza caused by different subtypes of influenza A virus occurred in the 20th century: an H1N1 virus in 1918; an H2N2 virus in 1957; and an H3N2 virus in 1968. Estimates of the number of cases and deaths in each pandemic vary and reflect the difficulty in using historical data to ascertain absolute numbers. However, each pandemic was characterised by a shift in the virus subtype, a high symptomatic infection risk, elevated mortality risks that were highest in young adults, an onset not restricted to the typical influenza season with successive pandemic waves, and replacement of the seasonal influenza A virus subtype with the pandemic strain [34, 47, 48].

The influenza pandemic of 1918-1919 is widely regarded as the most serious with estimated symptomatic infection risks of 20-60% in most countries and between 20-50 million deaths, or 1-2.5% of the world's population. The pandemics of 1957 and 1968-1969 were comparatively milder with respect to estimated symptomatic infection and mortality risks: there were approximately 2-3 million excess deaths worldwide (about 0.7% of the population) in 1957 and one million deaths (0.3%) in 1968-1969 [34, 49]. The age distribution of symptomatic infection risks also varied between the three pandemics: in 1918-1919 proportions were highest among children and young adults and declined with increasing age over 30; in 1957 proportions were highest in school-aged children, intermediate in young and

middle-aged adults and lowest among adults aged 50 years or more; in 1968-1969 symptomatic infection risks were stable across all age groups [50].

Influenza A(H1N1) virus was reintroduced into the human population in 1977. Although disease was characterised by classical influenza symptoms, cases were generally mild and almost entirely restricted to people aged 25 years or younger. The age distribution has been attributed to the absence of circulating H1N1 since 1957 (when it was replaced by H2N2) and a corresponding lack of exposure and immunity to H1N1 viruses in those born after then. Furthermore, the H1N1 strain did not replace the H3N2 that emerged in the 1968-1969 pandemic and thus strains of both subtypes have co-circulated in humans since 1977 [48].

The 'swine flu' pandemic of 2009 was the first influenza pandemic of the 21st century and also differed virologically and epidemiologically from the three 20th century pandemics. The pandemic virus, designated influenza A(H1N1)pdm09, emerged from a triple (avian, swine and human) reassortment rather than antigenic shift [51]. Furthermore, it replaced only the previously circulating seasonal H1N1 and not the H3N2 subtype. The cumulative incidence of infection was estimated by serological studies to be in the range 11-21% [52] and the majority of infections were relatively mild; between 30-50% of infections were estimated to be asymptomatic [53-55], with approximately 0.25% and 0.04% hospitalised and fatal respectively [56, 57]. Exposure to H1N1 viruses prior to the 1957 pandemic is believed to account for the very low proportion of adults aged over 60 years infected with influenza A(H1N1)pdm09 [52].

Vaccine

Vaccination is recognised as the most effective measure for reducing the impact of influenza [58]. Most current seasonal influenza vaccines contain antigens for two type A strains (one of each subtype H1N1 and H3N2) and one type B strain, although in August 2013 a quadrivalent vaccine containing an additional B strain was included in the Australian Register of Therapeutic Goods [59]. The vaccine strains are frequently replaced due to antigenic drift of circulating viruses. The WHO conducts biannual consultations and uses global influenza virus surveillance data to recommend which influenza virus strains should be included in the vaccine

for the following influenza season in the other hemisphere [60]. A period of 6-7 months is required for production before suitable quantities of vaccine are available for administration.

Both inactivated and live, attenuated influenza vaccines are available. In live attenuated influenza vaccine (LAIV), virus antigen is constituted as live-attenuated, cold-adapted, temperature-sensitive vaccine viruses. The LAIV is administered intranasally and may cause mild symptoms related to vaccine virus infection. LAIV is not licensed for use in Australia. The trivalent influenza vaccines (TIV) are comprised of subvirions or surface antigens purified from inactivated influenza virus. A number of different TIV preparations, with various age and route of administration indications, are licensed for use in Australia [61]. Evidence from clinical trials suggests that protection against viruses that are antigenically similar to those in the vaccine lasts for at least 6-8 months. Although the elderly have a weaker immune response to influenza vaccine [62], there is no clear evidence that immunity declines more rapidly compared to younger adult populations [63].

In Australia, TIV generally becomes available in March each year. The Australian Government funds influenza vaccination for certain risk groups, which includes: everyone aged 65 years and over; all Aboriginal and Torres Strait Islander people 15 years of age and over; any person six months of age and over with a condition predisposing them to severe influenza illness; and all pregnant women. Influenza vaccination is recommended, but not funded, for other risk groups (including children aged less than five years, residential and aged care facility residents, homeless people, those who may transmit influenza to persons at risk of complications from influenza infection, essential services workers and travellers) whilst others are vaccinated privately or through workplaces [61].

Following the emergence of the pandemic influenza A(H1N1)pdm09 virus and as recommended by the WHO, an A/California/7/2009 (H1N1)–like virus was used to produce a monovalent vaccine for Australia [64]. The Pandemic (H1N1) 2009 Vaccination Program in Australia ran from 30 September 2009 to 31 December 2010 and was publicly funded for all persons in Australia aged six months or older [65].

Vaccine effectiveness

Efficacy and effectiveness studies are used to determine the extent to which a specific intervention produces a beneficial result. Efficacy is measured under ideal conditions whereas measurement of effectiveness is conducted when the intervention is deployed in the field under routine circumstances [66]. Vaccine effectiveness (VE) is the percentage reduction in cases among vaccinated individuals and differs from year to year for influenza due to antigenic drift and variable dominance of circulating strains, and the different strain compositions of seasonal vaccines that result. Regular monitoring of VE is an important part of evaluating the publicly funded influenza vaccination program. Determining the efficacy and effectiveness of influenza vaccine is dependent on a number of factors, including: age; immunocompetence of the vaccine recipient; antigenic similarity of the vaccine virus strains to those circulating; and the specificity of the outcome measure [67]. Whilst clinical trials are used for establishing vaccine efficacy, it is impractical for them to be conducted on each seasonal influenza vaccine and licensure of influenza vaccine is therefore based on immunogenicity studies. However, immunogenicity does not necessarily correlate with effectiveness and properly designed observational studies provide a reliable and more practical means of calculating VE under field conditions [68, 69].

One observational study design to emerge as the preferred method for calculating influenza VE is the so-called 'case test-negative' design [70] that has been used in Europe [71], Canada [72] and the USA [73] since around 2007. It is a prospective variant of the traditional case control study design, in which the case or control (test-negative) status of the study participants is not known at the time of their recruitment into the study: patients presenting with ILI (or other defined acute respiratory illness) are tested for influenza and those that test positive and negative become cases and controls respectively. Influenza negative ILI patients are a convenient source of controls in the general practice setting and are more likely to be representative of the case source population in terms of propensity to consult for ILI.

In the decade prior to the 2009 pandemic there were few published studies estimating influenza efficacy or effectiveness in Australia, consisting only of a large randomised controlled trial conducted in Australia and New Zealand in 2008-9 [74] and another that estimated VE from an influenza A outbreak in a Victorian aged care facility in 2001-2 [75]. In a paper published in 2009, the Epidemiology Unit at the Victorian Infectious Diseases Reference Laboratory retrospectively applied the case test-negative design to an existing sentinel general practitioner surveillance dataset to establish proof of concept, although completeness of vaccination status data were relatively low and the VE estimates were not stratified by type/subtype or age group [76]. Given its relative infancy, methodology and understanding of the case test-negative study design continues to evolve. Early modelling suggested the design underestimates true VE under most conditions of test sensitivity, specificity and the ratio of influenza to non-influenza attack rates [77], whilst the classification and role of biases and confounding variables continue to be debated [70, 78-81].

Antivirals

Antiviral medications act by interrupting essential steps in the viral replication cycle and are used for both the treatment and prevention of influenza. The two major classes of antiviral drugs used for influenza virus infection are the M2 inhibitors and the neuraminidase inhibitors. The M2 inhibitors amantadine and rimantadine have been available since the 1960s and prevent replication of type A influenza viruses by blocking the M2 proton channel. However, their usefulness is limited because of widespread resistance, particularly in seasonal A(H3N2) viruses but also the pandemic influenza A(H1N1)pdm09 virus and some clades of A(H5N1) viruses [82]. Systematic reviews have found low to moderate quality evidence of effectiveness of amantadine and rimantadine in relieving or treating symptoms in healthy adults and children, and prevention of infection in children [83, 84].

Neuraminidase inhibitors (NIs) prevent the release and spread of progeny virions by blocking the neuramindase function. Two NIs (oseltamivir and zanamivir) are licensed globally for treatment and prevention of influenza, whilst peramivir and

laninamavir are only licensed in Japan. Influenza virus NI resistance profiles vary because resistance can be specific to a neuramindase subtype or a particular NI; an oseltamivir-resistant (and zanamivir-sensitive) seasonal influenza A(H1N1) strain emerged in 2007-2008 and rapidly became the dominant A(H1N1) virus worldwide before being replaced with oseltamivir-sensitive A(H1N1)pdm09 virus [85]. NIs are widely believed to be effective in reducing the severity and duration of influenza (particularly if used within 48 hours of symptom onset) and in the prevention of influenza illness when administered prophylactically. Indeed, antivirals for treatment and prophylaxis remain important components of pandemic plans, particularly for delaying and containing spread of a pandemic virus [25, 65, 67]. However, the logistical constraints on the ability to deliver sufficient quantities of antivirals is often overlooked in these plans [86]. In addition, assumptions about the effectiveness of NIs have been challenged, with concerns raised about the quality of evidence, particularly with respect to publication bias and problems with the design, conduct and availability of information from clinical trials [87, 88].

Non-pharmaceutical interventions

Given the limitations of supply, production, distribution and cost of vaccine and antiviral medication, pandemic plans also include non-pharmaceutical interventions to mitigate the spread of pandemic influenza virus. At the community level, these include isolation of patients and quarantine of contacts, encouragement of personal protection and hygiene measures (such as use of facemasks, coughing etiquette and hand-washing) and social distancing measures (such as the closure of schools and childcare centres and cancellation of large scale public events) [89].

Modelling studies based on US, UK and Australian populations have indicated that school closure can be effective at reducing the cumulative incidence of influenza [90-93]. However, the extent to which this occurs varies considerably and is probably due to different assumptions about relative attack rates in adults and children, the extent of mixing and contact outside school, and the number of symptomatic cases before closure is implemented [93]. To be most effective,

school closure must happen early, remain in place until prevalence returns to low levels and mixing of children prohibited during the closure. Implementation of school closure has been used with varying success in the control of influenza epidemics and pandemics, and the timing, extent and length of the closure are all important factors in the effectiveness of the intervention [94, 95].

Although effectively implemented social distancing measures are modelled to reduce the impact of pandemic influenza, policy makers must also consider the social and economic consequences of such measures. Surveys conducted in Australia following the public health response to influenza A(H1N1)pdm09 indicated high patient- and household-level compliance with quarantine requirements of 85-96% [96-98]. Parents in just over half of Victorian households affected by school closures took time off work to care for quarantined children, and of these 38% lost pay as a result [99]. Given that social distancing measures were only implemented for 2-3 weeks in Australia during the initial response to influenza A(H1N1)pdm09, it is unlikely high levels of public acceptance could be sustained; one study found willingness to comply with avoiding social gatherings for one month was 63% [98].

Screening of arrivals (particularly at airports), as well as exit screening in affected areas, are methods suggested to limit the spread of pandemic influenza across borders [100]. However, a number of modelling studies have indicated that screening or travel restrictions are unlikely to prevent, delay or slow global spread of an influenza pandemic because of the rapid initial growth rate of a pandemic, the large number of people infected and high proportion that are asymptomatic [101-103]. Further highlighting the ineffectiveness of border screening as a control measure is a review of non-contact infrared thermometers (NCITs), which were introduced at some international airports and gathering places to measure fever during the outbreak of severe acute respiratory syndrome in 2003. The positive predictive value of NCITs is low when fever prevalence is low, suggesting their efficacy would be limited at the early stages of a pandemic when they are primarily intended to be used [104]. Furthermore, NCITs will miss those using antipyretic medication or in the prodromal phase of illness.

Conclusion

The complexity of seasonal influenza epidemiology and virology is reflected in the broad range of methods and strategies utilised for its surveillance and control. Whilst elements of seasonal influenza remain unpredictable, the emergence of an influenza pandemic at any time without warning necessitates an urgent, large-scale response with additional social and political challenges, particularly with respect to mitigation measures. The 2009 pandemic provided the first *in situ* application and test of public health pandemic response plans, in which considerable effort had been invested in the preceding years.

This thesis reflects on the Australian experience responding to influenza A(H1N1)pdm09 by comparing conventional epidemiological assumptions with what was observed, investigating the role of severity in transmission, and examining the application and performance of the specific control measures of school closure and antiviral distribution in this context. The thesis also examines post-pandemic seasonal influenza epidemiology as well as effectiveness of vaccine – the most important influenza control measure – prior to, during and following the emergence of influenza A(H1N1)pdm09.

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Chapter 3

Research design

Research questions

This thesis seeks to answer the following research questions:

1. How did the epidemiology and public health response for influenza A(H1N1)pdm09 differ from expectations in pandemic planning?
2. What role did different levels of disease severity have in driving the initial spread of influenza A(H1N1)pdm09?
3. How has the epidemiology of seasonal influenza in Victoria changed since the emergence of influenza A(H1N1)pdm09?
4. How effective has influenza vaccine been in the prevention of laboratory confirmed influenza infection from 2007 to 2011?

Each question is addressed by a discrete chapter comprising multiple studies that have been published in peer-reviewed journals.

Research question 1: how did the epidemiology and public health response for influenza A(H1N1)pdm09 differ from expectations in pandemic planning?

Two studies were undertaken to address this research question and are included in Chapter 4. The first paper, on which I was a co-investigator, compared some of the virological and epidemiological assumptions about pandemic influenza viruses made from analysis of previous pandemics and in pandemic planning documents, to what was actually observed following the emergence of influenza A(H1N1)pdm09 [1]. I was the primary author of a second study and I analysed surveillance data on symptoms, antiviral treatment and prophylaxis, and school attendance of the first 1,000 cases of influenza A(H1N1)pdm09 notified to the Victorian Government Department of Health [2]. The findings of the analysis were used to make inferences about the impact of school closures and antiviral distribution in particular, which were key control strategies initially used by the Government to contain the spread of the pandemic.

Research question 2: what role did different levels of disease severity have in driving the initial spread of influenza A(H1N1)pdm09?

During the public health response to influenza A(H1N1)pdm09 in Victoria several lines of evidence, later supported by modelling, suggested community transmission of pandemic influenza was well established before cases were identified [3]. Along with anecdotal evidence and the observation that a large proportion of notified cases were relatively mild [4], this lead to the hypothesis that spread of influenza A(H1N1)pdm09 was largely driven by those with asymptomatic or clinically mild infections. Research question 2 addressed this hypothesis in two discrete and sequential stages, the first of which was a systematic review of the viral shedding duration in people infected by influenza A(H1N1)pdm09 virus [5]. This study arose from the absence of a such a review in the literature and the need to include estimates of influenza A(H1N1)pdm09 viral shedding duration (as a proxy for the infectious period) in the second study. The second study (which had not been submitted to a journal at the time of thesis submission) used deterministic mathematical modelling to estimate the relative importance of different levels of infection severity in transmission of influenza A(H1N1)pdm09 virus. Both of these studies, for which I was primary author, are included in Chapter 5.

Research question 3: how has the epidemiology of seasonal influenza in Victoria changed since the emergence of influenza A(H1N1)pdm09?

This research question is addressed in Chapter 6 by three surveillance studies that describe the epidemiology of influenza and influenza-like illness (ILI) conducted over consecutive influenza seasons from 2010-2012 inclusive [6-8]. I was primary author and/or chief investigator for each study in which I analysed Victoria ILI and laboratory confirmed influenza surveillance data from notifiable disease, sentinel general practices, a sentinel hospital network, locum service and strain typing databases.

Research question 4: how effective have influenza vaccines been in the prevention of laboratory confirmed influenza infection from 2007 to 2011?

To address this research question I used data from the Victorian sentinel GP surveillance database in a prospective case test-negative study design to estimate seasonal influenza vaccine effectiveness (VE) for the two years preceding and following the 2009 pandemic, and 2009 itself. This resulted in four papers that are included in Chapter 7 [9-12]. With the exception of the study measuring the effectiveness of 2009 seasonal trivalent influenza vaccine in which I was a co-investigator, I was primary author of each of the papers in Chapter 7. Whilst providing overall VE estimates, each study aimed to calculate estimates stratified by age and influenza type and subtype. The effectiveness of the monovalent pandemic influenza vaccine was also assessed, following the Pandemic (H1N1) 2009 Vaccination Program that ran from 30 September 2009 to 31 December 2010.

Research methodology

The research questions were investigated using four broad research methods:

1. Analysis of public health surveillance data.
2. Systematic review of the literature.
3. Deterministic mathematical modelling.
4. Application of sentinel surveillance data to a case test-negative study design.

The description of these broad methods below provides an overview for the thesis; more detailed and specific methodological techniques are contained within the published papers in subsequent chapters.

Analysis of public health surveillance data

The first and third research questions were investigated by descriptive analyses of a number of laboratory confirmed influenza and ILI surveillance datasets from a variety of clinical settings. Influenza surveillance systems are usually comprised of several different surveillance data sources due the wide and non-specific clinical spectrum and under-ascertainment of influenza infections [13]. The Victorian influenza surveillance system is comprised of multiple programs: notifiable laboratory confirmed influenza; a general practitioner sentinel surveillance

network; a metropolitan locum service; a sentinel hospital network; and reference laboratory typing.

Laboratory confirmed influenza is a scheduled notifiable disease in Victoria under the *Public Health and Wellbeing Act 2008* and *Public Health and Wellbeing Regulations 2009*; all medical practitioners and persons in charge of pathology services are required to notify identification, demographic and diagnostic information about cases to the Department of Health within five days of diagnosis [14, 15]. The Department of Health also receives requests for assistance with management of institutional respiratory outbreaks, for which data are collected.

The Victorian response to influenza A(H1N1)pdm09 was undertaken in accordance with the phases described in the *Australian Health Management Plan for Pandemic Influenza* [16]. During the initial 'Delay' and 'Contain' phases of the public health response – for which the objective is to delay entry of the virus and to contain the establishment of the pandemic strain – data about symptoms, case treatment, prophylaxis of contacts and school attended were collected from notified cases in addition to the scheduled fields.

The Victorian Infectious Diseases Reference Laboratory (VIDRL) coordinates the general practitioner sentinel surveillance (GPSS) program. It operates annually from May to October, when the influenza season usually occurs, and consists of approximately 100 general practitioners (GPs) in metropolitan and regional Victoria. Participating GPs make weekly reports on the total number of consultations, and age, sex and vaccination status of patients presenting with an ILI using an established case definition [17]. GPs collect a nose or throat swab from their ILI patients, chosen at their discretion, which are tested at VIDRL by polymerase chain reaction (PCR) for detection of type A and type B influenza viruses. Influenza A virus-positive samples are then subtyped by PCR as A(H1) or A(H3). GPs also collect additional data about symptoms, vaccination and comorbidity (for which influenza vaccination is indicated [18]) for those patients that are swabbed.

The Melbourne Medical Deputising Service (MMDS) provides urgent after-hours medical care across the Greater Melbourne and Geelong area. Records containing the diagnosis terms "influenza" and "flu" were extracted from the MMDS database each week to calculate ILI diagnoses as a proportion of total consultations. Records containing the terms "Fluvax", "at risk" and "immunisation" were excluded from the numerator to avoid inclusion of those immunised prophylactically.

The Influenza Complications Alert Network (FluCAN) was established in 2010 and is a national sentinel hospital program that collects surveillance data on hospitalised patients with laboratory confirmed influenza [19]. From 2012, data collected by the four Victorian FluCAN hospitals were incorporated into reporting for the Victorian influenza surveillance system.

Information on influenza strains circulating in Victoria is provided by the World Health Organization Collaborating Centre for Reference and Research on Influenza (WHOCCRRI). All influenza positive samples from the GPSS are forwarded to the Centre for strain characterisation along with a selection of influenza virus specimens and isolates from other Victorian diagnostic laboratories. Isolates are also tested for sensitivity to the antiviral drugs oseltamivir, zanamivir, peramivir and laninamivir.

Additional surveillance data were sourced for the first of two studies that addressed the first research question of how the epidemiology and public health response for influenza A(H1N1)pdm09 differed from expectations in pandemic planning (Chapter 4). Laboratory confirmed influenza and ILI data from similarly operated GP sentinel surveillance programs in New Zealand and Western Australia were descriptively analysed with GPSS data to compare the epidemiological characteristics of influenza A(H1N1)pdm09 virus with expectations based on previous pandemics [1]. I was a primary author of this study; working with jurisdictional representatives I was responsible for large parts of its design, analysis, interpretation and writing. In the second study, additional surveillance data collected by the Department of Health during the 'Delay' and 'Contain' phases of the influenza A(H1N1)pdm09 public health response were descriptively analysed to gain insights into viral transmission among school children and the

distribution of oseltamivir treatment and prophylaxis. I was principally responsible for all elements in the production of this research [2].

The third research question was addressed by a series of influenza and ILI surveillance studies utilising data from the Victorian Government Department of Health, GPSS, MMDS, FluCAN and the WHOCCRRI (Chapter 6). Working with representatives from the institutional custodians of the surveillance datasets and who were included as authors, I oversaw the data analyses and was responsible for design and production of the surveillance papers for the years 2010 [6], 2011 [7] and 2012 [8].

Temporal, age group, type/subtype and vaccination status distributions of the surveillance data were constructed using Microsoft Excel. Relative magnitude of influenza seasons was assessed using established thresholds for influenza seasons in Victoria [20, 21]. The chi squared and Fisher's exact tests were used to compare proportions, and the Mann-Whitney U test to compare time periods between events, with Stata (version 10.0; StataCorp LP). A p value of less than 0.05 was considered statistically significant. Maps were produced with ArcGIS software.

Systematic review of the literature

The period in which virus from clinical specimens can be detected from patients infected with influenza virus is generally equated with the period in which they are infectious to susceptible contacts, and is an important parameter in mathematical models for infectious diseases. In the development of a model to address the second research question of the role different levels of disease severity had in driving the spread of influenza A(H1N1)pdm09 virus (Chapter 5), a systematic review of the literature was first conducted to characterise the duration of shedding [5]. I had primary responsibility for all elements of this study.

Articles were sourced by searching the PubMed database, after which a two-stage filtering process was applied to select community-based studies that were of human subjects and also had data of sufficient quality and quantity from which influenza A(H1N1)pdm09 virus shedding duration was reported or could be

calculated. Reference lists of shortlisted studies were searched to identify additional articles.

Detailed review of articles identified considerable differences in the methods by which duration of viral shedding in each was calculated, including: the start point of shedding duration (either the day of symptom onset, first positive test or treatment initiation), the endpoint (either the day of the last positive or first negative test) and how days of shedding duration were calculated (either by counting the starting point day as one day of viral shedding, or using the days difference between the start and endpoints). To compare studies, a standard definition of viral shedding duration – the number of days from day of symptom(s) onset to the day of collection of the last specimen in which influenza A(H1N1)pdm09 was detected, inclusive – was applied to data abstracted from each shortlisted study. Study authors were contacted for clarification of their definitions or additional data if required. Where possible, data were stratified by clinical severity (classified by the study settings of community, hospital or intensive care), age group (child or adult), antiviral treatment and the type of laboratory test used.

Studies were compared by forest plots of summary measures of viral shedding duration (minimum, maximum, median, mean and 95% confidence interval) and the proportion of patients shedding virus by day of illness in survival curves. Meta-analyses using a random-effects model were conducted in Stata (version 10.1; StataCorp LP). Heterogeneity between studies was assessed by the I^2 test, but because there was significant heterogeneity (defined as $I^2<80\%$ and $p>0.1$) in most clinical severity groups, summary estimates of viral shedding duration were not reported.

Deterministic mathematical modelling

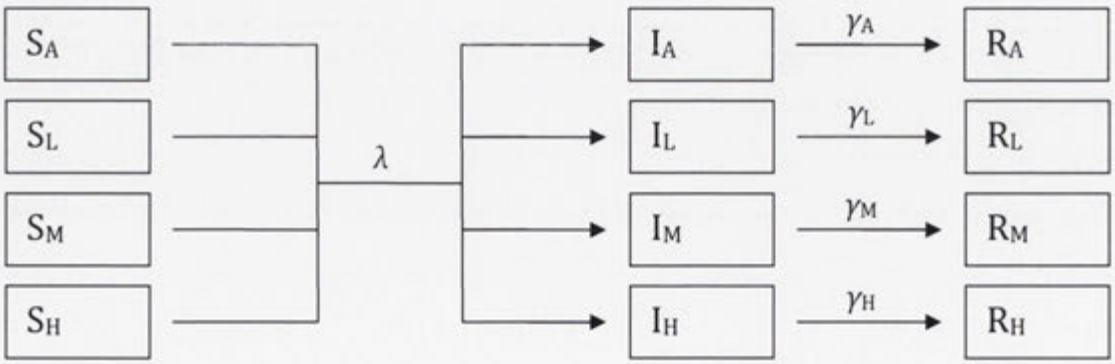
Mathematical models are a simplified representation of a complex phenomenon, and are a useful tool for understanding and predicting disease outcomes at a population level not afforded by traditional epidemiological approaches. Mathematical models are used for prediction and understanding but these applications are quite distinct. Models used for prediction (such as the effect of an intervention on disease transmission) need to be as accurate as possible, whilst

transparency and flexibility are more important qualities of models that are used to improve understanding how diseases spread and various complexities that affect their dynamics [22, 23].

The type of modelling method used is dependent on the research question: they may be individual, group-based (compartmental), transmission dynamic, static or network, and be deterministic and/or stochastic in nature [23]. A deterministic compartmental Susceptible-Infected-Recovered (SIR) model structure was developed to investigate the second research question of the role that different levels of disease severity had in driving the spread of the first wave of influenza A(H1N1)pdm09 in Australia (Chapter 5). Each infection stage class comprised four compartments representing four levels of disease severity: asymptomatic (A); low-level symptoms (L); moderate symptoms (M); and illness requiring hospitalisation (H).

The model is shown in figure 1. Susceptible individuals (S) flow to respective infected (I) compartments following exposure to an overall force of infection λ. Each level of infection severity has a force of infection that is the product of the severity level-specific transmission parameter β and the proportion infected (I). The sum of these comprise the overall force of infection and is represented schematically by the branched transition from S to I compartments. Infected individuals transition to recovered (R) at a recovery rate γ.

Figure 1. Influenza Susceptible-Infected-Recovered model with four levels of infection severity.



The transmission parameter β for each infection severity stratum was calculated as the product of relative proportional coefficients for infectivity (η) and mixing (μ), and a common fitting coefficient θ. The fitting coefficient was defined in terms of the overall effective reproduction number, R_e, to ensure R_e was kept fixed at a plausible value. The model assumed a population susceptible to influenza A(H1N1)pdm09 with no previous immunity from vaccination or infection, and that re-infections did not occur in the 250 day timeframe used for the first wave.

Literature searches were undertaken to determine plausible baseline values and ranges for the proportion of influenza A(H1N1)pdm09 infections that were asymptomatic and those which required hospitalisation. Division of the remaining proportion of symptomatic infections into low-level and moderate symptoms was calculated using 'Flutracking' ILI surveillance data. The Flutracking surveillance system provides weekly community-level ILI symptomatic infection risks not biased by health-seeking behaviour and clinician testing practices [24]. The proportion reported as taking one or no days off because of their ILI were classified as low-level symptoms, and the proportion taking two or more days off because of their ILI were classified as moderate symptoms.

The mixing parameters μ for each severity stratum were defined as proportions relative to the asymptomatic class (for which μ=1.0) and estimated by plausible assumptions, with the level of mixing decreasing as infection severity increased. The infectivity parameters η for each severity stratum were also defined as relative proportions, but were all set at η =1.0 given the lack of evidence of a relationship between viral load and clinical severity [25, 26]. The recovery rate γ for each severity category was calculated as the inverse of the duration of infectiousness, estimated from the systematic review of viral shedding duration [5].

MATLAB (Student version; MathWorks) was used to simulate the model using values of R_e within the limits of published estimates (range: 1.14-1.36) [27] that resulted in a total proportion of recovered individuals that was consistent with estimated age-standardised infection risks [28, 29]. Effective reproduction numbers for each infection severity stratum were calculated to determine the relative importance of each group in influenza A(H1N1)pdm09 virus transmission.

Triangular distributions of the parameter ranges (baseline value plus and minus 10%) were sampled 400 times using Latin hypercube sampling. Parameter outputs were then transformed into their ranks and partial rank correlation coefficients (PRCC) calculated [30]. The results of the PRCC were used to identify which parameters most influenced the model outcome and test the effect of their variation, within plausible limits, on the infection severity stratum-specific reproduction numbers.

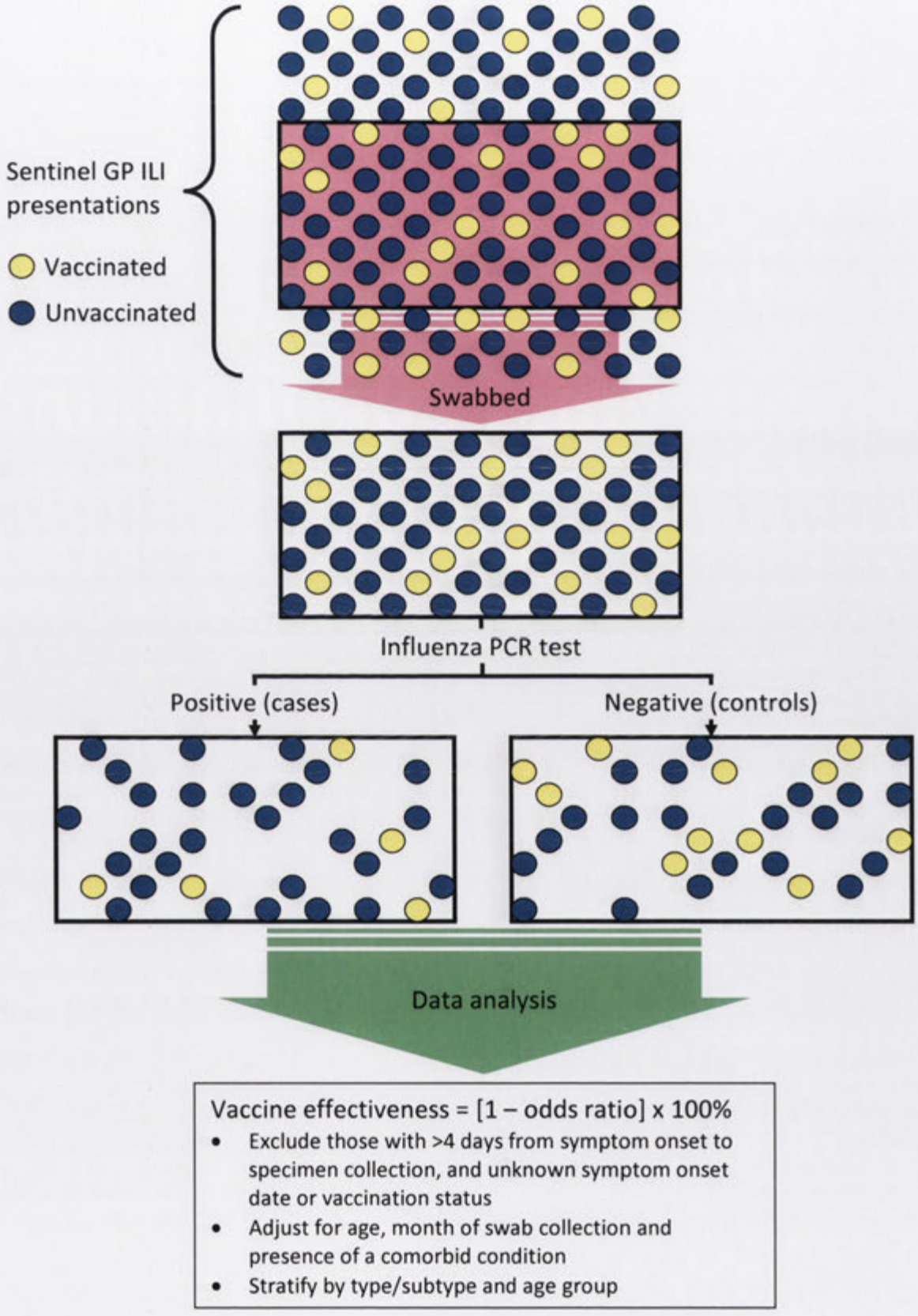
Application of sentinel surveillance data to a 'case test-negative' study design

The case test-negative study design was applied to GPSS laboratory testing data to measure influenza VE in Victoria from 2007-2011. It was first used to measure VE in Victoria on data from 2003-2007 to establish proof of concept, but was limited by low ascertainment of influenza vaccination status and relatively few stratified analyses [31].

Figure 2 shows schematically how GPSS patients are recruited into the study and vaccine effectiveness is calculated. As described above, sentinel GPs swabbed a sample of patients meeting the ILI case definition for influenza testing. Those testing positive comprised the cases and those testing negative comprised the controls.

Logistic regression was used to estimate the odds ratio of laboratory confirmed influenza in vaccinated versus unvaccinated persons. The odds ratio is the odds of a case being vaccinated divided by the odds of a control being vaccinated. VE was calculated as 1 minus the odds ratio, multiplied by 100%. Odds ratios were adjusted for age and month of specimen collection, as well as pandemic response phase in 2009 and the presence of a comorbid condition for which influenza vaccination is indicated in 2011 (when collection of that data field commenced). Primary analyses were restricted to those in which a swab was collected four or less days between symptom onset and specimen collection date, given the decreased likelihood of a positive result after this time.

Figure 2. Schema of case test-negative study design for measuring influenza vaccine effectiveness.



To answer the fourth research question, I undertook all analyses and calculated effectiveness of seasonal trivalent influenza vaccine for each year from 2007 to 2011 [9-12] by redeveloping the data cleaning and analysis methodology (Chapter 7). This included calculation of stratified type/subtype- and age group-specific VE estimates, inclusion of additional confounding variables into the model, and sensitivity analyses for assumptions made in the model. VE estimates for the monovalent pandemic vaccine (which was publicly funded for all Australians aged six months or older from 30 September 2009 to 31 December 2010 [32]) were also calculated [11]. With the exception of the 2009 season paper in which I was a co-investigator, I was principally responsible for interpretation and writing of all the VE studies.

Sensitivity analyses were conducted to determine the effects of: only including patients that presented within the defined influenza season; censoring records with longer time from illness onset to specimen collection; and assumptions about whether vaccination within 14 days of illness onset conferred an immune response.

Analyses were conducted in Stata (version 10.0; StataCorp LP). The chi squared test was used to compare proportions and the Mann-Whitney U test to compare time periods between events, with $p<0.05$ considered statistically significant.

Ethics

Human Research Ethics Committee was not required for studies using laboratory confirmed influenza datasets because data were collected as part of regulated notifiable disease surveillance. Influenza (laboratory confirmed) is a scheduled notifiable disease in Victoria and notification of all cases and prescribed data fields to the Department of Health is mandatory under the *Public Health and Wellbeing Act 2008* and *Public Health and Wellbeing Regulations 2009* [14, 15]. Written consent from patients is not required for notification of a notifiable infectious disease. Data in the studies were used and reported within the requirements of the Victorian *Health Records Act 2001* [33].

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Chapter 4

Pandemic planning in practice

About this chapter

The papers in this chapter used laboratory confirmed influenza and influenza-like illness surveillance data collected in 2009 and the following influenza season in 2010, as well as data from the published literature, to assess how the epidemiology and public health response for influenza A(H1N1)pdm09 differed from expectations in pandemic planning.

The first paper, published in the *Australian and New Zealand Journal of Public Health* highlighted differences between influenza A(H1N1)pdm09 and pandemic expectations with respect to timing of pandemic waves, mechanism of emergence of a pandemic strain, mortality risk, age distribution, strain replacement and effective reproductive number. In accordance with the copyright requirements of the journal publisher, the accepted version of this article – rather than a scan of the published version – is presented in this chapter. The second study, published in *PLoS One*, showed that the approach to school closure in Victoria during the initial public health response to influenza A(H1N1)pdm09 was ineffective in interrupting transmission and that antivirals could not be delivered to cases within the required timeframe.

Papers in this chapter

1. Grant KA, **Fielding JE**, Mercer GN, Carcione D, Lopez L, Smith D, Huang QS, Kelly HA. Comparison of the pandemic H1N1 2009 experience in the southern hemisphere with pandemic expectations. *Aust N Z J Public Health* 2012; 36: 364-368.
2. **Fielding JE**, Bergeri I, Higgins N, Kelly HA, Meagher J, McBryde ES, Moran R, Hellard ME, Lester RA. The spread of influenza A(H1N1)pdm09 in Victorian school children in 2009: implications for revised pandemic planning. *PLoS One* 2013; 8: e57265.

Comparison of the pandemic H1N1 2009 experience in the southern hemisphere with pandemic expectations

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Keywords

Influenza; surveillance; pandemic.

Abstract

Objective

To describe the epidemiological characteristics of the 2009 H1N1 pandemic virus (pH1N1) over the 2009 and 2010 influenza seasons in Australia and New Zealand (NZ) and compare them with expectations based on previous pandemics.

Methods

Laboratory-confirmed influenza and influenza-like illness (ILI) data were collected from established general practitioner sentinel surveillance schemes in NZ, Victoria and Western Australia (WA) throughout the 2009 and 2010 winter influenza seasons. Respiratory swabs from a sample of ILI patients were tested for influenza type and subtype. ILI rates and laboratory-confirmed influenza data were analysed by age group and over time. Morbidity, mortality and reproductive number data were collated from the published literature.

Results

Peak ILI rates and the percentage of influenza-positive swabs from ILI patients from all sentinel surveillance schemes were considerably lower in 2010 than 2009. Compared to the population, cases of ILI were over-represented in the young. While the age distributions in NZ and WA remained consistent, ILI cases were significantly younger in Victoria in 2009 compared to 2010. In Victoria, laboratory-confirmed pH1N1 comprised up to 97% of influenza-positive swabs in 2009 but only 56–87% in 2010. Mortality and hospitalisations were lower in 2010. The effective reproduction number (R) for pH1N1 was estimated to be 1.2–1.5 in NZ and WA, similar to estimated R values for seasonal influenza. Data from the surveillance systems indicated differences in the epidemiology of pH1N1 compared to expectations based on previous pandemics. In particular, there was no evidence of a second pandemic wave associated with increased mortality, and complete influenza strain replacement did not occur.

Implications

Pandemic planning needs to accommodate the potential for influenza viruses to produce pandemics of various infectiousness and degrees of severity.

Introduction

Influenza pandemics in the last century – in 1918, 1957 and 1968 – were caused by the influenza A virus subtypes H1N1, H2N2 and H3N2 respectively. These pandemics are generally accepted to have been characterised by: successive waves, most marked in the 1918–19 pandemic; a shift in the virus subtype, with subsequent replacement of the previous circulating influenza A strains with the pandemic strain; higher excess mortality, especially in younger age groups, generally associated with a younger age of infection; and an increased reproduction number (R – the average number of secondary cases infected by one infectious case).[1-3]

Influenza A(H1N1) virus circulated in humans from 1918 until 1957, reappeared in 1977 and has since co-circulated with the influenza A virus H3N2 subtype.[4] Influenza A(H1N1)pdm09 (hereafter pH1N1) which arose through a novel reassortment rather than antigenic shift, emerged in North America in April 2009, early in the Southern Hemisphere influenza season. There was concurrent out-of-season influenza activity in the Northern Hemisphere, followed by an in-season second wave.[5]

Here, we use influenza-like illness (ILI) and laboratory confirmed pH1N1 infection data from sentinel surveillance systems in New Zealand (NZ) and two Australian States, Victoria and Western Australia (WA), as well as data on hospitalisations, mortality and the effective reproduction number to summarise epidemiological characteristics of the pH1N1 virus over two Southern Hemisphere influenza seasons. We compare the results from two Southern Hemisphere countries with expectations based on observations from previous pandemics.[1-3]

Methods

General practitioner (GP) sentinel surveillance for influenza and influenza-like illness (ILI) is conducted in NZ and Victoria throughout each winter influenza season, usually from May to September, but in 2009 was extended to the end of the year to monitor pH1N1. GP sentinel surveillance operates year-round in WA. In NZ, ILI is defined as acute upper respiratory tract infection characterised by abrupt

onset and two of the following: fever, chills, headache and myalgia; in Victoria and WA the ILI definition is fever (measured or reported), cough and fatigue.[6,7]

Participating GPs reported weekly consultation rates for ILI, the denominator of which in NZ was the patient population of the practice and, in Victoria and WA, the total number of consultations for that week. Age of all ILI patients was collected by each surveillance system. Proportional age group distributions of ILI cases in 2009 and 2010 and the total State/country population were compared for each surveillance scheme.

Respiratory swabs were collected systematically by participating GPs in NZ from the first ILI patient seen on each Monday, Tuesday and Wednesday, and were tested at the Institute of Environmental Science and Research Limited (ESR) and regional hospital laboratories in Auckland, Waikato and Christchurch. In Victoria and WA combined nose/throat swabs were collected at the GPs' discretion and tested at the Victorian Infectious Diseases Reference Laboratory and PathWest Laboratory Medicine WA, respectively. Swabs were tested by polymerase chain reaction (PCR) at all laboratories in Australia and NZ. All specimens were typed as influenza A or B. Sub-typing was attempted for all specimens; those that could not be sub-typed as influenza A(H1N1) or A(H3N2) were classified as 'untyped'.[8-10]

Data from weeks 18 to 40 (May to September) for both years from the three surveillance schemes were collated and analysed using Microsoft Excel and Stata (version 10.0, StataCorp LP). The chi squared test was used to compare proportions with $p<0.05$ considered statistically significant.

Hospitalisation and mortality data, and estimates of R, were collated from the published literature.[11-17] We compared surveillance results from our data analysis and the published data on morbidity, mortality and R with the expectations from previous pandemics as described above.[1-3]

Results

ILI and laboratory confirmed influenza

Compared to the high levels in 2009, peak ILI rates from all three sentinel surveillance systems were considerably lower in 2010 (Figure 1). In Victoria and WA, the peak ILI rates in 2010 were low in comparison to previous seasons and approximately one-third of those in 2009: 8.9 versus 23.0 ILI patients per 1000 consultations in Victoria, and 21.1 versus 56.9 patients per 1000 consultations in WA. In NZ the peak ILI rate in 2010 (151.6 per 100,000 population) was similar to previous seasons of high ILI activity in 2003 and 2005 and about half that in 2009 (284.0 per 100,000 population).

Figure 1a. Sentinel surveillance influenza-like illness rates, Victoria and Western Australia, 2003–2010.

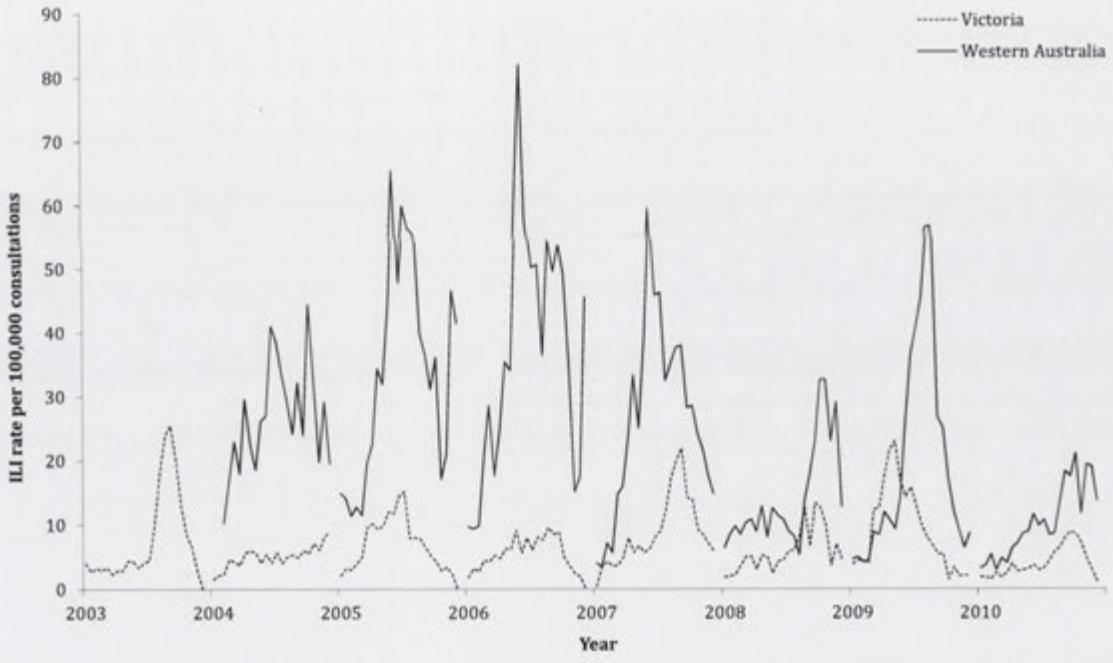
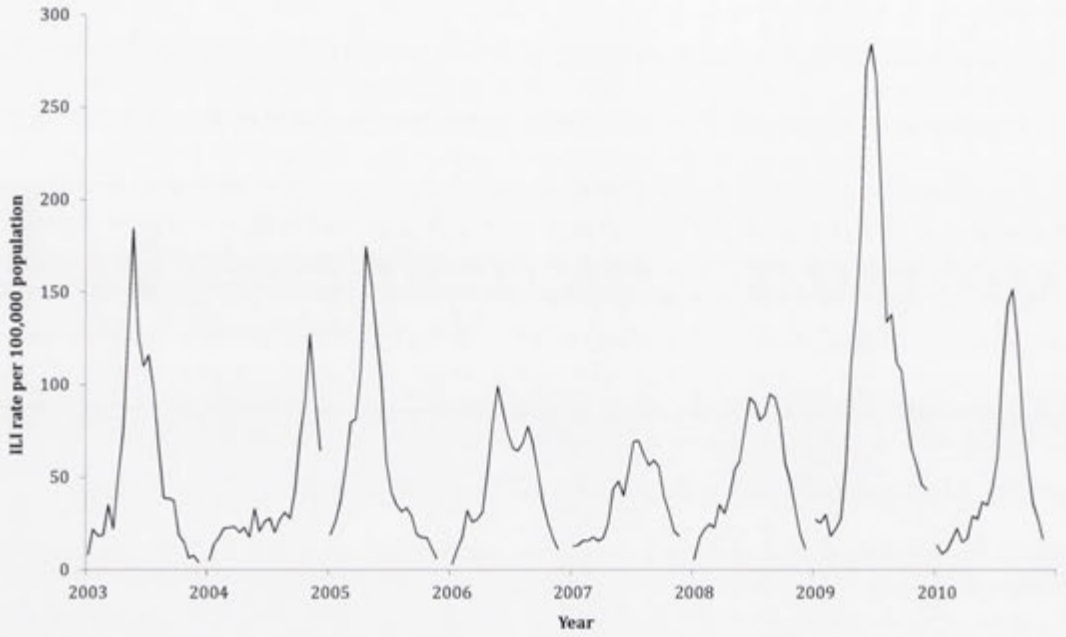
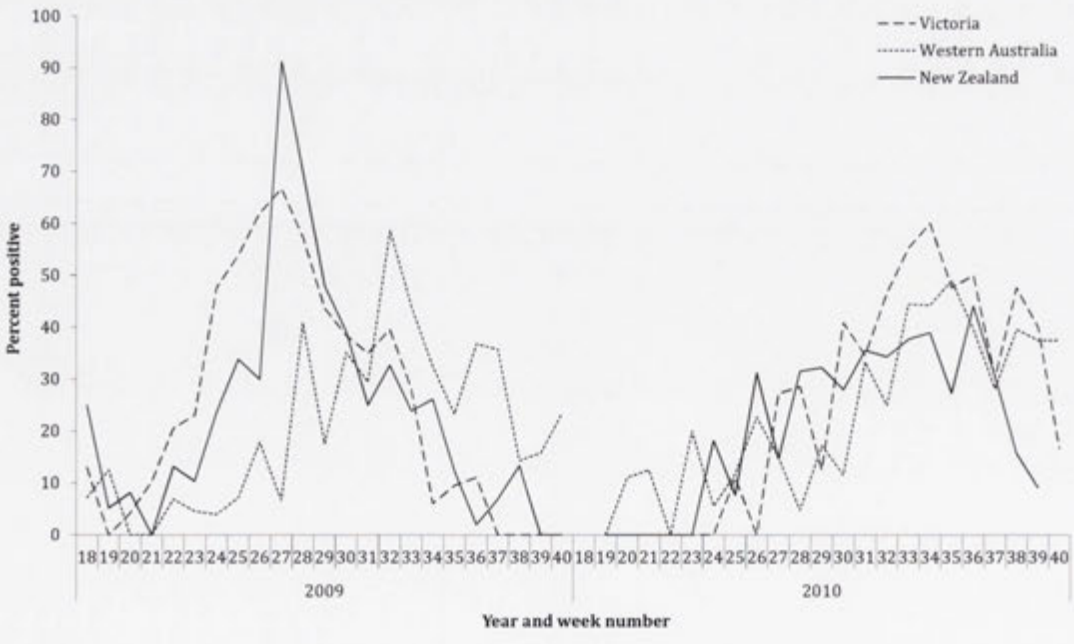


Figure 1b. Sentinel surveillance influenza-like illness rates, New Zealand, 2003–2010.



The percentage of swabs from ILI patients that were positive for influenza in 2010 was lower than in 2009 for all three surveillance systems (Figure 2). Comparing 2010 to 2009, the percentage positive peaked at 60% versus 67%, 44% versus 59% and 44% versus 91% in Victoria, WA and NZ respectively.

Figure 2. Percentage of sentinel surveillance swabs positive for influenza by week and surveillance scheme, 2009–2010.



Hospitalisations and deaths

Up until mid-October 2010, 732 hospitalisations and 15 confirmed deaths from pH1N1 had been reported in NZ, equating to a case fatality risk (CFR) of 8.5 per 100,000, similar to 2009 (9.0 per 100,000). The median age of those who died was higher in 2010 (50 years) than in 2009 (40 years). Hospital admissions in NZ were lower in 2010 (732) compared to 2009 (1,122). The age distribution of notifications and hospitalisations for pH1N1 was similar in 2009 and 2010 in NZ, with highest rates being in children under 5 years (80 and 51 per 100,000 population, respectively).[6,18]

In Australia in 2009 there were 191 confirmed deaths from pH1N1 (median age 53 years) and 4,992 hospitalised cases (median age 31 years). In 2010, there were 22 deaths at a median age of 51 years.[12] Estimates of the CFR were not available for either year. We could find no published data on hospitalisations in 2010 for Australia.

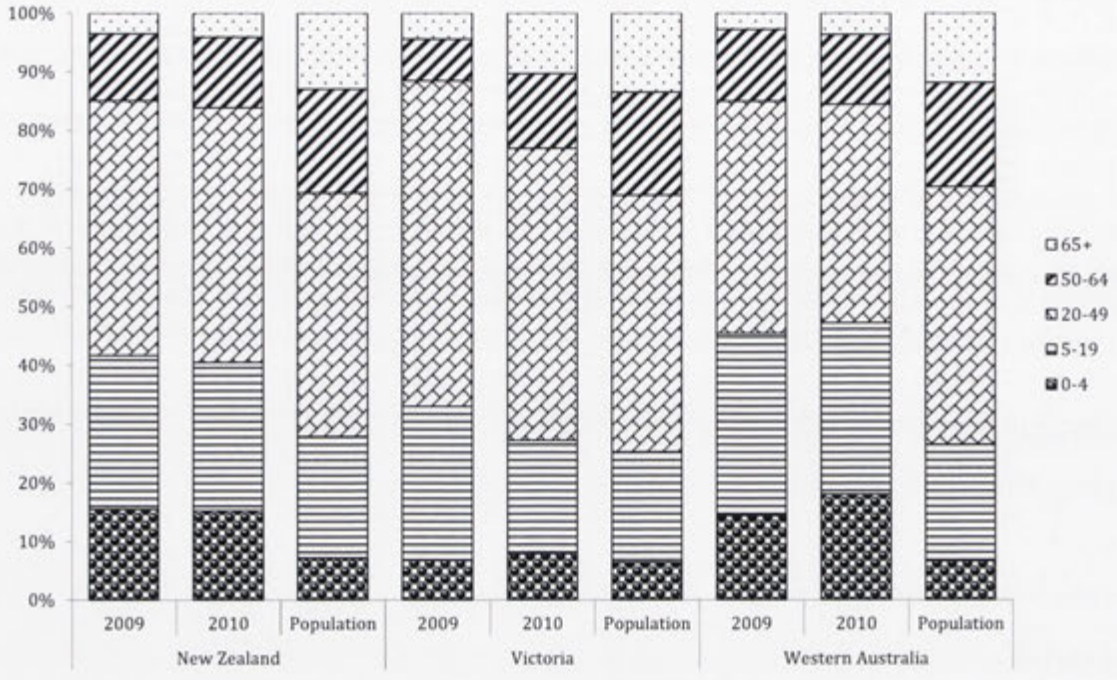
Age distribution

Compared to the population distributions of the age group categories, those aged 0–19 years were significantly over-represented in the ILI cases in NZ, Victoria and WA in 2009 ($p<0.001$ for all surveillance schemes). This trend continued in 2010 for both the NZ and WA surveillance schemes, with no significant difference to the age distributions observed in 2009 ($p=0.35$ in NZ and $p=0.14$ in WA). In contrast, ILI cases in Victoria were significantly younger in 2009 compared to 2010 ($p<0.001$) (Figure 3).

The majority of confirmed pH1N1 cases in 2010 were in the 5–19 and 20–49 age groups (Table 1).

The median ages of those with confirmed pH1N1 infection were 24, 26 and 17 years in NZ, Victoria and WA respectively. Although there were low numbers of H3N2 detections, the median ages of those infected were higher than for those infected with pH1N1in NZ (46 years) and WA (36 years) but not in Victoria (18 years). The median age of those infected with type B influenza (4, 12 and 11 years in NZ, WA and Victoria respectively) was lower than for influenza A (Table 1).

Figure 3. Proportional age distribution of sentinel surveillance influenza-like illness cases and total population by surveillance scheme, 2009–2010.



Strain circulation

As had been the case in all surveillance schemes in 2009,[19-21] pH1N1 was the most commonly identified strain in 2010, particularly in Victoria and NZ (87% and 76% of tested swabs respectively) (Table 1). Compared to the other surveillance schemes, a significantly higher proportion of influenza positive swabs (40%, $p<0.001$) in WA in 2010 were type B, of which 59% were detected in the 5–19 year old age group. There were no detections of the previous seasonal H1N1 virus from any surveillance scheme. Influenza A (H3N2) was detected in relatively low numbers in 2010 in all surveillance schemes.

Table 1. Sentinel surveillance swabs positive for influenza by surveillance scheme, type/subtype and age group, 2010.

Age group (years)	NZ				Victoria				WA			
	Flu A n (%)			Flu B n (%)	Flu A n (%)			Flu B n (%)	Flu A n (%)			Flu B n (%)
	pH1N1	H3	Untyped		pH1N1	H3	Untyped		pH1N1	H3	Untyped	
0-4	23 (8)	0 (0)	4 (5)	1 (100)	6 (4)	1 (14)	1 (9)	0 (0)	6 (6)	0 (0)	0 (0)	10 (14)
5-19	87 (32)	0 (0)	19 (23)	0 (0)	49 (33)	3 (43)	2 (18)	3 (60)	47 (47)	1 (14)	0 (0)	42 (59)
20-49	131 (48)	2 (67)	50 (40)	0 (0)	78 (52)	3 (43)	7 (64)	2 (40)	43 (43)	4 (57)	0 (0)	17 (24)
50-64	31 (11)	1 (33)	9 (20)	0 (0)	16 (11)	0 (0)	1 (9)	0 (0)	4 (4)	1 (14)	0 (0)	1 (1)
65+	2 (1)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (14)	0 (0)	1 (1)
Total	274 (76)	3 (1)	83 (23)	1 (0.3)	149 (87)	7 (4)	11 (6)	5 (3)	101 (56)	7 (4)	0 (0)	71 (40)
Median age	24	46	27	4	26	18	34	12	17	36	-	11

Reproduction number

The effective reproduction number was estimated using a stochastic version of a standard susceptible-infected-removed (SIR) model with Bayesian inference and accounted for the effect of imported cases.[13] The mean effective reproduction number (R) during the peak of transmission was estimated for pH1N1 in 2009 WA as 1.2–1.4[13] and for NZ as 1.2–1.5,[14-16] although earlier estimates of a higher R had also been reported in NZ.[16,17] In NZ and WA the estimated effective reproduction number was initially around 1.6–2.0, but rapidly declined to 1.2–1.4. This early higher estimate is expected from the nature of the estimation procedure and is not indicative of the population-wide reproduction number in the early stages of the outbreak.[16,22] It was not possible to estimate an unbiased R for Victoria because of undetected early transmission of pH1N1 prior to testing.[13]

Comparison with pandemic expectations

The differences between observations from 2009–10 in Australia and NZ, and expectations based on previous pandemics, are summarised in Table 2. Evidence from the three surveillance systems in the Southern Hemisphere shows that pH1N1 differed substantially from pandemic expectations. It did not cause a second pandemic wave associated with increased mortality. It replaced the previous H1N1 seasonal influenza subtype, but did not replace the H3N2 subtype. It was not associated with a higher reproduction number and, although there was increased mortality in younger age groups, overall laboratory-confirmed mortality was lower than the excess mortality modelled to occur with seasonal influenza. These two measures are not strictly comparable and capture of all laboratory-confirmed deaths was likely to have been incomplete.

While previous influenza pandemics have been caused by antigenic shift in the influenza subtype, leading to higher rates of infection in a naïve population, pH1N1 was characterised by a novel reassortant. In previous pandemics, all influenza A viruses were replaced by the pandemic strain,[2] whereas in 2009 and 2010 influenza A(H3N2) continued to circulate, albeit at low levels, and only the seasonal H1N1 strain was replaced by pH1N1.

Table 2. Comparison of pandemic expectations with observations from Australia and New Zealand 2009–10.

Pandemic expectation	Evidence from the pH1N1 pandemic in Australia and NZ
Sometimes multiple waves	Seasonal waves
Possibility of second wave with an increase in mortality and morbidity	Decrease in mortality and morbidity in second season
Pandemic strain resulted from an antigenic shift	Pandemic strain resulted from a novel reassortant of a circulating subtype[23]
Increased mortality overall with case fatality risk up to 2%	Probable decreased mortality overall with case fatality risk <0.01%
Increased morbidity and mortality in younger people	Increased morbidity and mortality in younger people
Younger age of infection	Younger age of infection (possibly an H1N1 characteristic)
All influenza A viruses replaced by pandemic strain	A(H1N1) replaced only; A(H3N2) continues to circulate
R mean: 2.0; range: 1.4-2.8[24,25]	R = 1.2-1.5[13-17,26,27]

Discussion

Data from three sentinel surveillance systems highlight the importance of using a variety of information sources to describe the epidemiology of influenza. We found differences in the ILI rates across the three surveillance schemes, which may be subject to local influences, such as media, differences in the way surveillance is conducted or targeted vaccination programs. These differences may also reflect real differences in viral circulation or, most likely, a combination of these factors. However, data on laboratory-confirmed influenza, assessed by the percentage of respiratory swabs positive for influenza, showed that the seasons of 2009 and 2010 were generally consistent between the three surveillance schemes in terms of timing and relative magnitude of the influenza epidemics. The higher number of tests for influenza in 2009 was most likely due to increased testing caused by increased concern about pH1N1 and targeted testing of patients, for example,

those who were quarantined pending a negative laboratory result. Examining the proportion of swabs that test positive for influenza is an informative way to adjust for different testing practices between jurisdictions.[28]

The most plausible explanations for differential levels of ILI activity in 2010 recorded by the three surveillance systems are: early arrival of pH1N1 into Victoria and subsequent spread of the virus before interventions had commenced;[13] high pH1N1 infection rates in both Australia and NZ during the first pandemic season;[9,20] geographic variation in the reach of pH1N1 in NZ in 2009;[6,9] and limited antigenic drift of the pH1N1 virus.[1,29] The role of population immunity and benefits from the vaccination programs in lower ILI activity hospital admissions and deaths in 2010 are less clear because complete vaccination coverage data from both the 2009 monovalent pandemic vaccine program (funded for all Australians but only for health care workers in NZ) and the 2010 trivalent seasonal vaccine are not available for comparison in both countries.

The effective reproduction number for pH1N1 was likely to have been in the range 1.2–1.5, similar to seasonal influenza and lower than previous pandemics. Values in the range 1.2–1.4 are consistent with estimates of R obtained from seroprevalence surveys of pH1N1.[26,27] R has been estimated to be 2.0 (with a range of 1.4–2.8) for the 1918 pandemic, 1.6 for the pandemic of 1957 and 1.8 for the 1968 pandemic. R varies year-to-year for seasonal influenza with a mean around 1.3 and a range of 0.9–2.1.[2,24,25,30]

While a shift in distribution to the younger age groups is a distinctive feature of pandemics, it is possible that the younger age of infection of pH1N1 in both years is due to the younger age of infection of characteristic of influenza A(H1N1) viruses.[31,32] The age of infection tends to increase in the years following pandemics. There was a suggestion of this trend in the median age of ILI infections in Victoria in 2010, but not in WA or NZ.

In summary, the pandemic caused by pH1N1 was very different to pandemic expectations, many of which informed pandemic planning in Australia and around the world. Early recognition of these differences may partly explain the public and

professional disquiet about Australia's response to the pandemic.[33,34] Recognition of the full range of the potential for influenza viruses to produce pandemics of various infectiousness (roughly measured by R), and degrees of severity (roughly measured by the risk of hospitalisation and death), reinforces the call for revised pandemic planning to accommodate plans that are calibrated on both spread and severity.[35]

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The Spread of Influenza A(H1N1)pdm09 in Victorian School Children in 2009: Implications for Revised Pandemic Planning

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Abstract

Background: Victoria was the first state in Australia to experience community transmission of influenza A(H1N1)pdm09. We undertook a descriptive epidemiological analysis of the first 1,000 notified cases to describe the epidemic associated with school children and explore implications for school closure and antiviral distribution policy in revised pandemic plans.

Methods: Records of the first 1,000 laboratory-confirmed cases of influenza A(H1N1)pdm09 notified to the Victorian Government Department of Health between 20 May and 5 June 2009 were extracted from the state's notifiable infectious diseases database. Descriptive analyses were conducted on case demographics, symptoms, case treatment, prophylaxis of contacts and distribution of cases in schools.

Results: Two-thirds of the first 1,000 cases were school-aged (5–17 years) with cases in 203 schools, particularly along the north and western peripheries of the metropolitan area. Cases in one school accounted for nearly 8% of all cases but the school was not closed until nine days after symptom onset of the first identified case. Amongst all cases, cough (85%) was the most commonly reported symptom followed by fever (68%) although this was significantly higher in primary school children (76%). The risk of hospitalisation was 2%. The median time between illness onset and notification of laboratory confirmation was four days, with only 10% of cases notified within two days of onset and thus eligible for oseltamivir treatment. Nearly 6,000 contacts were followed up for prophylaxis.

Conclusions: With a generally mild clinical course and widespread transmission before its detection, limited and short-term school closures appeared to have minimal impact on influenza A(H1N1)pdm09 transmission. Antiviral treatment could rarely be delivered to cases within 48 hours of symptom onset. These scenarios and lessons learned from them need to be incorporated into revisions of pandemic plans.

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Introduction

Influenza A(H1N1)pdm09 was identified in Mexico and the United States (US) in April 2009 [1]. It spread rapidly around the globe and by 12 May cases had been reported in 30 countries, including Australia's first case in the state of Queensland on 9 May [2,3]. The second Australian case was reported in Victoria eleven days later [4], after which notifications of confirmed cases in Victoria accelerated much more rapidly than in other states and territories [5]. The vast majority of these cases occurred in metropolitan area of the state capital Melbourne. By early June there were over 1,000 cases in Victoria [6], more than all the other Australian states combined. This lead to Melbourne being referred to in some popular media outlets as the "swine flu capital of the world" [7].

Australia's response to influenza A(H1N1)pdm09 was undertaken in accordance with the phases described in the Australian Health Management Plan for Pandemic Influenza (AHMPPI) [8], which was shifted from *Delay* to *Contain* on 22 May in response to evidence of local transmission in Victoria [3]. During the *Delay* and *Contain* phases testing was recommended for all suspected cases in the community. As the number of notified cases in Victoria increased, investigation of all suspected cases became unsustainable and Victoria announced its move to a *Modified Sustain* phase on 3 June; other jurisdictions remained in *Contain* [4]. Following an announcement by the Australian Government on 17 June, all

Australian jurisdictions subsequently moved to a new *Protect* phase [3], with Victoria implementing this phase on 23 June. Testing during *Modified Sustain* and *Protect* was generally focussed on those most at risk of moderate to severe illness (including those with certain chronic medical conditions or obesity, Indigenous Australians, pregnant women, young children and infants and health care workers) and those presenting with moderate to severe disease [3,4].

School closure and distribution of antiviral medication are important components of the recommended response to pandemic influenza and both strategies were implemented in Victoria [9]. We reviewed the epidemiological data of the first 1,000 notified cases of confirmed influenza A(H1N1)pdm09 in Victoria to gain further insights into viral transmission among school children and the implications of this transmission on administration of oseltamivir for treatment and prophylaxis and for school closures. Insights from this study can inform revised pandemic plans.

Methods

Laboratory confirmed influenza is a scheduled Group B notifiable disease under the Victorian Health (Infectious Diseases) Regulations 2001. Medical practitioners and pathology services are required to notify cases, including prescribed demographic, illness and outcome fields, to the Victorian Government Department of Health (the department) in writing within five days of diagnosis.

All confirmed influenza A(H1N1)pdm09 cases notified during the *Delay* and *Contain* phases were investigated and demographic and illness data were collected. Data on school attended were also collected for cases aged from five to 17 years inclusive. Attempts were made to identify all close contacts of confirmed cases – defined as within one metre of the confirmed case (while infectious) for more than 15 minutes or in the same room as a confirmed case for more than four hours – for provision of prophylaxis and/or quarantine advice as indicated.

During the *Delay* and *Contain* phases, testing for influenza A(H1N1)pdm09 at the state reference laboratory was authorised by the department for all suspected cases, defined as a person with fever and recent onset of at least one of rhinorrhoea, nasal congestion, sore throat or cough. A case was confirmed if influenza A(H1N1)pdm09 was detected by polymerase chain reaction.

All case data were entered into the department's Notifiable Infectious Diseases Surveillance (NIDS) database. Records of the first 1,000 notified cases of confirmed influenza A(H1N1)pdm09 cases were extracted from the NIDS database and analysed descriptively with Microsoft Excel software. Using Stata (Version 10.0) statistical software, the χ^2 and Fisher's exact tests were used to compare proportions, and the Mann-Whitney U test to compare time between diagnostic events and the number of contacts per case. A p value of less than 0.05 was considered significant. Mapping was undertaken with ArcGIS software.

Ethics Statement

Approval from the Victorian Government Department of Health Human Research Ethics Committee was not required for this study because data were collected as part of regulated notifiable disease surveillance. Influenza (laboratory confirmed) is a scheduled notifiable disease in Victoria and notification of all cases and prescribed data fields to the Department of Health is mandatory under the Health (Infectious Diseases) Regulations 2001. Written consent from patients is not required for notification of a notifiable infectious disease. Data in the study were used and reported within the requirements of the Victorian Health Records Act 2001.

Results

The initial detection of influenza A(H1N1)pdm09 in Victoria has been described in detail elsewhere [10,11]. Briefly, the first case was confirmed on 20 May and increased to a peak of more than 250 cases on 2 June; the 1,000th case was confirmed on 5 June. Only eight (0.8%) of the first 1,000 notified cases had a reported history of travel to an area affected by influenza A(H1N1)pdm09. Ages of cases ranged from five months to 79 years with a median of 15 years. The modal five-year age groups were 10–14 and 15–19 years (figure 1).

Unspecified symptoms were reported for 14 cases and "flu-like symptoms" reported for 25 cases. An illness onset date was nominated for 389 cases but no symptoms were reported. Data about specific symptoms were available for 520 cases (52%) and are shown in table 1. Cough was the most commonly reported symptom (85% of cases) followed by fever (68%), runny nose (66%) and sore throat (62%). There was no statistically significant difference in the percentage of cases with reported symptoms when stratified by age groups of less than school age (<5 years), primary school age (5–11 years), secondary school age (12–17 years) and adults (≥18 years). However, when comparing primary and secondary school-aged children, a significantly higher percentage of primary school children reported fever (76% to 64%; $p = 0.02$).

Twenty-two cases (2%) were reported to have been hospitalised; eight (1%) of the 707 cases in children (aged less than 18 years) were hospitalised. No deaths were reported. Among the hospitalised children, six (75%) had reported risk factors including asthma (two cases) and one case each with diabetes, pulmonary disease, hypertension and muscular dystrophy.

Epidemiology in Schools

Children of school age (5–17 years) accounted for 668 of the first 1,000 confirmed cases, for whom data on primary or secondary school attended were available for 599 (90%). Data were also available for three students aged 18 years and six teachers, representing 203 schools. Among the remaining 69 school-aged children, school attended was unknown for 63, two were in higher education institutions, two had not started school, one was not at school and the other was an overseas visitor.

One school accounted for 77 confirmed cases and six schools (3%) had between 10 and 25 cases. The remaining schools had less than ten notified cases each, of which most (145 schools, 74%) had two or fewer cases. The school with the largest number of confirmed cases was a selective school with no geographic enrolment restrictions, and the 77 cases' residences represented 26 of Melbourne's 30 metropolitan local government areas.

In general, cases appeared first in schools along the northern corridor of the metropolitan area and then became established in outer northern and western suburbs at the same time as a cluster in the inner eastern suburbs (figure 2). Relatively few schools in the eastern suburbs were affected until 3 June. The lower number of cases in the final panel reflects the delay between disease onset and notification, and end of the detailed follow-up of the first 1,000 cases.

An epidemic curve by age group for the school with 77 cases ("School A") showed a predominance of cases in 14–15 year-olds in the first half of the 11-day period with an increasing proportion of 16–17 year-olds in the second half (figure 3). School A was closed for the week commencing 1 June, nine days after symptom onset in the first case.

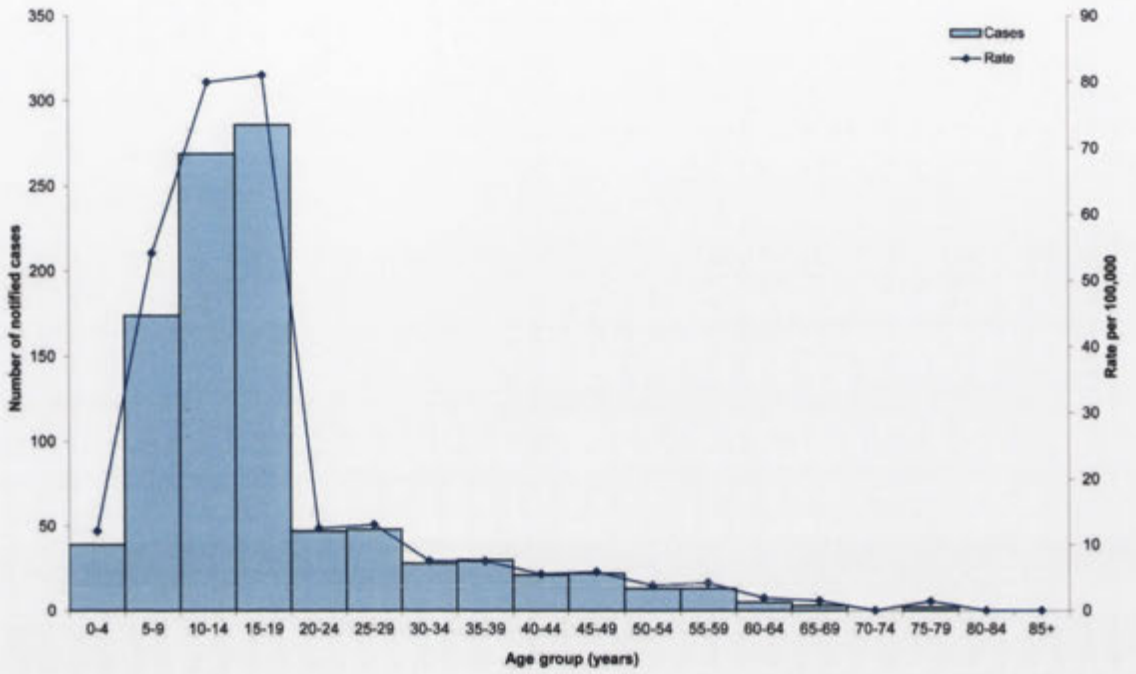

Figure 1. Confirmed influenza A(H1N1)pdm09 cases and rate per 100,000 population by age group, Victoria, 2009.
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The median time between illness onset and notification of laboratory confirmation among school children was four days (interquartile range [IQR]: 3–6) (figure 4). The median time from illness onset to medical practitioner presentation and specimen collection was two days (IQR: 1–3), as was specimen collection to confirmatory laboratory result, following which the Department of Health was notified within 12 hours.

Treatment and Prophylaxis

Treatment data were available for 897 cases (90%) of whom 206 (23%) were prescribed treatment doses of oseltamivir. The proportion of the 691 cases (77%) who did not receive oseltamivir, was significantly higher among school-aged children (80%) compared to adults (73%) and those less than school age (62%) ($p = 0.009$). Most cases (666/691, 96%) who did not receive oseltamivir were not eligible because more than 48 hours had elapsed since symptom onset. For the remaining 25 cases, the reason was not stated for 14, five were pregnant, alternate treatments were prescribed for four, one declined treatment, it was contraindicated in another and one was unable to source oseltamivir.

Of the 666 cases ineligible for oseltamivir treatment because more than 48 hours had elapsed since symptom onset, 253 (38%) had a specimen collected within one day of symptom onset.

Table 1. Reported symptoms for 520 of first 1,000 confirmed influenza A(H1N1)pdm09 cases with data by age group and order of case notification, Victoria, 2009.

	Age group (years)					Order of case notification			
Symptom	**<5**	**5–11**	**12–17**	**≥18**	**p value**	**First 100**	**Next 900**	**p value**	**Total (%)**
Cough	16 (76)	106 (85)	178 (86)	143 (86)	0.68	58 (78)	385 (86)	0.08	443 (85)
Fever	13 (62)	95 (76)	133 (64)	111 (67)	0.13	49 (66)	303 (68)	0.77	352 (68)
Runny nose	16 (76)	82 (66)	143 (69)	103 (62)	0.42	40 (54)	304 (68)	0.02	344 (66)
Sore throat	9 (43)	72 (58)	140 (67)	99 (60)	0.07	35 (47)	285 (64)	0.007	320 (62)
Fatigue	5 (24)	45 (36)	62 (30)	62 (37)	0.31	10 (14)	164 (37)	<0.001	174 (33)
Vomiting	3 (14)	17 (14)	20 (10)	16 (10)	0.61	4 (5)	52 (12)	0.15	56 (11)
Diarrhoea	1 (5)	13 (10)	13 (6)	14 (8)	0.53	0	41 (9)	0.002	41 (8)
Total with symptoms reported	**21**	**125**	**208**	**166**		**74**	**446**		**520**

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Figure 2. Confirmed influenza A(H1N1)pdm09 cases aged 5–17 years by school and date of onset, Victoria, 2009.
doi:10.1371/journal.pone.0057265.g002

Laboratory confirmation was made within one day of specimen collection for 182 (27%) cases and within two days for 417 (63%). Only 69 (10%) of the 666 cases were notified within two days of onset.

Follow-up of cases identified 5,825 eligible contacts to whom oseltamivir prophylaxis doses were distributed. Contacts were not identified for 71 (7%) cases. The number of contacts per case was significantly higher for school-aged children (median = 4, IQR: 3–7) compared to adults (median = 4, IQR: 2–6) ($p<0.0001$).

Comparison between the First 100 and Next 900 Cases

Due to the increasing workload associated with the rapid rise in notifications, follow-up of cases was by necessity less complete as the epidemic evolved. We therefore compared the first 100 cases to the following 900 to determine if the different approach to follow-up resulted in any substantial differences in outcome.

Symptoms were reported for 74% of the first 100 cases compared to 50% of the following 900 ($p<0.001$). However, with the exception of fever which was similar for both groups, specific symptoms were reported for a lower proportion of the first 100 cases (table 1). A non-significantly lower proportion of the next 900 cases were hospitalised (2.1% versus 3.0%) ($p = 0.57$). No difference between the two groups was observed for the time from onset to specimen collection ($p = 0.91$) but it took longer for the group of 900 cases to be diagnosed following specimen collection (median = 2 days, IQR: 1–3 versus median = 1 day, IQR: 1–2) ($p<0.0001$). A significantly higher number of contacts for the first 100 cases (median = 10, IQR: 6–21) were followed up compared to the following 900 (median = 4, IQR: 3–6) ($p<0.0001$). The median number of contacts per school-aged child was 12 (IQR: 7–31) and nine (IQR: 6–12) for adults who comprised the first 100 cases, but was four (IQR: 3–6) for school-aged children and three (IQR: 2–5) for adults in the group of 900 cases.

Discussion

Comprising two-thirds of the first 1,000 notified cases, this study is consistent with a review of serological studies that estimated a higher cumulative incidence of influenza A(H1N1)pdm09 infection (prior to the initiation of population-based vaccination against the pandemic strain) in school-aged children of 24–43% compared to pre-school-aged children (16–28%), young adults (12–15%) and older adults (2–3%) [12]. Further evidence of the pivotal role of school-aged children in the spread of influenza A(H1N1)pdm09 was demonstrated in this study by transmission within and from School A, which alone accounted for 8% of the first 1,000 notified cases. The school drew its student population from across the Melbourne metropolitan area, enabling wide geographic dissemination of cases. Rapid transmission had occurred through all the school's year levels before cases were recognised and student interactions restricted by school closure.

Transmission was also likely facilitated by the generally mild clinical presentation, as evidenced by 32% of notified cases

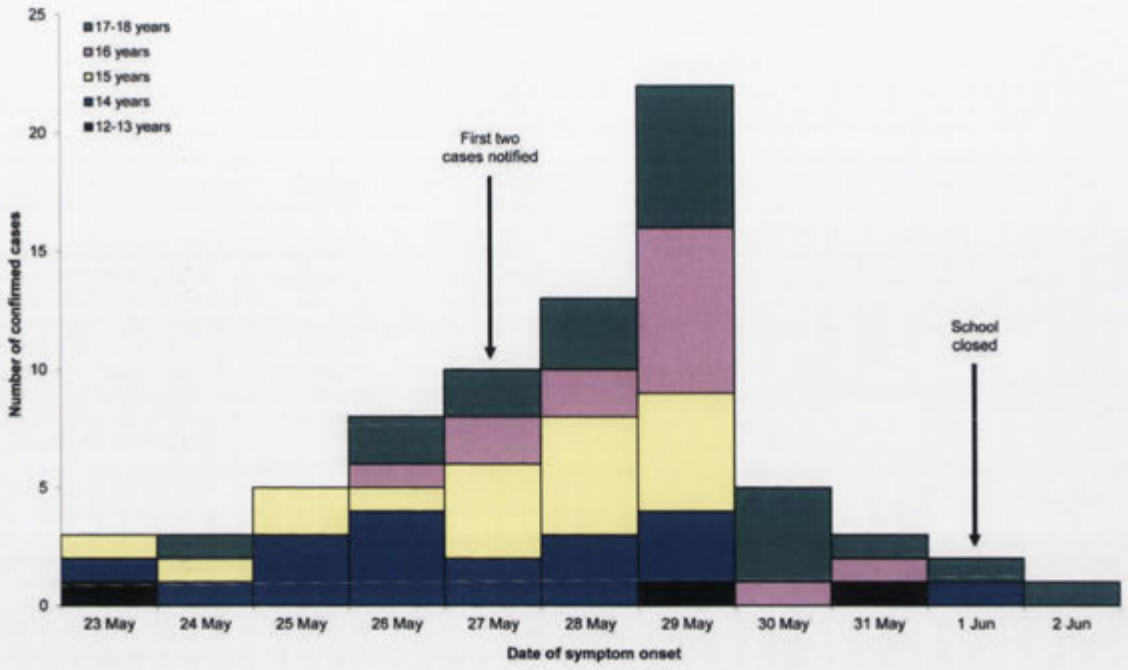

Figure 3. Confirmed influenza A(H1N1)pdm09 cases at School A by date of onset and age group, Victoria, 2009.
doi:10.1371/journal.pone.0057265.g003

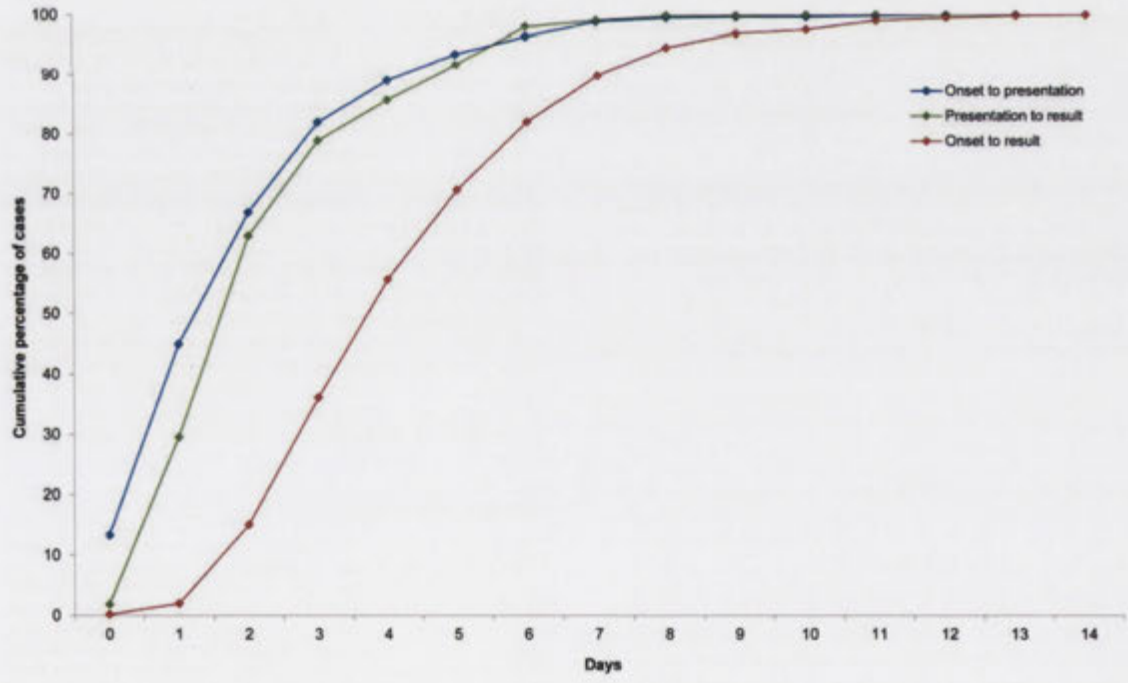

Figure 4. Confirmed influenza A(H1N1)pdm09 cases aged 5–17 years by days from onset to specimen collection and test result, Victoria, 2009.
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without a reported fever and only 2% being hospitalised, consistent with findings from elsewhere around the globe [13,14]. Detection of the local epidemic was probably further delayed by the initial case definition criterion for testing of recent overseas travel. Thus, many – presumably infectious – cases were probably not tested, or even saw a clinician, for their illnesses. This hypothesis is supported by modelling which suggested community transmission of the pandemic virus was most likely established in Victoria by late April and was certainly established by the time of its detection [15]. Although the case definition for departmentally authorised testing of suspected influenza A(H1N1)pdm09 cases required a fever, nearly one third of the cases were sampled for influenza testing without a fever. The reason for this is unclear, but given these cases had at least one other reported symptom suggests that other clinical criteria for testing were being recognised by clinicians.

School closure is a commonly suggested mitigation measure for influenza pandemics and the pandemic plans of Australia and Victoria provided for this contingency [8,16]. Closure of schools to control influenza epidemics and pandemics has been used to varying effect, with timing of the closure(s) – as well as trigger, extent and length – of crucial importance for the intervention's effectiveness [17]. Modelling using US [18,19] and Australian [20,21] populations has suggested school closure can be effective at reducing the final attack rate (cumulative incidence) of influenza but the magnitude of the reduction is highly variable. This variation is likely due to assumptions about differential attack rates in adults and children, the extent of mixing and contact outside school, and the number of symptomatic cases before closure is implemented [21].

In general though, school closure is modelled to be most effective if schools are closed early and remain closed until prevalence returns to low levels and children and teenagers stay at home during closure. There is evidence that closure of kindergartens and schools in Hong Kong for up to one month prior to the commencement of the 2009 summer vacation was effective in the mitigation of influenza A(H1N1)pdm09, with an estimated 70% reduction in intra-age transmission concurrent with school closures [22]. Furthermore, a study in two communities in Dallas/Fort Worth, Texas indicated that reported rates of respiratory illness were lower in a community which closed its schools for eight consecutive days compared to another community in which no schools were closed [23]. However, closure was implemented early when influenza activity was low.

The approach to school closure in Victoria applied to specific schools and classrooms in which two or more confirmed cases had been identified, for the duration of one week. With the exception of isolation for confirmed cases there were no restrictions of student movements. Our study has confirmed the need for a pre-emptive decision on school closure as indicated by theory and practice; in Victoria too few schools were closed too late and for too short a period to have had any discernible impact on the impact of influenza A(H1N1)pdm09 transmission. Specifically in School A the delay between disease onset and notification meant transmission in the school was already well established before the need to close it was identified.

The rapid emergence of affected schools and modelling that estimated establishment of community transmission in Victoria around late April [11,15] suggested influenza A(H1N1)pdm09 prevalence was high by the time it was detected, and probably too late for widespread school closure to be effective. Whilst pre-emptive, widespread and extended school closure is anticipated to effectively interrupt the transmission of pandemic influenza, it raises concerns about expected compliance with social restrictions, workforce shortages and economic impacts. A study of Victorian households affected by school and classroom closures found 90% of households understood what they were meant to do in the quarantine period [24] and 85% complied with the requirement to stay at home [25]. However, these households were only affected by closures of up to one week and this contrasts with a study among families in Western Australia, which found that school closures caused considerable disruption for families in arranging childcare and poor compliance among those placed in home quarantine [26].

Whilst more than 6,000 treatment and prophylactic doses of oseltamivir associated with the first 1,000 notified cases were distributed to cases and contacts, antiviral treatment could rarely be delivered to cases or their close contacts within 48 hours of symptom onset. It is likely that much of this distribution inefficiency was a consequence of its centralised nature and delays associated with notification. However this centralised system during the *Contain* phase was considered necessary as access to oseltamivir from the National Medical Stockpile was conditional on laboratory confirmation of cases.

Several limitations were associated with the methods of case identification and data collection in this study. The presence of symptoms as a criterion for testing meant that those with subclinical infections were not represented, and although only 52% of first 1,000 cases had recorded symptoms, that a further 39% of cases had a reported illness onset date suggests that most of remainder were missing data. Data quality and the capacity of case investigation officers to follow up cases completely and undertake contact tracing is likely to have progressively diminished as the number of notified cases increased. This suggestion is supported by the difference in reported symptoms and higher median number of contacts followed up per case for the first 100 notified cases compared to the following 900 cases.

Many countries are now reflecting on their 2009 pandemic experiences and responses to review and revise their pandemic plans. Influenza A(H1N1)pdm09 had a generally mild clinical course resulting in apparent widespread dissemination in Victorian school children prior to its detection, meaning that school closure, particularly short-term and isolated closures, were of little or no benefit as a mitigation measure. Pandemic plans need to be refined and flexible to incorporate such scenarios. Indeed, depending on the perceived pandemic severity, it may be better to keep schools open and waive the requirement for laboratory confirmation earlier and to treat clinically compatible children cases, or recommend nothing more than standard respiratory precautions for those exhibiting symptoms. Furthermore, in the wake of this experience consideration should be given to a decentralised, or direct clinician access to the Australia's National Medical Stockpile, model of antiviral distribution during the early phases of a pandemic. Certainly it is important to include the ramifications of observations from this study in revised pandemic plans.

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Author Contributions

Conceived and designed the experiments: JEF IB HAK MEH. Performed the experiments: JEF NH JM RM RAL. Analyzed the data: JEF IB NH JM ESM. Wrote the paper: JEF HAK.

Chapter 5

Role of severity in pandemic spread

About this chapter

This chapter investigates the relative importance of different levels of disease severity in transmission of the first influenza A(H1N1)pdm09 pandemic wave in Australia. This question was approached in two studies, the first of which was a systematic review of the literature to characterise the duration of shedding of influenza A(H1N1)pdm09 virus and identify any effects of severity of illness, age, receipt of antiviral treatment and the type of laboratory test used. The second study used the results of the review of viral shedding duration, as a proxy for duration of infectiousness, to help parameterise a deterministic mathematical model comprising four levels of influenza A(H1N1)pdm09 virus infection severity: asymptomatic; low-level symptoms; moderate symptoms; and hospitalisation required.

The systematic review, published in *Influenza and Other Respiratory Viruses*, found that duration of viral shedding generally increased with severity of clinical presentation and was shorter when antiviral treatment was administered within 48 hours of illness onset. There was no evidence of longer shedding duration of influenza in children compared with adults. In accordance with the copyright requirements of the journal publisher, the accepted version of this article – rather than a scan of the published version – is presented in this chapter. With effective reproduction numbers greater than one, the modelling study showed that those with low-level symptoms and asymptomatic infections were responsible for most influenza A(H1N1)pdm09 virus transmission in the first pandemic wave. The manuscript of the modelling study presented in this chapter had not been submitted to a journal at the time of thesis submission.

Papers in this chapter

1. **Fielding JE**, Kelly HA, Mercer GN, Glass K. Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity but not age. *Influenza Other Respir Viruses* 2013: 8; 142-150.
2. **Fielding JE**, Glass K, Kelly HA, Mercer GN. Transmission of the first influenza A(H1N1)pdm09 pandemic wave in Australia was driven by undetected infections: pandemic response implications.

Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity, but not age

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Keywords

Adult; antiviral agents; child; influenza A virus, H1N1 subtype; influenza, human; virus shedding.

Abstract

Duration of viral shedding following infection is an important determinant of disease transmission, informing both control policies and disease modelling. We undertook a systematic literature review of the duration of influenza A(H1N1)pdm09 virus shedding to examine the effects of age, severity of illness and receipt of antiviral treatment. Studies were identified by searching the PubMed database using the keywords 'H1N1', 'pandemic', 'pandemics', 'shed' and 'shedding'. Any study of humans with an outcome measure of viral shedding was eligible for inclusion in the review. Comparisons by age, degree of severity and antiviral treatment were made with forest plots. The search returned 214 articles of which 22 were eligible for the review. Significant statistical heterogeneity between studies precluded meta-analysis. The mean duration of viral shedding generally increased with severity of clinical presentation, but we found no evidence of longer shedding duration of influenza A(H1N1)pdm09 among children compared with adults. Shorter viral shedding duration was observed when oseltamivir treatment was administered within 48 hours of illness onset. Considerable differences in the design and analysis of viral shedding studies limit their comparison and highlight the need for a standardised approach. These insights have implications not only for pandemic planning, but also for informing responses and study of seasonal influenza now that the A(H1N1)pdm09 virus has become established as the seasonal H1N1 influenza virus.

Introduction

Prior to 2009, pandemic plans assumed that all influenza pandemics arise from the emergence of a different antigenic subtype, as was observed for the three pandemics of the 20th Century.[1-3] However, the influenza A(H1N1)pdm09 strain responsible for the 2009 pandemic arose from a sequence of reassortment events rather than antigenic shift and had a generally mild course of illness with lower than expected mortality.[4,5] Nevertheless, its high transmissibility – particularly in younger age groups – and rapid global spread compared with pre-2009 seasonal influenza necessitated a pandemic response, and research studies were rapidly undertaken in various settings and populations around the globe to further characterise the clinical, virological and epidemiological features of infection.

The World Health Organization (WHO) recommends countries incorporate non-pharmaceutical interventions (such as isolation of patients and quarantine of contacts, social distancing and travel restrictions) and use of antivirals for treatment and prophylaxis into their pandemic plans to reduce transmission of pandemic influenza virus within populations.[6,7] Along with understanding how and when a pandemic influenza virus is transmitted, the duration of infectiousness is a critical parameter in determining the most effective application of these mitigation measures.

The detection of virus from clinical specimens is generally equated to influenza infectiousness, with the duration dependent on several factors including age, clinical illness, treatment with antiviral agents and virus detection method.[8,9] We undertook a systematic review of published literature to characterise the duration of shedding of influenza A(H1N1)pdm09 virus and identify any effects of severity of illness, age, receipt of antiviral treatment and the type of laboratory test used.

Methods

Search strategy and selection criteria

A literature search of the PubMed database, filtered for publication dates from 2009 onwards, was undertaken on 15 March 2013 using the keywords: H1N1[All Fields] and shedding[All Fields]; 'pandemics'[MeSH Terms] or 'pandemics'[All Fields] or 'pandemic'[All Fields]) and shedding[All Fields]; shed H1N1[All Fields]

and shed[All Fields]; ('pandemics'[MeSH Terms] or 'pandemics'[All Fields] or 'pandemic'[All Fields]) and shed[All Fields]. Any study of humans with an outcome measure of viral shedding using any test method was eligible for inclusion in the review.

Titles and abstracts of articles returned from the searches were reviewed and were excluded from further evaluation if they: did not comprise human subjects; did not measure virus shedding; measured shedding of non-pandemic/seasonal influenza, live attenuated vaccine or oseltamivir-resistant virus only; were restricted to specialised or high-risk populations (such as patients with HIV, cancer, who were transplant recipients or otherwise immunocompromised); had five or fewer participants; or were not written in English. Shortlisted articles were then evaluated in more detail, and their reference lists searched to identify additional potentially relevant articles.

During the detailed evaluation process, studies were excluded if there were not at least three specimen collection attempts from each participant (unless a negative result or loss to follow up) in the 7 days from presentation; viral shedding was reported as mean or median virus titre, viral load or reverse-transcription polymerase chain reaction (RT-PCR) cycle threshold; or shedding duration was not reported or could not be calculated for each patient as from the day of symptom(s) onset to day of collection of the last specimen in which virus was detected. Where possible, we adjusted the data in papers that used a different definition of viral shedding duration: one day was added to the duration of viral shedding if the definition was not inclusive of the day of symptom(s) onset (e.g. defined as 'days since' or 'days after' onset); one day was subtracted from the duration of viral shedding if the definition was reported to be the day that the first negative specimen was collected and specimens were collected daily, otherwise the study was excluded from analysis.

Two investigators (JEF and KG) read all the articles shortlisted from the search, applied the exclusion criteria and extracted the data separately. Differences were resolved by discussion and consensus.

Data abstraction

For each paper, we collected information on the number and age group (child or adult as defined in the manuscript, or <15 years/≥15 years respectively if not explicitly stated) of study participants, respiratory specimen sampling method and frequency, the type(s) of test used to detect influenza virus or viral RNA, the defined interval for viral shedding duration and endpoint of patient follow-up, the clinical severity (classified by the study setting: community, hospital or intensive care), antiviral treatment for study participants and – where given – those who were treated in a timely manner (generally considered to be within 48 hours of symptom(s) onset). Unless otherwise described, severity was classified as community-based illness if study participants were part of studies undertaken during the containment phase of the pandemic when many countries required isolation of patients (usually in hospitals) despite the presence of only mild illness.

We defined viral shedding duration as the number of days from day of symptom(s) onset to the day of collection of the last specimen in which influenza A(H1N1)pdm09 was detected, inclusive. Pre-symptomatic shedding and asymptomatic shedding in two studies were described separately. Summary measures of viral shedding duration (minimum, maximum, median, mean and 95% confidence interval) for each study were derived from patient record-level data, values reported in the body text, tables or survival curves. Data on the proportions of total study participants shedding virus by day of illness were extracted from tables or survival/Kaplan–Meier curves in 14 of the 22 reviewed studies. Summary measures and the proportion of participants shedding virus by day of illness were also extracted and/or calculated for the clinical severity, age group and antiviral treatment strata if the data were appropriately reported and there were six or more cases in the stratum.

Data analysis

Meta-analyses using a random-effects model were conducted in Stata, version 10.1 (StataCorp LP, College Station, Texas, USA). Heterogeneity between studies was assessed by the I^2 test, and summary estimates calculated if $I^2 < 80\%$ and $P > 0.1$. To compare findings between studies, summary measures of viral shedding

duration are presented in forest plots and the proportion of patients shedding virus by day of illness in survival curves. In instances where all summary measures were not reported or able to calculated from the reported data within the paper, or the definition of viral shedding duration was not given or ambiguous, the corresponding author was contacted to provide them.

Results

A total of 214 citations were returned from the search, of which 167 were excluded following title and abstract review. Searching of article reference lists identified an additional four papers, resulting in 51 papers being evaluated in detail. A further 29 studies were excluded, mainly because of differences in the method by which virus shedding and shedding duration were measured (Table 1). A total of 22 studies were included in the review, with the number of participants in each ranging from 15 to 421. All included studies were observational in nature, with considerable heterogeneity of specimen collection method and frequency (Table 2). All studies measured viral shedding by PCR; six also measured shedding by culture. The corresponding authors of 19 studies were contacted for supplementary summary data or clarification of methodology, with responses received from nine (47%).

The mean and standard deviation of duration of viral shedding duration were available for 18 (82%) of the 22 included studies. Meta-analyses were conducted on studies grouped by the study settings of community-based cases (13 studies), hospitalised cases (three studies) and ICU cases (two studies), for which statistical heterogeneity as indicated by I^2 values was 97% ($P < 0.001$), 45% ($P = 0.165$) and 86% ($P = 0.008$), respectively. Given the significant heterogeneity in most groups, the combined estimates of viral shedding duration are not reported.

Table 1. Identified studies and reasons for exclusion.

Criteria	Number of studies
Identified from search	214
Excluded after title and abstract review	167
Did not comprise human subjects	81
Did not measure virus shedding	30
Non-pandemic, vaccine or oseltamivir-resistant virus shedding	26
Restricted to specialised or high-risk populations	20
Five or fewer participants	2
Not written in English	7
Unable to be retrieved	1
Additional inclusions after search of shortlisted articles	4
Excluded after detailed evaluation	29
Shedding reported as mean virus titre/load or RT-PCR cycle threshold	10
Unable to determine patient shedding duration as onset to last positive	13
<3 specimens per patient collected and/or <7 days of follow-up	3
Study data were a subset of another included study	3
Included in the review	22

Table 2. Participant profiles and methodologies of studies included in the review.

Study	Participants	Age groups	Clinical presentation	Treatment	Specimen type*	Sampling frequency	Test method
Beutel *et al.*[10]	25	Adults	Hospitalised (intensive care)	Oseltamivir (96%)	NPS	Twice weekly	PCR
Bhattarai *et al.*[11]	26	Children & adults	Community	Oseltamivir (12%)	NPS	Every 48 hours until 2 negative or indeterminate and negative results	PCR & culture
Cao *et al.*[12]	421	Children & adults	Community	Oseltamivir (82%)	PS or NPS	Daily until 2 consecutive negative results	PCR
Chin *et al.*[13]	15	Adults	Hospitalised	Oseltamivir (100%)	OPS	Every 2 days until 2 consecutive negative results	PCR
Cowling *et al.*[14]	45	Children & adults	Community	Strata: oseltamivir & no treatment	NTS	Three times over 7 days	PCR & culture
Duan *et al.*[15]	122	Adults	Community (quarantine & hospital observation)	Oseltamivir (100%)	PS or NPS	Daily for 7 days	PCR
Esposito *et al.*[16]	74	Children	Hospitalised	None treated	NPS	On day 3 post-onset and every day until 2 negative results	PCR
Hien *et al.*[17]	292	Children & adults	Community (hospital observation)	Oseltamivir (100%)	NTS	Either daily, days 1 and 5 after admission or days 1, 3 and 5 after admission	PCR
Jia *et al.*[18]	67	Adults	Community (hospital outpatients)	Chinese traditional medicine (no antivirals)	NPS	Daily for 14 days	PCR
Kay *et al.*[19]	16	Adults	Community	Oseltamivir (100%)	Nasal wash	Every Monday, Wednesday and Friday	PCR & culture
Killingley *et al.*[20]	19	Children & adults	Community & hospitalised	Strata: oseltamivir & no treatment	NS	Daily for 10 days (adults) or 14 days (children)	PCR & culture

Study	Participants	Age groups	Clinical presentation	Treatment	Specimen type*	Sampling frequency	Test method
Leung *et al.*[21]	56	Children & adults	Community (hospital observation)	Oseltamivir (96%)	NPA, NPS, NTS or TS at discretion of treating physician	At discretion of treating physician	PCR & culture
Ling *et al.*[22]	70	Adults	Community (hospital observation)	Oseltamivir (100%)	NTS	Daily until negative result	PCR
Loeb *et al.*[23]	97	Children & adults	Asymptomatic & community	Not specified	NS	Daily for 7 days then every 2 days for 3 weeks	PCR
Malato *et al.*[24]	17	Adults	Hospitalised (intensive care)	Oseltamivir (76%)	NS, broncho-alveolar lavage fluids, respiratory secretions	Not specified	PCR
Meschi *et al.*[25]	27	Adults	Hospitalised	Strata: oseltamivir & no treatment	NPS	Not specified but ≥3 per patient	PCR
Petersen *et al.*[26]	20	Adults	Hospitalised (intensive care)	Oseltamivir or zanamivir (76%)	NS or tracheal secretions	At least every 2 days	PCR
Suess *et al.*[9]	37	Children & adults	Community	Oseltamivir (35%)	Nasal wash	Daily	PCR
Suryaprasad *et al.*[27]	35	Children & adults	Community	Strata: oseltamivir & no treatment	NPS	Every 2 days until 10 days after fever cessation	PCR
To *et al.*[28]	22	Children & adults	Community (hospital observation)	Oseltamivir (95%)	NPA or NPS	Not specified	PCR
Waiboci *et al.*[29]	106	Children & adults	Community (hospital outpatients)	Oseltamivir (2%)	OP/NP specimens	Every 2 days	PCR
Xiao *et al.*[30]	156	Children & adults	Community (hospital observation)	Oseltamivir (100%)	NPS	Daily until 2 consecutive negative results	PCR

*NPS, nasopharyngeal swab; PS, pharyngeal swab; OPS, oropharyngoeal swab; NTS, nose and throat swab; NS, nasal swab; TS, throat swab; NPA, nasopharyngeal aspirate.

Severity of clinical presentation

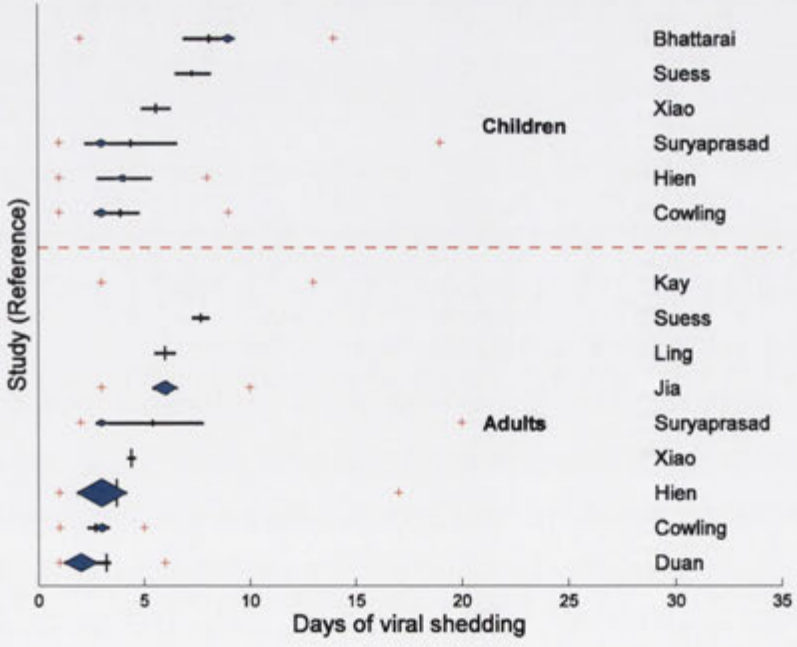
A relatively defined gradient of viral shedding duration was observed when summary measures were stratified by study setting, as a proxy for severity of clinical presentation (Figure 1). The mean duration of viral shedding was 3–9 days for community-based cases (15 studies), 7–10 days for hospitalised cases (four studies) and 13–18 days for those admitted to intensive care (three studies). The ranges of median viral shedding duration across the studies by respective settings were similar to the range of means (Figure 1). The studies involving those hospitalised and admitted to intensive care had relatively wide 95% confidence intervals, with generally smaller study sizes and a wider range of shedding duration. Shedding duration was longer for a higher proportion of hospitalised cases and longer still among cases in intensive care, with 80% or more cases still shedding virus at 18 days in two of the three studies (see survival curves in Supplementary Data). The maximum shedding duration in these studies was 28, 32 and 158 days. Between 71% and 86% of patients in the three studies of intensive care patients had one or more risk factors for severe influenza such as pregnancy, obesity, cardiovascular disease, diabetes mellitus, immunosuppressive therapy or chronic pulmonary, renal or liver disease.

Age

Given the small number of studies among hospitalised and intensive care patients, age stratification was restricted to studies of community-based cases. Summary measures of viral shedding duration were available for 15 adult or children strata from ten studies. There was little difference in the ranges of mean viral shedding duration between the adults (3–8 days) and children (4–8 days) with similar observations for the respective median values (Figure 2). Comparison of viral shedding duration measured by PCR between community-based child and adult cases was made directly in five studies; children had longer shedding duration in three of the studies, two by a mean of 1.2 days[14,30] (of which $P < 0.01$ for one of the studies)[30] and the other by 0.4 day[17] but was longer in adults in the other studies by 0.4[9] and 1.0 days.[27] An additional paper that compared shedding duration in community-based cases but measured by viral culture found a mean of 5.7 days in children compared with 3.7 days in adults ($P = 0.03$).[21]

Figure 1. Shedding duration of influenza A(H1N1)pdm09 by study and patient setting. (Legend: cross = minimum and maximum; middle of diamond = median; area of diamond = study size; vertical line = mean; horizontal line = 95% confidence interval).

Figure 2. Shedding duration of influenza A(H1N1)pdm09 in studies of community-based cases, by study and age group.



Asymptomatic shedding

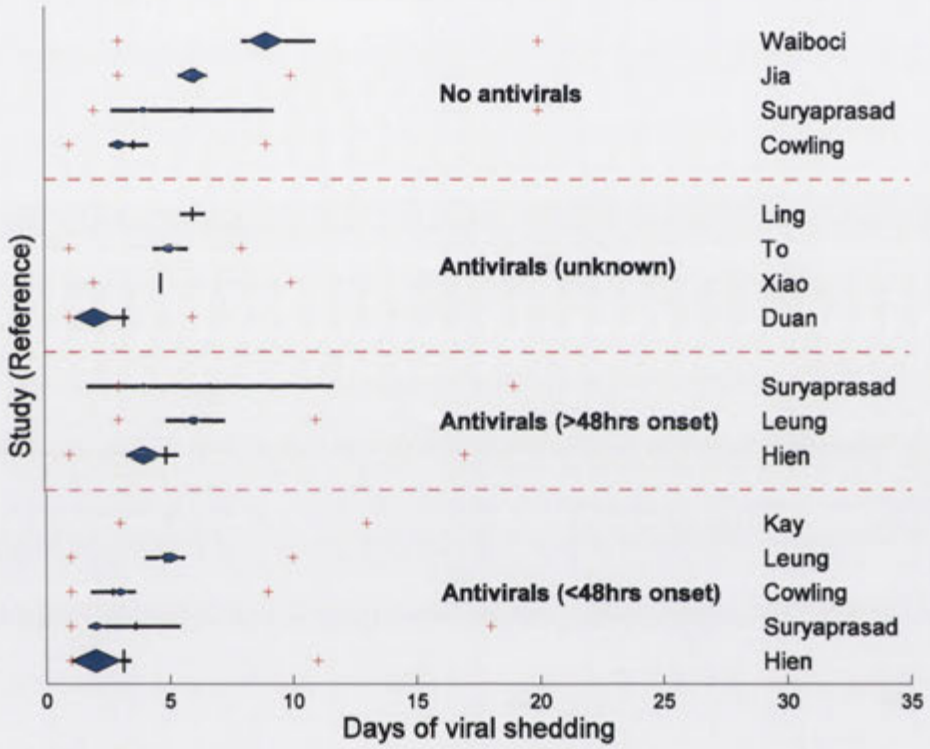
One study by Loeb *et al.*,[23] conducted over several influenza seasons among a cohort of relatively isolated communal farming communities, measured shedding duration for cases of asymptomatic influenza A(H1N1)pdm09. Of the 97 participants in the study, 12 (12%) were asymptomatic and had a mean viral shedding duration of 3.2 days (95% CI: 2.0–4.4) compared with 4.8 days (95% CI: 4.2–5.4) for all participants. Only one other study by Suess *et al.*[9] described asymptomatic cases. Surveillance of 30 laboratory-confirmed index cases identified 15 secondary cases, of which three (20%) were asymptomatic, although no data on shedding duration were available. The study by Loeb *et al.* was also the only one included in the review to systematically assess pre-symptomatic shedding and compare shedding duration of influenza A(H1N1)pdm09 with pre-2009 seasonal influenza over a 2-year study period. The study found that nine (11%) of 85 symptomatic cases shed virus in the day before acute respiratory illness onset and three (4%) up to 3 days before onset and that with a mean shedding duration of 4.8 days, influenza A(H1N1)pdm09 was comparable to seasonal H1N1 and type B influenza (5.2 and 4.9 days respectively) but longer than seasonal H1N1 (3.4 days, $P = 0.03$).[23]

Antiviral treatment

Summary measures of viral shedding duration stratified by treatment modality were available from 11 studies of community-based cases, of which four further differentiated by whether or not oseltamivir was administered within 48 hours of illness onset. The range of mean values for viral shedding duration in studies of those treated with oseltamivir within 48 hours of illness onset (3–5 days) was lower than those for which treatment was administered after 48 hours of onset (5–7 days) and for those not treated (4–9 days) (Figure 3). Similar results were observed for median values of shedding duration (Figure 3). Several studies directly compared treatment modalities. Hien *et al.*[17] observed statistically significant shorter shedding duration among those treated within 48 hours of onset compared with those treated after 48 hours; this observation was also made by Leung *et al.*,[21] but the difference was only statistically significant when shedding was measured by viral culture rather than RT-PCR. Similarly, shorter shedding

duration was found by Cowling *et al.* and Suryaprasad *et al.* in those treated within 48 hours of illness onset compared with treatment after 48 hours or no treatment, but the difference was not significant.[14,27] In contrast, a study of hospitalised cases by Meschi *et al.*[25] noted a shorter, but not statistically significant, shedding duration in untreated cases compared with those who received oseltamivir.

Figure 3. Shedding duration of influenza A(H1N1)pdm09 in studies of community-based cases, by study and antiviral treatment.



Culture versus RT-PCR

In addition to RT-PCR, five studies measured viral shedding by culture. Two studies measured viral shedding by culture for all study participants,[19,21] and for 63%[20] and 73%[11,14] of patients in the other three studies. With the exception of one study in which median values were the same and the means differed by 0.3 day,[14] the mean and median durations of viral shedding were 1.5–2 days shorter when measured by culture. The maximum shedding duration was shorter by 2–3 days in four studies[14,19-21] and 6 days in the other.[11]

Discussion

Several studies have reported that duration of pre-2009 seasonal influenza virus shedding is longer in children[31-33] and has become a widely accepted assumption in text books[34] and pandemic planning documents.[6] However, we did not demonstrate longer shedding duration of influenza A (H1N1)pdm09 among children compared with adults, either between or within studies. Three of the five studies in the review that directly compared shedding duration in adults to children observed shedding to be longer in children, whilst three other studies not included in the review – primarily because shedding was measured as virus titre or load – were also split in their findings: two studies found significantly longer shedding duration in children,[35,36] whilst no difference was found in another.[37] A further two studies reported no difference in the proportion of adults and children with prolonged viral shedding of more than 7 days.[38,39] If not related to statistical anomalies, the absence of a difference in influenza A(H1N1)pdm09 shedding duration between children and adults may in part be explained by their similar susceptibility to the then-novel pandemic strain,[40] as opposed to pre-2009 seasonal influenza in which adults have more previous exposures and greater cross-protective immunity. However, there are few papers comparing viral shedding across several years to compare shedding in the pandemic and seasonal strains to support this hypothesis; whilst one study found a significantly longer duration of pandemic virus shedding compared with H3N2,[23] another found little difference.[14]

As to be expected, progressively longer shedding duration cases of influenza A(H1N1)pdm09 infection were observed when studies were stratified into community (mean and median range: 2–9 days), hospital (6–10 days) and intensive care (13–20 days) settings. Prolonged shedding of more than 14 days was still seen for a small proportion (less than 20%) of patients in several of the community-based studies, but is not unexpected given that prolonged shedding can occur even in immunocompetent patients with non-mutated virus.[41] With 70% or more of the cases in the three studies in ICU settings reported to have one or more risk factors for severe infection, the higher median values for duration of infection (11–20 days) and an upper range of 158 days are consistent with studies

restricted to immunocompromised patients.[42-44] The observation of generally shorter viral shedding duration in studies where cases received oseltamivir treatment within 48 hours of illness onset was consistent with the literature,[45] despite relatively few strata for comparison. However, the author of one hospital-based study in which longer shedding was observed in treated patients compared with untreated patients[25] indicated by correspondence that this was probably a consequence of the treated group including patients with a more severe clinical presentation, suggesting that at least in some instances, differential inclination to treat can influence reported viral shedding duration.

The biggest challenge in extracting and compiling individual study data for this review was the variation in definitions, where provided, of the primary outcome measure of duration of viral shedding. The variability applied to the start point of shedding duration (either the day of symptom onset, first positive test or treatment initiation), the endpoint (either the day of the last positive or first negative test) and how days of shedding duration were calculated (either by counting the starting point day as one day of viral shedding, or using the days difference between the start and endpoints). The latter component of shedding duration was particularly poorly defined in many studies and in the absence of confirmation from corresponding authors needed to be assumed based on table, figure or axis titles, or descriptions in the main text. Using the day of the last positive result as the viral shedding duration endpoint is an additional limitation because it will underestimate viral shedding duration in studies where patients are not sampled every day. Kay *et al.*[19] used statistical modelling to account for the gap between last positive and first of two consecutive negatives as the endpoint of viral shedding. Loss of study participants to follow up, an inevitability particularly during the early stages of a pandemic, will also underestimate viral shedding duration. Furthermore, it cannot be assumed that patients are shedding the same quantity of virus throughout the course of their illness (as demonstrated by shedding studies measuring viral load,[14,37,46,47] most of which were outside the scope of this review) or indeed continually shed virus throughout the course of their infection. More than half of the reviewed studies attempted to avoid underestimation of viral shedding duration caused by intermittent shedding by

requiring at least two consecutive negative specimens as an endpoint of testing follow-up, which is shown schematically for several cases in three of the reviewed studies.[11,17,27] Whilst a standardised measure of viral shedding duration was able to be applied to 22 studies in this review, numerous adjustments and assumptions were needed, and a further 13 had to be excluded. The development and adoption of standard parameters, which we have proposed in Box 1, would assist in simple and rapid assessment and comparison of influenza viral shedding duration that could reliably inform mathematical modelling (for which small variations in viral shedding duration, as a proxy for the period of infectiousness, are very sensitive) and exclusion policies, particularly during the early stages of a pandemic.

Box 1. Proposed standard parameters for measurement and reporting of influenza viral shedding duration.

- Unless measuring pre-symptomatic or asymptomatic shedding, the duration of viral shedding should be defined as from the day of symptom(s) onset to the day on which the last positive specimen was collected.
- Counting of the number of days of viral shedding duration should be inclusive of (rather than the difference between) the day of symptom(s) onset and the day on which last positive specimen was collected.
- Specimen collection should continue until two consecutively collected specimens both test negative.
- Where administratively possible, specimens should be collected daily but not less than one every 2 days.
- The age threshold for classification as a child or adult should be clearly defined.
- Record the date (or day with respect to symptom onset) of the commencement of antiviral therapy, or that no antiviral therapy was administered.

Additional methodological heterogeneity between studies also limits the scope of the review findings and precluded meta-analysis. Eleven different specimen types were collected with varying frequency in the 22 studies included in the review and likely have varying sensitivities, particularly during the later stages of infection.

Supporting this are two studies that showed higher influenza A(H1N1)pdm09 viral loads[48] and sensitivity[9,49] of RT-PCR testing of nasopharyngeal aspirate and nasal wash specimens compared with nasopharyngeal and nose/throat swabs. Detection of virus by RT-PCR is a more sensitive method than viral culture, and this was shown by Cheng *et al.*[49] for influenza A(H1N1)pdm09 and reflected in the relative measures of viral shedding duration in the four studies in the review that compared the two methods. An advantage of viral culture is that it provides a measure of viable/infectious virus, whereas PCR may also detect non-viable viral RNA; however, the extent to which detection of non-viable RNA contributes to measures of viral shedding duration is unclear. Studies included in the review also differed by the age at which participants were classified as children, varying from 12 years or less to 15 years or less. However, given little difference in viral shedding duration was observed between children and adults in general, the impact of this variation in definitions is likely to be neutral. A further limitation of the review is that there was little insight into pre-symptomatic and asymptomatic shedding; only one study examined these but given its setting in isolated communal farming communities in Canada is unlikely to be representative.[23] One study that studied shedding in household contacts of index cases but was excluded from the review because viral shedding was reported as median viral load showed asymptomatic shedding in 12% and pre-symptomatic shedding up to 4 days prior to symptom onset in one (4%) of 28 secondary cases.[37]

This review has provided insights into viral shedding duration of influenza A(H1N1)pdm09 and the relative effects of age, clinical severity and oseltamivir treatment. Additional reviews examining viral loads and correlation of symptoms over time may provide further insights into the relative infectivity and transmissibility of influenza A(H1N1)pdm09 and are warranted now that influenza A(H1N1)pdm09 has become established as the seasonal H1N1 influenza virus and that there is a large body of literature examining its properties. Understanding the infectivity of emerging novel influenza strains by synthesis of the wide array of research studies could be greatly enhanced by a standardised approach to measurement of viral shedding, and such guidelines would be a useful addition to

global research planning documents such as the 'WHO Public Health Research Agenda for Influenza'.[50]

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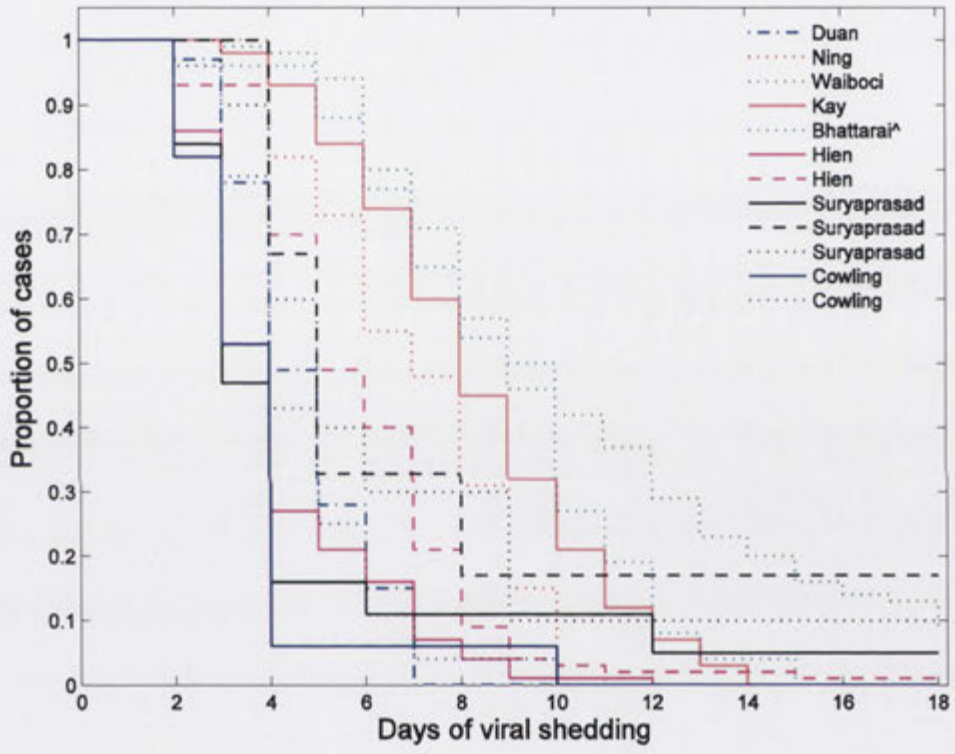
Supporting Information

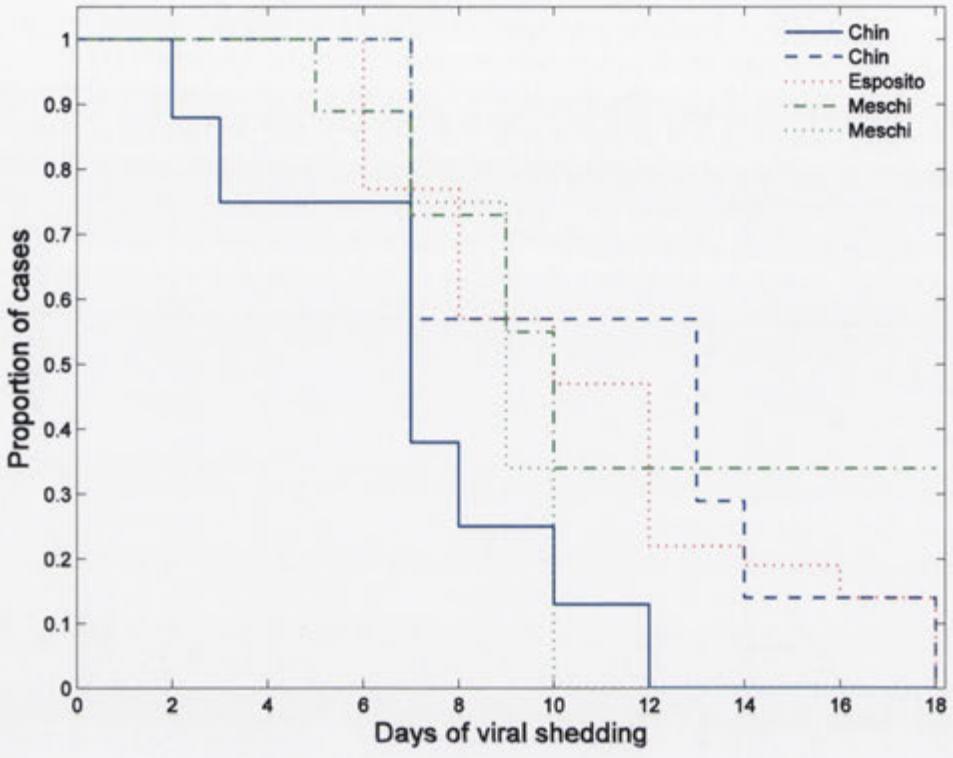
Legend for figures: solid line = treated with 48 hours of onset; dashed line = treated after 48 hours of illness onset; dashed and dotted line = treatment timing unspecified; dotted line = no treatment

Appendix Figure 1. Proportion of community setting study cases positive for influenza A(H1N1)pdm09 by day of virus shedding and oseltamivir treatment.

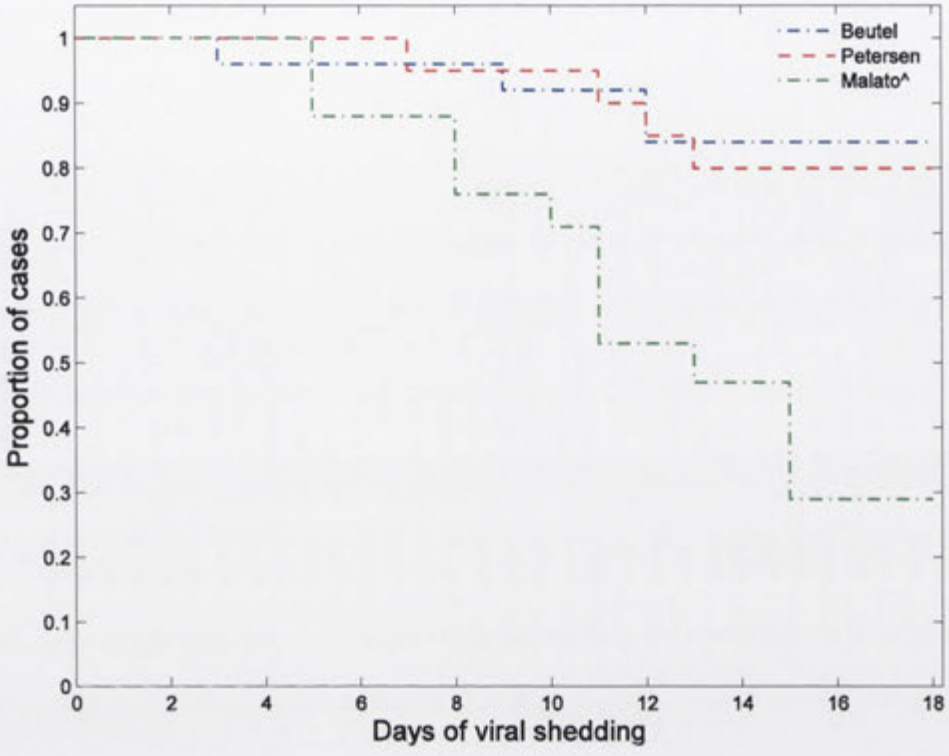


^ 12% received oseltamivir

Appendix Figure 2. Proportion of hospital setting study cases positive for influenza A(H1N1)pdm09 by day of virus shedding and oseltamivir treatment.



Appendix Figure 3. Proportion of ICU setting study cases positive for influenza A(H1N1)pdm09 by day of virus shedding and oseltamivir treatment.



Transmission of the first influenza A(H1N1)pdm09 pandemic wave in Australia was driven by undetected infections: pandemic response implications

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Keywords

Epidemiology; influenza; modelling; pandemic; transmission.

Abstract

Background

During the first wave of influenza A(H1N1)pdm09 in Victoria, Australia the rapid increase in notified cases and the high proportion with relatively mild symptoms suggested that community transmission was established before cases were identified. This lead to the hypothesis that those with low-level infections were the main drivers of the pandemic. A mathematical model was developed to estimate the relative importance of different levels of disease severity in transmission of the first pandemic wave.

Methods

A deterministic susceptible-infected-recovered model was constructed to describe the first pandemic wave in a population structured by disease severity levels of asymptomatic, low-level symptoms, moderate symptoms and severe symptoms requiring hospitalisation. The model incorporated mixing, infectivity and duration of infectiousness parameters to calculate effective reproduction numbers for each severity level.

Results

With effective reproduction numbers of 1.82 and 1.32 respectively, those with low-level symptoms, and those with asymptomatic infections were responsible for most of the transmission. The effective reproduction numbers for infections resulting in moderate symptoms and hospitalisation were less than one. The same relative effects were observed in sensitivity analyses of parameters in the model.

Conclusions

Transmission of influenza A(H1N1)pdm09 was largely driven by those essentially invisible to the health system. The delay in detection and high proportion of relatively mild infections limited the effectiveness of case-based control measures, such as school closures and antiviral distribution to cases and their contacts. Revision of pandemic plans need to incorporate milder scenarios, with a graded approach to implementation of control measures.

Introduction

Influenza A(H1N1)pdm09 was identified in the United States and Mexico in April 2009 and spread rapidly around the globe [1, 2]. In temperate countries of the northern hemisphere, the pandemic strain emerged outside of the cooler months during which seasonal influenza epidemics typically occur, resulting in a first pandemic wave of moderate magnitude followed by a larger second in-season wave [3, 4]. In contrast, both waves in temperate southern hemisphere countries occurred in-season, with a considerably lower overall cumulative incidence of symptomatic infection and impact in terms of severe illness in the second wave [5].

Although Australia's first case was reported in Queensland on 9 May, the second reported case in Victoria 11 days later was followed by a rapid increase in notified cases that was not observed in other states or territories [6, 7]. As the pandemic response progressed it became evident that despite the large number of notified cases, a high proportion had relatively mild symptoms and much lower case fatality risk compared to previous pandemics [8]. Influenza-like illness activity and proportion of influenza tests positive as measured by other surveillance systems was also moderate compared to other influenza seasons [9, 10]. Furthermore, there was a suggestion, supported by modelling, that community transmission of influenza A(H1N1)pdm09 in Victoria was well established before cases were identified [11].

These observations lead to the hypothesis that those with asymptomatic or clinically mild infections were driving the spread of the pandemic. To investigate this hypothesis, we developed a deterministic mathematical model to estimate the relative importance of different levels of disease severity in transmission of the first pandemic wave of influenza A(H1N1)pdm09 virus. We used data from observational studies to parameterise the model using the Australian population as an example.

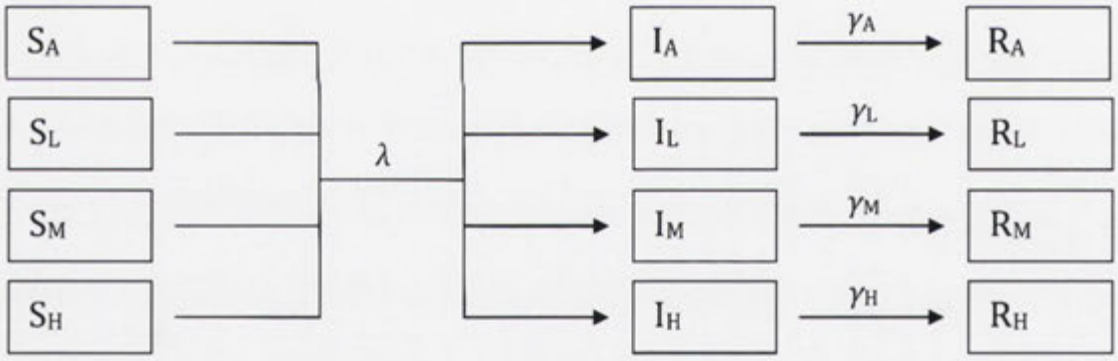
Methods

Model structure

A deterministic susceptible-infected-recovered (SIR) model was constructed to describe the first wave of influenza A(H1N1)pdm09 transmission in a population

structured by severity of infection. Four levels of infection severity were defined in the model: asymptomatic; low-level symptoms; moderate symptoms; and hospitalisation required, denoted by the subscript letters 'A', 'L', 'M' and 'H' respectively (figure 1). Based on published outcome data and detailed further below, the population was proportionally assigned to the four infection severity compartments of susceptible individuals (S). This stratification of the susceptible population assumed that susceptibility is defined before exposure by multiple determinants of infection severity, including underlying health status and immunity from prior infection and/or vaccination. The clinical course will then be determined by underlying susceptibility, the probability of exposure, the mode of virus transmission and the virus dose at exposure.

Figure 1: Basic influenza model with the four levels of infection severity asymptomatic (A), low-level symptoms (L), moderate symptoms (M) and hospitalised (H), where force of infection $\lambda = \beta_A.I_A + \beta_L.I_L.+ \beta_M.I_M + \beta_H.I_H$.



The transmission parameter β for each infection severity stratum was calculated as the product of relative proportional coefficients for infectivity (η) and mixing (μ), and a common fitting coefficient θ. However, multiple studies have found no difference between viral loads and clinical severity, ranging from asymptomatic infection to acute respiratory distress syndrome [12-19], thereby making infectivity parameters η for each infection severity category equivalent and redundant in the model. Therefore $\beta_i = \theta.\mu_i$ where i is one of A, L, M or H. The fitting coefficient was defined in terms of the overall effective reproduction number, R_e, to

ensure R_e was kept fixed at a plausible value as described below. We assumed that all infection severity groups had the same susceptibility and thus the same infection pressure acting on them. Therefore, the overall reproduction number is the sum of the reproduction numbers for each infection severity stratum i and calculated by

$$R_e = \Sigma\, p_i.(\beta_i / \gamma_i)$$

where p_i is the proportion in each severity stratum A, L, M or H, and $\beta_i = \theta.\mu_i$ and γ is described below. The equation can be rearranged to calculate θ by

$$\theta = R_e / (\Sigma\, p_i.\mu_i / \gamma_i)$$

Susceptible individuals flow to respective infected (I) compartments following exposure to a force of infection λ, where $\lambda = \Sigma\, \beta_i.I_i$ (figure 1). The branched transition from susceptible to infected compartments in figure 1 schematically represents the component parts of the force of infection, which acts on each compartment. Infected individuals transition to recovered (R) at a recovery rate γ. Given its emergence as a pandemic strain, the model assumed a population susceptible to influenza A(H1N1)pdm09 with no previous immunity from vaccination or infection, and that re-infections did not occur in the timeframe considered.

Selection of baseline parameters

Parameter descriptors, values and sources used in the model are summarised in table 1. The proportional distribution of the susceptible population among the four infection severity compartments was estimated from published observational studies of influenza A(H1N1)pdm09 infections. The reported proportion of asymptomatic infections (p_A) varied widely by study setting and population, but was estimated at 0.35 based on several household and school transmission studies [18, 20, 21]. Reported estimates of the hospitalised proportion (p_H) were universally small at around 0.0025 [22, 23]. To divide the remaining 0.6475 proportion of symptomatic infections between cases with low-level and moderate symptoms, we used data from the New South Wales Population Health Survey which collected all-age community-level influenza-like illness (ILI) data across the

state from July to September 2009 [24]. Of the survey participants reporting an ILI, an average of 76% were unable to undertake normal duties for two or more days (classified as moderate symptoms and denoted as 'q') and 24% ($1 - q$) were unable to undertake normal duties for one day or less because of their ILI (classified as low-level symptoms). Thus, 0.1554 and 0.4921 proportions of the susceptible population (p_L and p_M) were assigned to the low-level and moderate symptoms compartments respectively.

Table 1. List of model parameters and their values.

Parameter	Notation*	Baseline value	Source(s)
Population proportion	p_A, p_L, p_M, p_H	0.35, 0.1554, 0.4921, 0.0025	[18, 20-24]
Proportion of symptomatic cases requiring ≥2 days off normal duties	q	0.76	[24]
Mixing coefficient	μ_A, μ_L, μ_M, μ_H	1.0, 0.9, 0.4, 0.1	-
Recovery rate	γ_A, γ_L, γ_M, γ_H	1/8.3, 1/4.9, 1/4.9, 1/3.2	[25]

*Subscripts denote infection severity categories of asymptomatic (A), low-level symptoms (L), moderate symptoms (M) and hospitalised (H)

The relative mixing parameters μ were defined as proportions relative to the asymptomatic class (μ_A=1.0), with the level of mixing decreasing as infection severity increased. In the absence of published observational data, we made plausible assumptions regarding the relative mixing of each severity category. Given those with low-level symptoms were defined as being unable to undertake normal duties for one or no days because of illness, a slightly lower relative degree of mixing (μ_L=0.9) was assumed. However, mixing was considered to be much lower for infections with moderate symptoms that prevented normal duties for two or more days (μ_M=0.4) and required hospitalisation (μ_H=0.1).

Studies have indicated heterogeneity in the length of viral shedding duration between different severity classes. The parameters γ_i define the recovery rate in

each severity category and are calculated as the inverse of the duration of infectiousness. Viral shedding duration was used as a proxy for duration of infectiousness values determined using weighted averages of medians from a systematic review of influenza A(H1N1)pdm09 virus shedding for asymptomatic, community-based and hospitalised cases [25]. The studies included in the review did not differentiate viral shedding of low level and moderate symptoms, thus the same weighted average of median duration from community-based cases was used for both these infection severity categories. As our focus here is on cumulative incidence and the relative contribution of each severity class to transmission, we do not model shedding dynamics in the individual, and assume a consistent level of viral shedding over the course of infection. Where this assumption may affect parameters, such as the mixing parameters μ_i, we have conducted further sensitivity analyses.

Model fitting and sensitivity analysis

MATLAB (Student version; MathWorks) was used to simulate the model using values of R_e within the limits of published estimates (range: 1.14-1.36) [26] that resulted in a total proportion of recovered individuals that was consistent with estimated age-standardised infection risks of 19% and 21% in two all-age studies in Australia and New Zealand respectively [23, 27]. The differential equations for the model are given in the Supplementary Material. Infection severity stratum-specific reproduction numbers were then calculated to determine the relative importance of each group in influenza A(H1N1)pdm09 virus transmission.

Sensitivity analyses were also undertaken in MATLAB to assess the relative influence of the proportional population distribution, mixing and recovery rate parameters on the risk of infection, with a fixed overall reproduction number. Given the proportions of low-level and moderate symptoms parameters p_L and p_M are dependent on q, only q was included in the sensitivity analysis. The mixing coefficient μ_A was also excluded from the sensitivity analysis because it is the reference value against which the other mixing parameters were compared. Triangular distributions of the ten parameter ranges (baseline value plus and minus 10%) were sampled 400 times using Latin hypercube sampling. Parameter

outputs were then transformed into their ranks and partial rank correlation coefficients (PRCC) calculated. Parameters with a PRCC closer to -1 and +1 indicated a stronger impact on the model output, with the direction indicating a negative or positive correlation [28].

The results of the PRCC were also used to identify important parameters and test the effect of their variation, within plausible limits, on the infection severity stratum-specific reproduction numbers. The flexibility of the plausible assumptions used to generate the baseline values for the relative mixing parameters μ_L and μ_M was tested by lowering μ_L from 0.9 to 0.7 and increasing μ_M from 0.4 to 0.6. The effect of a slower recovery rate from a one-day-longer duration of infectiousness for the moderate symptoms group (γ_M) was also examined. The q parameter was varied from a baseline value of 0.76 to 0.42, based on data from the Australian Flutracking surveillance system which provides weekly community-level ILI symptomatic infection risks not biased by health-seeking behaviour and clinician testing practices; in the 2011 and 2012 influenza seasons, an average of 42% of Flutracking participants reporting an ILI took two or more days off work or normal duties because of their illness [29]. The effect of lowering the proportion of asymptomatic cases (p_A) from 0.35 to 0.13 (the average of three studies in Canada [15], Germany [17] and China [30]) was also tested.

Results

Using the baseline population proportion distribution, mixing and recovery rate parameters, a value of R_e = 1.14 at the lower limit of published range resulted in a cumulative infection risk of 24%, slightly higher than the age-standardized estimates of 19% and 21% for Australia and New Zealand respectively (figure 2). Figure 3 shows the model stratified by each severity stratum and the contribution of each to the infection risk: asymptomatic (8.5%); low-level symptoms (3.8%); moderate symptoms (11.9%); and hospitalised (0.06%). Asymptomatic infections peaked first at 95 days, followed two days later by those with low-level and moderate symptoms, and hospitalised cases at 100 days.

Figure 2. Cumulative incidence of influenza A(H1N1)pdm09, summed over all infection severity categories, over time in susceptible, infected and recovered populations.

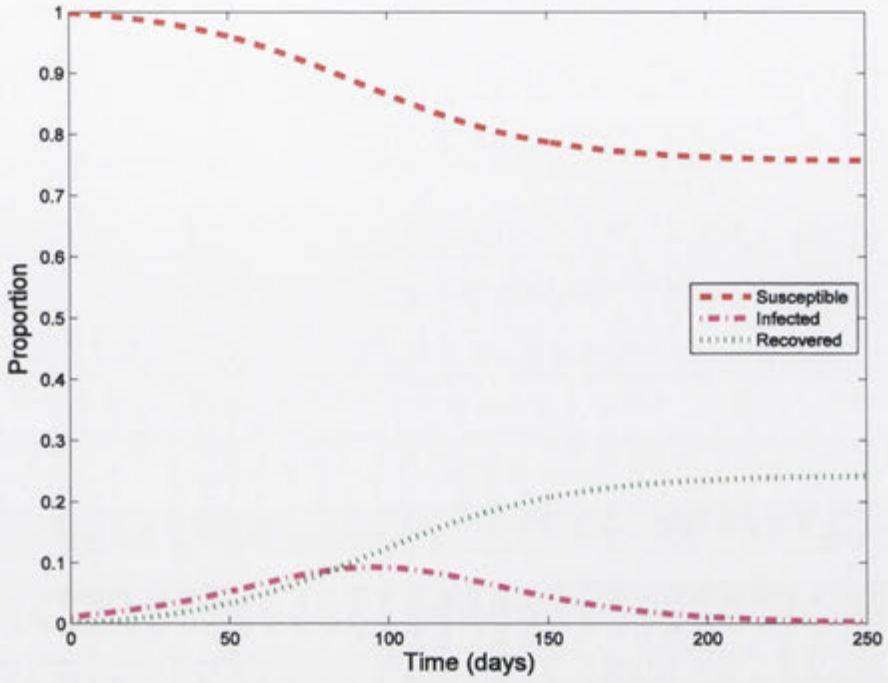
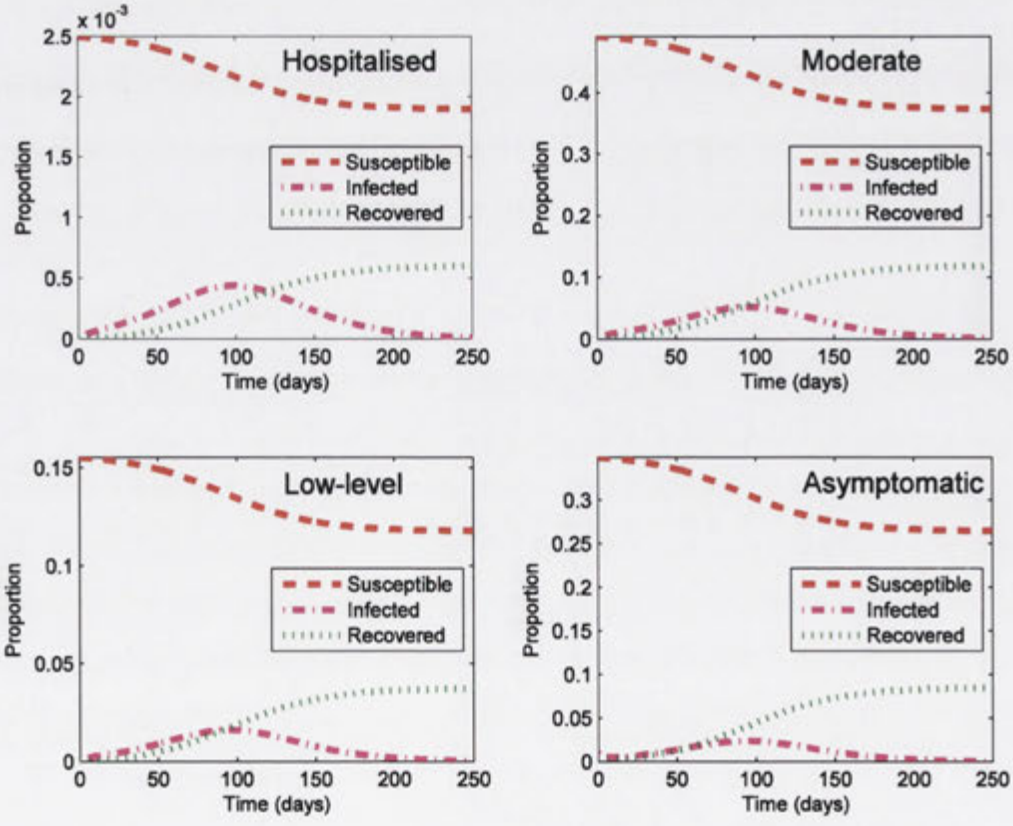


Figure 3. Cumulative incidence of influenza A(H1N1)pdm09 over time in susceptible, infected and recovered populations, by infection severity.



Effective reproduction numbers for each infection severity category are shown in table 2. Under the baseline parameter settings the low-level symptoms infection severity group accounts for the greatest transmission (R_L=1.82) followed by the asymptomatic group (R_A=1.32). The effective reproduction numbers in the moderate symptoms and hospitalised groups were less than 1.

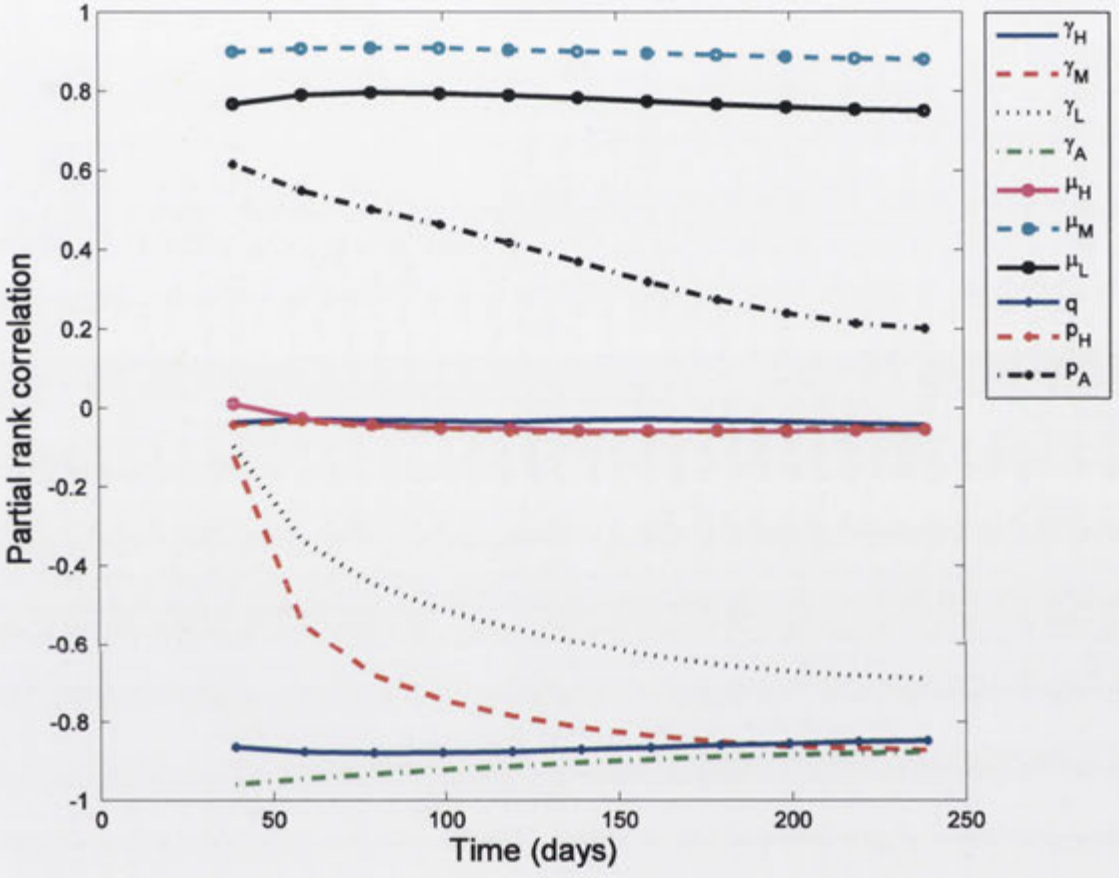
Table 2. Effective reproduction number by severity category and parameter values.

Infection severity	Baseline	R_e after parameter adjustment from baseline				
	R_e	p_A=0.13	μ_L=0.7	μ_M=0.6	q=0.42	γ_M=1/5.9
Asymptomatic	**1.32**	1.39	1.39	1.12	1.10	1.23
Low-level symptoms	**1.82**	1.92	1.49	1.55	1.52	1.70
Moderate symptoms	**0.81**	0.85	0.85	1.03	0.68	0.91
Hospitalised	**0.34**	0.36	0.36	0.29	0.29	0.32

The transformation of parameter uncertainty into PRCC showed that none of the hospitalised severity category parameters (proportion, mixing or recovery rate) had a discernible impact on the infection risk, with PRCC values near zero (figure 4). The mixing (μ) parameters for low-level and moderate symptoms were strongly and positively correlated with infection risk, particularly moderate symptoms for which the final PRCC=0.88. With PRCC values of −0.88 and −0.87 respectively, the recovery rate (γ) parameters for asymptomatic infection and those with moderate symptoms were strongly and negatively correlated with infection risk. The recovery rate for low-level symptoms was less important, but like the recovery rate for moderate symptoms, increased in importance from negligible levels at the start of the epidemic period. The importance of the proportion of asymptomatic infections also varied over the course of the epidemic, initially moderately and positively correlated with infection but declining to near neutrality by the end. However, ILI resulting in inability to undertake normal duties for two or more days (notated as q and a proxy for the proportion with moderate symptoms) was very

important throughout the epidemic with PRCC=−0.85. We used triangular distributions here for simplicity and to ensure that parameter values remained realistic, however normal distributions gave similar results.

Figure 4. Partial rank correlation for infection severity proportion, mixing and recovery rate parameters* over time.



*See table 1 for detailed parameter descriptions

Variation of important model parameters, as identified by PRCC analysis, generally resulted in little difference in the broad trends observed from baseline values (table 2). The most marked change in the infection severity stratum-specific reproduction numbers occurred with raising the moderate symptoms mixing coefficient from 0.4 to 0.6 and although this resulted in an effective reproduction number of just greater than one for the moderate symptoms group, it was still highest for the low-level symptoms group. Decreasing the *q* parameter (representing the proportion of health survey participants reporting an ILI during the first pandemic wave that were unable to undertake normal duties for two or

more days) from 0.76 to 0.42 resulted in decreases in the effective reproduction number for all infection severity strata. The effect of lowering the proportion of asymptomatic cases from 0.35 to 0.13 had a relatively minor effect on infection severity stratum-specific reproduction numbers. Importantly, under all alternative scenarios the effective reproduction numbers for the asymptomatic and low-level symptoms groups were greater than one and higher than those for the moderate symptoms and hospitalised groups.

Discussion

Using a simple deterministic mathematical model, we show that transmission during the first wave of influenza A(H1N1)pdm09 was primarily driven by those with low-level symptoms (broadly defined as symptoms resulting in inability to undertake normal duties for zero or one days) and, to a lesser extent, asymptomatic infections. Given such infections do not necessitate medical attendance (except perhaps for a certificate of absence) and are very unlikely to be tested, they remain largely silent to the health system. In contrast, infections resulting in moderate symptoms (inability to undertake normal duties for two or more days) or hospitalisation that generally are detected by the health system both had effective reproduction numbers less than one and a comparatively minor role in influenza A(H1N1)pdm09 transmission.

Development of the model necessitated a number of important assumptions, particularly with respect to baseline parameter values. Whilst most parameter values were sourced directly from the published literature, the relative mixing coefficients (μ) of each infection severity category were based on data on health-seeking behaviour, together with plausible assumptions concerning the behaviour of each category. The mixing coefficients for the low-level and moderate symptoms infection severity category in particular were influential model parameters. Nevertheless, sensitivity analyses using more conservative estimates of mixing coefficients were still broadly consistent with the baseline observation that asymptomatic and low-level symptoms infections were the most important drivers of transmission. Indeed, whilst reducing the mixing coefficient resulted in a lower effective reproduction number for the low-level symptoms group, this also

resulted in an increase in transmission from those with asymptomatic infections. The model does not account for possible higher levels of mixing in hospitalised patients prior to hospitalisation, although any effect is likely to be minimal given the low proportion and importance of infection resulting in hospitalisation.

Searches of the literature also identified heterogeneity in other parameter values, in particular the proportion of asymptomatic cases. The baseline value was set at 0.35 based on several transmission studies from Hong Kong, China and the USA [18, 20, 21], and comparable to estimates of asymptomatic infection for seasonal type A/H1N1, A/H3N2 and type B influenza of 31-38% [31]. At the lower end of the reported range were three studies with a reported asymptomatic proportion of 10-17% [15, 17, 30], but using an average of 17% in a sensitivity analysis had little effect on the infection severity stratum-specific reproduction numbers, as anticipated from the PRCC analysis. Other retrospective serological studies conducted in New Zealand [23], Austria [32] and a USA marine and naval cohort [33] indicated proportions of asymptomatic infections to be 45%, 84% and 53% respectively and were likely affected by recall bias and therefore not assessed in the sensitivity analysis.

With the exception of infections resulting in hospitalisation, the recovery rate parameters for all infection severity categories were important components of the model. Whilst these values were calculated from a systematic review of influenza A(H1N1)pdm09 virus shedding [25], they are also couched with some uncertainty. Firstly, the model assumes that the degree of infectiousness remains constant throughout the duration of viral shedding, and whilst there is some evidence that infectiousness wanes over this period it is highly variable and difficult to quantify [14-17, 20, 34, 35]. Secondly, most viral shedding studies used reverse transcriptase polymerase chain reaction (RT-PCR) to detect virus, which cannot differentiate between viable and non-viable virus and thus may overestimate the duration of viral shedding. However, this is likely to be at least partially offset (among those with symptomatic infections) by pre-symptomatic shedding. Pre-symptomatic influenza A(H1N1)pdm09 virus shedding has been reported in at

least two studies for as long as three days before onset in less than 5% of cases [15, 36], although our model has not incorporated these data.

Several other limitations should be considered when interpreting the findings of this study. Due to scarcity of published data on absenteeism as a result of laboratory confirmed influenza, the proportional division of symptomatic infections into those manifesting with low-level and moderate symptoms used data on days unable to undertake normal duties because of ILI. Whilst ILI is a non-specific outcome and will likely incorporate upper respiratory tract infections that are generally considered to be milder than influenza (which also frequently causes lower respiratory or systemic symptoms [37]), the positive predictive value of the syndromic ILI definition for influenza is likely to be relatively high because the data were collected during the peak of the first pandemic wave [24]. Nevertheless, testing of a wide range of the proportions with moderate and low-level symptoms in the sensitivity analysis showed the same relative differences between the effective reproduction numbers of each infection severity stratum. Finally, the model was developed and should be interpreted in the context of the first in-season wave of influenza A(H1N1)pdm09 in Australia. It assumed a population immunologically naïve to the virus and resulted in highest incidence in younger age groups [5], who likely have a different infection severity profile to other age groups. Estimating the relative importance of different levels of disease severity in influenza A(H1N1)pdm09 transmission in the northern hemisphere, subsequent pandemic waves in the southern hemisphere and seasonal influenza (that the pandemic strain has since become) would require the incorporation of immunity (either from prior infection or vaccination) and age group stratification.

Public health implications

Whilst the model structure requires modification to investigate the role of infection severity in post-pandemic influenza transmission, its finding that low-grade and asymptomatic infections were the drivers of the first influenza A(H1N1)pdm09 wave in Australia helps explain why community transmission was apparently already well-established by the time influenza A(H1N1)pdm09 was detected. Furthermore, that transmission was being driven by those essentially

invisible to the health system suggests that case-based pandemic control strategies such as antiviral distribution may not always be very effective. Whilst population-based interventions such as school closures may be more likely to be effective in interrupting transmission, such measures will probably be of little value when such a high proportion of infections are relatively mild. Public health plans and responses to pandemics in the future need to accommodate this contingency.

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Supplementary Material

Differential equations

The force of infection is given by:

$\lambda = \beta_A.I_A + \beta_L.I_L.+ \beta_M.I_M + \beta_H.I_H$

The differential equations that require solving are:

$dS_A/dt = -\lambda.S_A$

$dS_L/dt = -\lambda.S_L$

$dS_M/dt = -\lambda.S_M$

$dS_H/dt = -\lambda.S_H$

$dI_A/dt = \lambda.S_A - \gamma_A.I_A$

$dI_L/dt = \lambda.S_L - \gamma_L.I_L$

$dI_M/dt = \lambda.S_M - \gamma_M.I_M$

$dI_H/dt = \lambda.S_H - \gamma_H.I_H$

$dR_A/dt = \gamma_A.I_A$

$dR_L/dt = \gamma_L.I_L$

$dR_M/dt = \gamma_M.I_M$

$dR_H/dt = \gamma_H.I_H$

subject to the initial conditions $S_A(0) = 0.35 - I_A(0)$, $S_H(0) = 0.0025$, $S_L(0) = (1 - (S_A + S_H)).(1 - q)$, $S_M(0) = (1 - (S_A + S_H)).(q)$, $I_A(0) = 0.001$, and $I_L(0) = I_M(0) = I_H(0) = R_A = R_L(0) = R_M(0) = R_H(0) = 0$.

Chapter 6

Post-pandemic influenza epidemiology

About this chapter

This chapter describes the epidemiology of laboratory confirmed influenza and influenza-like illness (ILI) over consecutive influenza seasons from 2010 to 2012 inclusive, published as three articles in the *Western Pacific Surveillance and Response Journal* and the *Victorian Infectious Diseases Bulletin*. The studies were conducted using data from established notifiable disease, sentinel general practice, sentinel hospital, locum service and laboratory surveillance programs.

The studies showed that following the emergence of influenza A(H1N1)pdm09, influenza and ILI activity measured by most programs returned to normal seasonal levels from 2010 to 2012, although an increase in notified cases of laboratory confirmed influenza suggested a large increase in testing. Pre-pandemic H1N1 influenza strains were not detected, indicating replacement by influenza A(H1N1) 2009 which remained the dominant circulating strain in 2010. After comprising a higher proportion of cases in 2011, influenza A(H3N2) became the dominant circulating subtype in Victoria in 2012, accompanied by increases in older and hospitalised cases.

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Surveillance Report

Continued dominance of pandemic A(H1N1) 2009 influenza in Victoria, Australia in 2010

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The 2010 Victorian influenza season was characterized by normal seasonal influenza activity and the dominance of the pandemic A(H1N1) 2009 strain. General Practice Sentinel Surveillance rates peaked at 9.4 ILI cases per 1000 consultations in week 36 for metropolitan practices, and at 10.5 ILI cases per 1000 in the following week for rural practices. Of the 678 ILI cases, 23% were vaccinated, a significantly higher percentage than in previous years. A significantly higher percentage of ILI patients were swabbed in 2010 compared to 2003–2008, but similar to 2009, with a similar percentage being positive for influenza as in previous years. Vaccination rates increased with patient age. Melbourne Medical Deputising Service rates peaked in week 35 at 19.1 ILI cases per 1000 consultations. Of the 1914 cases of influenza notified to the Department of Health, Victoria, 1812 (95%) were influenza A infections – 1001 (55%) pandemic A(H1N1) 2009, 4 (<1%) A(H3N2) and 807 (45%) not subtyped; 88 (5%) were influenza B; and 14 (<1%) were influenza A and B co-infections. The World Health Organization Collaborating Centre for Reference and Research on Influenza tested 403 isolates of which 261 were positive for influenza, 250 of which were influenza A and 11 were influenza B. Ninety-two per cent of the influenza A viruses were pandemic A(H1N1) 2009, and following antigenic analysis all of these were found to be similar to the current vaccine strain. Three viruses (0.9%) were found to be oseltamivir resistant due to an H275Y mutation in the neuraminidase gene.

Victoria is Australia's second most populous state with a temperate climate and an annual influenza season that usually occurs between May and September. Given the wide clinical spectrum and variable levels of diagnostic testing for influenza, several surveillance programmes that target different populations are used to monitor activity of influenza and influenza-like illness (ILI) in Victoria. A sentinel general practice (GP) programme for the surveillance of ILI in Victoria has been coordinated by the Victorian Infectious Diseases Reference Laboratory (VIDRL) in partnership with the Victorian Government Department of Health since 1993. Laboratory testing of a sample of ILI cases from the surveillance programme commenced in 1998.[1] VIDRL also monitors diagnoses of ILI made by the locum medical practitioners through the Melbourne Medical Deputising Service (MMDS). The Department of Health coordinates the surveillance of all laboratory-confirmed influenza in Victoria, a prescribed group B notifiable disease under the *Victorian Public Health and Well-being Act 2008* and *Public Health and Well-being Regulations 2009*. The department also investigates notified institutional outbreaks of respiratory illness under the auspices of this legislation.

The objectives of the influenza surveillance system are to:

- monitor the epidemiology of laboratory-confirmed influenza in Victoria;
- identify the onset, duration and relative severity of annual influenza seasons in Victoria;
- provide samples for the characterization of circulating influenza strains in the community to assist in the evaluation of the current season and formulation of the following season's vaccine;
- provide potential for early recognition of new influenza viruses and new or emerging respiratory diseases; and
- estimate influenza vaccine effectiveness each year.

Victoria was the first Australian jurisdiction to report widespread transmission – particularly among schoolchildren – when pandemic influenza A(H1N1) 2009 emerged in mid-2009. While notification data suggested unprecedented levels of disease in the

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Figure 1. **Distribution of sentinel surveillance practices in metropolitan and rural Victoria, 2010**

Metropolitan

Rural

community, ILI data suggested a season characterized as higher than normal seasonal activity.[2] The pandemic strain continued to be dominant around the world into the 2009/2010 northern hemisphere influenza season and there was considerable interest in the epidemiology of a likely second southern hemisphere pandemic wave during the 2010 influenza season. Here we summarize the epidemiological findings from the Victorian influenza surveillance system during the 2010 season.

METHODS

General Practice Sentinel Surveillance

In 2010, 61 GPs from 23 metropolitan practices and 26 GPs from nine rural practices participated in the VIDRL GP Sentinel Surveillance (GPSS) programme (**Figure 1**), which is approved for continuing professional development points by the Royal Australian College of General Practitioners and the Australian College of Rural and Remote Medicine for participation. The GPSS programme for 2010 operated from 3 May to 24 October (weeks 19–43) inclusive.

The 87 participating GPs reported total number of consultations per week and age, sex and vaccination status of any patients presenting with ILI. GPs submitted the data weekly by fax or online submission (http://www.victorianflusurveillance.com.au). A case of ILI was defined as fever, cough and fatigue/malaise.[3] ILI rates were calculated as the number of ILI patients per 1000 consultations and were compared to previously established activity thresholds (normal seasonal activity, higher than expected activity and epidemic activity) for Victorian influenza seasons.[4]

GPs were requested to collect nose and throat swabs, sent in the same viral transport medium, from patients presenting within four days or less since the onset of symptoms. Patients were chosen at the discretion of the GP. Data collected on swabbed patients included: age, sex, symptoms (fever, cough, fatigue, myalgia, other), vaccination status (for pandemic H1N1 vaccine and seasonal vaccine), date of vaccination/s and Aboriginal and/or Torres Strait Islander status. RNA was extracted from clinical specimens and real-time polymerase chain reaction (PCR) used to detect the presence of influenza A virus matrix gene. Influenza positive samples were confirmed as positive or negative for pandemic A(H1N1) 2009 in a second real-time PCR that incorporated primers and probes specific for the hemagglutinin gene of the pandemic A(H1N1) 2009 virus. Influenza B viruses were identified by a separate PCR.

Melbourne Medical Deputising Service

The MMDS is the largest medical locum service in Australia and has contributed to Victorian influenza surveillance since 2003. It provides a 24-hour medical service to patients in their own homes or aged care facilities. Weekly rates of influenza-related diagnoses by MMDS clinicians per 1000 consultations were calculated from records returned from the MMDS clinical database using the search terms "influenza" and "flu." To avoid inclusion of those immunized prophylactically, records that contained the terms "Fluvax," "at risk"

and "immunization" were excluded from the rate calculation.

Notifications of laboratory-confirmed influenza to the Victorian Department of Health

Under the *Victorian Public Health and Well-being Act 2008* and *Public Health and Well-being Regulations 2009* medical practitioners and pathology services are required to notify laboratory-confirmed influenza cases to the Department of Health within five days of a positive test result. Records of all laboratory-confirmed influenza cases with a 2010 notification date were extracted for analysis from the Department of Health Notifiable Infectious Diseases Surveillance database on 17 May 2011.

Outbreak investigations

The Victorian Department of Health investigates notified respiratory outbreaks in institutional settings under the *Victorian Public Health and Well-being Act 2008* and *Public Health and Well-being Regulations 2009*. An outbreak is defined as three or more cases of newly acquired influenza-like illness within 72 hours in residents or staff of a setting or facility.

Strain typing

Seven laboratories referred specimens and isolates collected in Victoria during 2010 to the WHO Collaborating Centre for Reference and Research on Influenza, Victoria, Australia (WHO Collaborating Centre), although the selection method varied by laboratory. Tissue culture was attempted for all of the specimens/isolates received. Viruses that were successfully cultured were analysed by haemagglutination inhibition assay to determine antigenic similarity to the current vaccine strains and by sequencing and a neuraminidase inhibition assay to determine antiviral susceptibility.

Data from the surveillance systems were analysed descriptively using Microsoft Excel software. The χ^2 test was used to compare proportions in Stata version 10.0 statistical software, with $P < 0.05$ considered significant.

RESULTS

General Practice Sentinel Surveillance

For the 25 week surveillance period, an average of 93% (81/87) of GPs submitted tally sheets to VIDRL each week. GPs reported having conducted 172 411 consultations (121 270 metropolitan and 51 141 rural) and identified 678 ILI cases (527 metropolitan and 151 rural) during the season, corresponding to metropolitan and rural rates of 4.4 and 3.0 ILI cases per 1000 consultations, respectively.

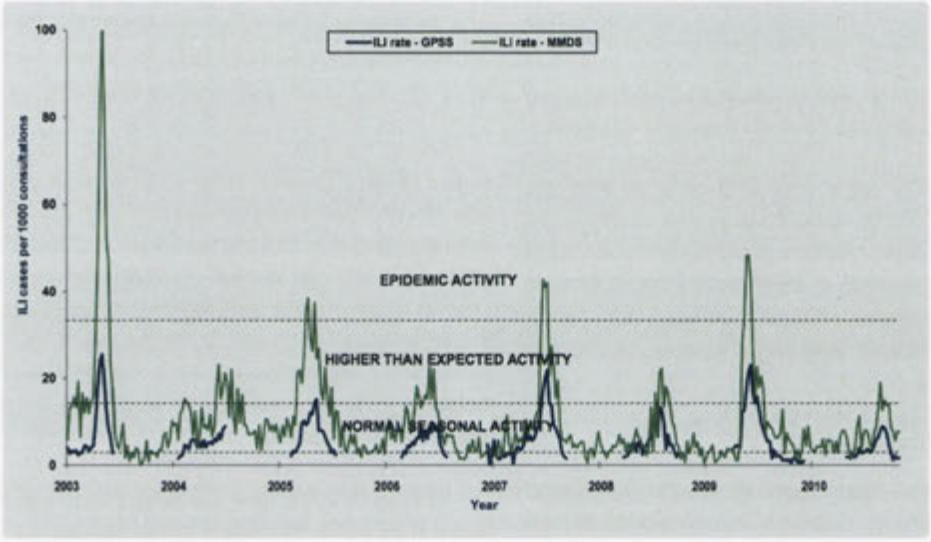
Among the 678 ILI cases reported by GPs, the median age was 33 years (range: 1–91 years) and 50% were female. Twenty-three per cent of ILI cases were vaccinated in 2010. Of those vaccinated in 2010, 26% received the seasonal vaccine only, 38% had both the seasonal vaccine, which included the pandemic strain, and the monovalent pandemic vaccine, and 15% had the pandemic monovalent pandemic vaccine only. The remaining 20% were reported as vaccinated, but the vaccine was not specified.

ILI rates in 2010 were low compared to previous years and fell within the range of normal seasonal activity (**Figure 2**). The combined ILI rate began to increase in week 32 (week commencing 2 August) peaking at 9.4 ILI cases per 1000 consultations in week 36 for metropolitan practices, and at 10.5 ILI cases per 1000 in the following week for rural practices (**Figure 3**). Rates had declined to baseline levels by week 41.

GPs swabbed a total of 478 (71%) ILI patients in 2010, of which 170 (36%) tested positive for influenza. In 2010, 166 (98%) of influenza positive swabs were influenza A and the remainder were influenza B. Of the 166 influenza A viruses detected, 148 (89%) were pandemic A(H1N1) 2009 influenza, seven (4%) were subtype A(H3N2) and the remaining 11 (7%) were not further subtyped (**Table 1**).

Among the influenza-positive patients, 155 (91%) were reported as not vaccinated and 13 (8%) were vaccinated with the pandemic and/or seasonal vaccine(s) (**Table 1**). Higher proportions of swabbed ILI patients who tested negative for influenza were reported as vaccinated. Three patients (one influenza positive and two influenza negative) were reported as receiving an unspecified influenza vaccine and the vaccination status of 11 patients (two influenza positive and nine influenza negative) was unknown. Of the 94 patients reported as vaccinated, 42 (44%) had received the seasonal vaccine, 26 (28%) the pandemic vaccine, 23 (25%) both vaccines and 3 (3%) had an unspecified vaccine. Excluding those with unknown vaccination status, the

Figure 2. **General Practice Sentinel Surveillance and Melbourne Medical Deputising Service influenza-like illness consultation rates, Victoria, 2003 to 2010**



proportion of vaccinated influenza-positive patients (7%) was significantly lower than the proportion of vaccinated influenza-negative patients (27%; $P < 0.001$). The proportion of swabbed patients that were vaccinated with either vaccine increased with age, particularly among those that tested negative for influenza (**Figure 4**).

The median age of pandemic A(H1N1) 2009 cases identified from the GPSS was 26 years (range: 1–63 years), compared to 18 years for both influenza A(H3N2) (range: 4–34 years) and influenza B (range: 7–28 years), although there were relatively few cases of the latter two infections. Most

Figure 3. **General Practice Sentinel Surveillance and Melbourne Medical Deputising Service influenza-like illness rates and routinely notified laboratory-confirmed influenza cases by week, Victoria, 2010**

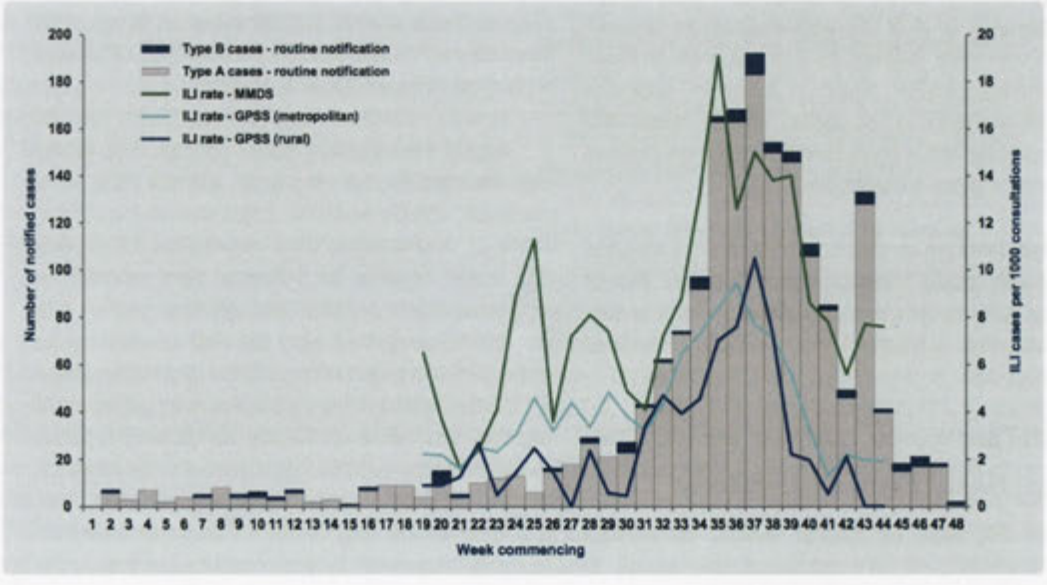


Table 1. **Number (%) General Practice Sentinel Surveillance swabs by influenza type/subtype, vaccination status and median age, Victoria, 2010**

Influenza type/subtype	Total	Vaccinated seasonal (%)	Vaccinated pandemic (%)	Vaccinated both (%)	Vaccinated Unspecified (%)	Not vaccinated (%)	Unknown vaccination status (%)	Median age (years)
All influenza	**170**	**4 (2)**	**6 (4)**	**2 (1)**	**1 (1)**	**155 (91)**	**2 (1)**	**26**
Pandemic A(H1N1) 2009	148	4 (3)	6 (4)	2 (1)	1 (1)	133 (90)	2 (1)	26
A(H3N2)	7	0	0	0	0	7 (100)	0	18
A (not subtyped)	11	0	0	0	0	11 (100)	0	34
B	4	0	0	0	0	4 (100)	0	18
Influenza negative	**308**	**38 (12)**	**20 (7)**	**21 (7)**	**2 (1)**	**218 (71)**	**9 (3)**	**35**
Total	**478**	**42**	**26**	**23**	**3**	**373**	**11**	**32**

cases (75%) identified from the GPSS were aged from 5 to 39 years (**Figure 5**).

Melbourne Medical Deputising Service

A total of 441 patients were diagnosed with "flu" or "influenza" by the MMDS during the 2010 surveillance season, corresponding to an overall rate of 8.4 ILI cases per 1000 consultations. Like the GPSS ILI rate, the MMDS rate, with a peak of 19.1 ILI per 1000 consultations, was low compared to previous seasons (**Figure 2**). The peak occurred in week 35 (week commencing 23 August) before the peaks of the GPSS ILI rate and cases of laboratory-confirmed influenza notified to the Department of Health (**Figure 3**).

Notifications of laboratory-confirmed influenza to the Victorian Department of Health

Excluding notifications of cases associated with the GPSS and outbreaks, there were 1914 cases of influenza routinely notified to the Department of Health in 2010. Of these, 1812 (95%) were influenza A infections, 88 (5%) were influenza B and 14 (1%) were influenza A and B co-infections.

Figure 4. **General Practice Sentinel Surveillance swabs by influenza and vaccination status and age group, Victoria, 2010**

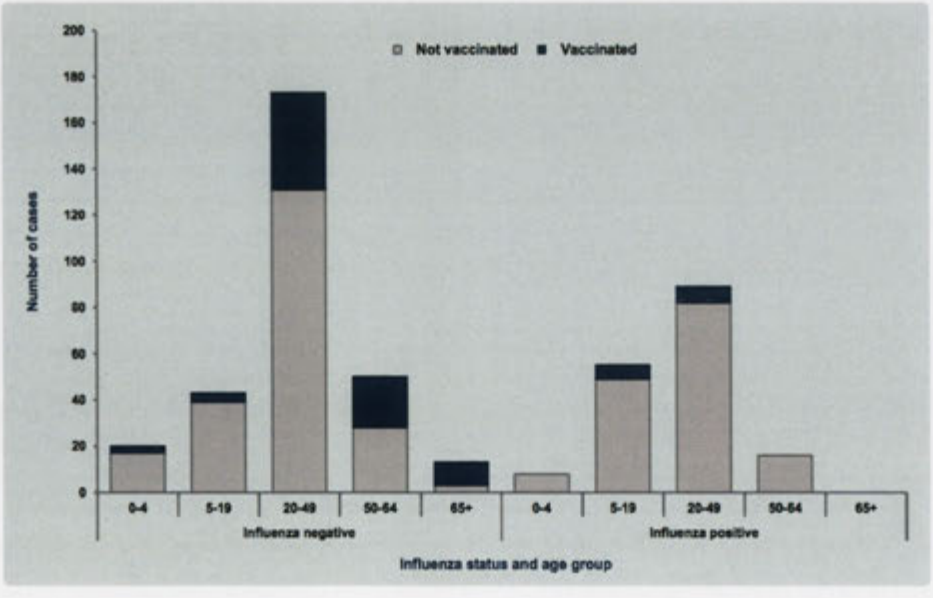
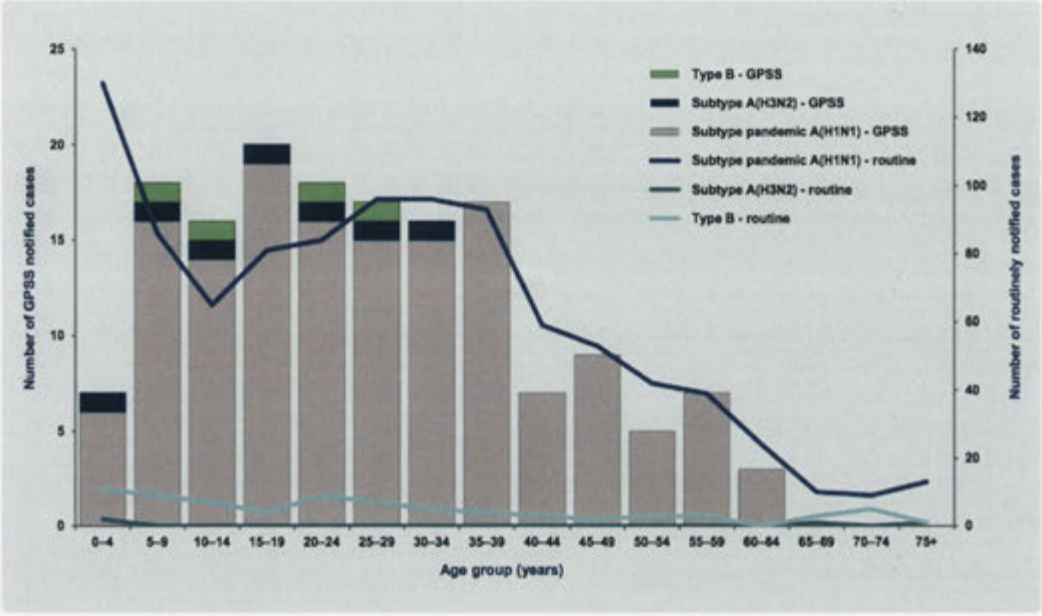


Figure 5. **Notified cases of laboratory confirmed influenza by age group and notification sources, Victoria, 2010**



The number of routinely notified cases of laboratory-confirmed influenza, particularly influenza A, increased from week 31 in a pattern that was generally consistent with GPSS ILI rates (**Figure 3**). Notified cases of both influenza A and influenza B influenza peaked in week 37 (week commencing 6 September), the same week as the GPSS rural ILI rate peak and one week after that of the GPSS metropolitan ILI rate.

Of the 1812 influenza A cases, 1001 (55%) were pandemic A(H1N1) 2009, 4 (<1%) were A(H3N2) and 807 (45%) were not subtyped. The median ages for influenza cases were 28 years (range: 0–95 years) for routinely notified pandemic A(H1N1), 21 years (range: 0–94 years) for A(H3N2) and 24 years (range: 0–80 years) for influenza B cases. The highest proportion of notified cases of pandemic A(H1N1) 2009 was in the 0–4 years age group (13%) while those aged 5–39 years accounted for 61% of the routinely notified cases (**Figure 5**). Overall, there was a 1:1 male-to-female ratio among the routinely notified cases.

Four cases aged 1 month, 27, 50 and 68 years, notified in weeks 34, 33, 35 and 39, respectively, were reported to have died as a result of influenza A virus infections (three due to pandemic A(H1N1) 2009 and the other not subtyped).

Outbreak investigations

Six respiratory outbreaks were notified to the Department of Health in 2010: one in week 26 (week commencing 21 June), one in week 35 (23 August), one in week 38 (13 September), one in week 41 (4 October) and two in week 44 (25 October). Four of the six outbreaks occurred in aged care facilities, one outbreak occurred in an assisted residential service, and one in a military facility. There were between three and 24 cases associated with each outbreak, corresponding to attack rates of 10%–45%. Of the four outbreaks in aged care facilities, all were caused by influenza A virus, of which two were influenza A (not further subtyped), one was due to a mixed infection [non-H1N1 and pandemic A(H1N1) 2009], and one was due to A(H3N2). The outbreaks in the assisted residential service and the military facility were typed as pandemic A(H1N1) 2009.

Strain typing

Of the 403 specimens and three isolates received at the WHO Collaborating Centre from Victoria, 261 (64%) yielded an influenza-positive isolate following cell culture. Of these, 250 (96%) were influenza A and 11 (4%) were influenza B. The majority (n = 231; 92%) of the influenza A viruses were pandemic A(H1N1) 2009, with 17 (7%) A(H3N2); two specimens contained mixed

viral populations of pandemic A(H1N1) 2009 and A(H3N2) viruses. Following antigenic analysis, all of the pandemic A(H1N1) 2009 strains were found to be similar to the current vaccine strain A/California/7/2009 (apart from two low reactors). All A(H3N2) strains were similar to the current vaccine strain A/Perth/16/2009 (apart from two low reactors) and all influenza B strains were of the B/Victoria/2/87 lineage and similar to the current vaccine strain B/Brisbane/60/2008 (apart from one low reactor). All (n = 261) of the Victorian influenza-positive isolates and 45 clinical specimens were tested for susceptibility to the neuraminidase inhibitors oseltamivir and zanamivir. Three viruses were found to be oseltamivir resistant due to a H275Y mutation in the neuraminidase gene. Two of the resistant strains came from otherwise healthy patients that were not under oseltamivir treatment,[5] while the third was isolated from a hospitalized child undergoing oseltamivir treatment.

DISCUSSION

The 2010 influenza season in Victoria was characterized by dominance of the pandemic A(H1N1) 2009 strain, which, as a seasonal second wave, was not only mild in magnitude as measured by ILI activity rates in comparison to the first wave (also in-season) in 2009 but also compared to previous seasons back to 2003. Almost 90% of GPSS swabs that tested positive for influenza were typed as pandemic A(H1N1) 2009, with the remainder comprised of influenza A(H3N2), influenza A (not subtyped) and influenza B. This distribution was generally consistent among notified cases to the Department of Health for which typing data were available. Pre-pandemic H1N1 influenza strains were not detected in 2010, suggesting the pandemic A(H1N1) 2009 strain has displaced seasonal A(H1N1).

Although ILI and influenza activity was lower, the dominance of pandemic A(H1N1) 2009 resulted in similarities between the 2009 and 2010 seasons, particularly the concentration of cases among children and young adults, the relatively low number of overall deaths and few reported ILI or influenza outbreaks in aged care facilities.[2] Furthermore, the proportion of GPSS ILI cases that were swabbed was approximately 70%, compared to 35%–50% from 2003 to 2008, (P < 0.001) but similar to 2009 (68%), indicating heightened doctor and/or patient concern with respect to confirmation of pandemic influenza infection. The proportion of GPSS swabs positive for influenza was 36%, similar to the 39% in 2009[2] and the average of 36% for the years 2003 to 2007.[6]

Each of the surveillance systems indicated that the 2010 influenza season, effectively the second pandemic A(H1N1) 2009 influenza wave, was considerably milder in terms of influenza cases and ILI activity compared to the first season in 2009. This trend was noted in other southern hemisphere countries,[7] but contrasts with the northern hemisphere and previous pandemics in which a mild first wave was followed by a second of generally greater activity and severity.[8–10] The concurrent emergence of pandemic A(H1N1) 2009 globally resulted in an out-of-season first wave followed by an in-season second wave in the northern hemisphere. That the first wave in the southern hemisphere was in-season and followed by pandemic and seasonal influenza vaccination programmes may have induced sufficient levels of population immunity – suggested by serosurveys to be in the range of 16% to 26.7%[11–15] – to help explain the difference in the relative magnitudes of the waves in each hemisphere. Also, 23% of ILI cases were vaccinated in 2010, which is significantly higher than the 13%–17% observed from 2005 to 2009 (P < 0.02).

The 2010 trivalent southern hemisphere influenza vaccine contained the pandemic A(H1N1) 2009 strain (A/California/7/2009) as well as A/Perth/16/2009 (H3N2) and B/Brisbane/60/2008. Antigenic analysis by the WHO Collaborating Centre indicated good matching with circulating strains in Victoria to those in the vaccine, suggesting the seasonal vaccine was effective during the 2010 season. This inference was supported by the significantly higher percentage of vaccinated influenza-negative ILI patients compared to those that tested positive for influenza. Using a test-negative case control study design, the GPSS data were used to demonstrate a statistically significant protective effect of the 2010 seasonal trivalent influenza vaccine against pandemic A(H1N1) 2009 infection. The vaccine effectiveness estimate was 79% (95% C.I.: 33%–93%) after adjusting for age and month of specimen collection.[16]

As observed in previous years, the MMDS ILI rate peaked slightly earlier than the corresponding GPSS rate, which in turn preceded the peak in notified cases of laboratory confirmed influenza. Thus, although less

specific, the ILI systems provided a more timely indication of influenza activity than notifiable disease data.

Given their varied source populations (e.g. those that seek health care from GPs and locums and the hospitalized young or elderly[17] that make up a higher proportion of notified cases) the surveillance systems assist in providing comprehensive influenza and ILI surveillance in Victoria. However there are several limitations of the surveillance. In 2010 there was no systematic or timely hospital (emergency department and inpatient) or mortality surveillance. The Influenza Complications Alert Network will commence in five Victorian hospitals in 2011 and thus provide more clinical and burden of disease data associated with hospitalized influenza. A further limitation of the system is the use of different ILI case definitions by the GPSS and the MMDS. Although it is difficult to speculate about the relative sensitivity and specificity of each system, it is comparison of ILI rate trends over time – rather than absolute values between each system – that best informs the level of ILI activity.

Victorian influenza surveillance system reports are available at https://www.victorianflusurveillance.com.au/.

Conflicts of interest

None declared.

Funding

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Higher proportion of older influenza A(H1N1)pdm09 cases in Victoria, 2011

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The influenza surveillance system in Victoria is comprised of several components, including a general practitioner sentinel surveillance system, surveillance for influenza-like illness (ILI) in consultations made by the Melbourne Medical Deputising Service, laboratory confirmed influenza notified to the Victorian Department of Health and strain typing performed by the World Health Organization Collaborating Centre for Reference and Research on Influenza.

As measured by ILI from both the MMDS and GPSS, the 2011 influenza season in Victoria was mild compared to previous seasons and was not dominated by any type or subtype of influenza. There were 13 laboratory confirmed influenza outbreaks in 2011, nearly all of which were in aged care facilities.

GPs continue to swab more patients, a trend started in 2009, with a significantly lower percent of these testing positive for influenza than previous years. The proportion of ILI and swabbed patients who were vaccinated was also significantly lower in 2011 than previously. Strain analysis undertaken by the WHO Collaborating Centre indicated a good antigenic match between the 2011 vaccine and circulating strains.

The Victorian influenza surveillance system continues to provide a reliable, consistent system for monitoring the epidemiology of ILI and laboratory confirmed influenza in Victoria.

Background

A sentinel general practice (GP) program for the surveillance of influenza-like illness (ILI) has been coordinated by the Victorian Infectious Diseases Reference Laboratory (VIDRL) in partnership with the Victorian Government Department of Health (DH) since 1993. Laboratory testing of a sample of ILI cases from the surveillance program commenced in 1998.[1] The program operates between May and October each year and is approved for continuing professional development points by the Royal Australian College of General Practitioners and the Australian College of Rural and Remote Medicine. VIDRL also monitors diagnoses of ILI made by the locum medical practitioners through the Melbourne Medical Deputising Service (MMDS). The DH coordinates the surveillance of all laboratory confirmed influenza in Victoria, a prescribed Group B notifiable disease under the Victorian *Public Health and Wellbeing Act 2008* and Public Health and Wellbeing Regulations 2009 for which notification is required within five days of diagnosis.

The objectives of the influenza surveillance system are to:

- monitor the epidemiology of laboratory confirmed influenza in Victoria;
- identify the onset, duration and relative severity of annual influenza seasons in Victoria;
- provide samples for the characterisation of circulating influenza strains in the community to assist in the evaluation of the current season; and formulation of the following season's vaccine;
- provide potential for early recognition of new influenza viruses and new or emerging respiratory diseases; and
- estimate influenza vaccine effectiveness each year.

In this paper we summarise findings from the Victorian influenza surveillance system in 2011.

Methods

General practice sentinel surveillance

In 2011, 94 GPs (65 from 23 metropolitan practices and 29 from 13 rural practices) participated in the VIDRL GP Sentinel Surveillance (GPSS) program (Figures 1a and 1b). The GPSS program for 2011 operated from 2 May to 30 October (weeks 18–43) inclusive in which participating GPs reported total number of consultations per week and age, sex and vaccination status of any patients presenting with influenza like illness (ILI). GPs

Figure 1a: Distribution of sentinel surveillance practices in metropolitan Victoria, 2011

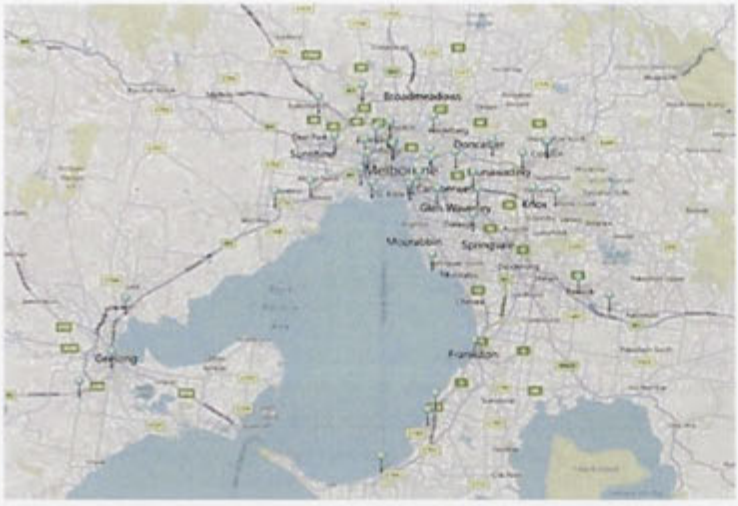
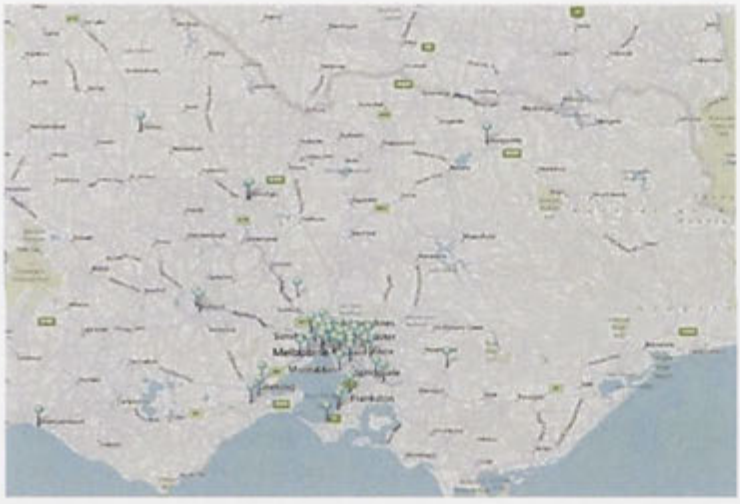


Figure 1b: Distribution of sentinel surveillance practices in rural Victoria, 2011



submitted the data weekly by fax or online submission (http://www.victorianflusurveillance.com.au). A case of ILI was defined as fever, cough and fatigue/malaise.[2] ILI rates were calculated as the number of ILI patients per 1,000 consultations and compared to previously established activity thresholds for Victorian influenza seasons.[3]

GPs were requested to collect either a nose or throat swab from patients presenting within four days of the onset of symptoms, chosen at the discretion of the GP. Data collected on swabbed patients included: age, sex, symptoms (fever; cough; fatigue; myalgia; other), vaccination status (for 2011 and the previous 2010 vaccine), date of vaccination/s and the presence of a co-morbidity for which influenza vaccination is recommended.[4]

RNA was extracted from clinical specimens and in-house validated real-time multiplex PCR assays were used to detect type A influenza viruses (matrix gene), type B influenza viruses (nucleoprotein gene) and type C influenza viruses (matrix gene). Influenza A virus-positive samples were sub-typed using individual real-time PCR assays incorporating primers and probes specific for the haemagglutinin gene of A(H1N1)pdm09,[5] pre-pandemic A(H1N1) and A(H3N2) strains.

Melbourne medical deputising service

The MMDS is the largest medical locum service in Australia and has contributed to the Victorian influenza surveillance system since 2003. The MMDS provides a 24-hour medical service to patients in their own home or aged care facility in the Melbourne metropolitan area and Geelong. Weekly rates of influenza-related diagnoses by MMDS clinicians per 1,000 consultations were calculated from records returned from the MMDS clinical database using the search terms 'influenza' and 'flu'. To avoid inclusion of those immunised prophylactically, records that contained the terms 'Fluvax', 'at risk' and 'immunisation' were excluded from the rate calculation.

Notified laboratory confirmed influenza

Records of all laboratory confirmed influenza cases with a 2011 notification date were extracted from the department's Notifiable Infectious Diseases Surveillance database on 24 February 2012. For the purposes of analysis, 'routinely notified cases' were those identified by clinical presentation, and excluded those

identified from outbreak investigations and the GPSS.

Data from the three surveillance programs were analysed descriptively using Microsoft Excel software. The chi squared test was used to compare proportions in Stata version 10.0 statistical software, with $p<0.05$ considered statistically significant.

Strain typing

A selection of specimens and isolates collected in Victoria during 2011 were referred to the WHO Collaborating Centre for Reference and Research on Influenza (WHO Collaborating Centre). Tissue culture was attempted for all of the specimens/isolates received. Viruses that were successfully cultured were analysed by a haemagglutination inhibition assay to determine antigenic similarity to the current vaccine strains and a neuraminidase inhibition assay to determine susceptibility to the antiviral drugs oseltamivir and zanamivir. The haemagglutinin and neuraminidase genes of a selection of specimens and isolates were genetically analysed by Sanger sequencing or pyrosequencing.

Results

General practice sentinel surveillance

For the 26 week surveillance period, an average of 94 per cent (88/94) of GPs submitted tally sheets to VIDRL. GPs reported having conducted 194,469 consultations (135,593 metropolitan and 58,876 rural) and identified 945 ILI cases (769 metropolitan and 176 rural), corresponding to metropolitan and rural rates across the surveillance period of 5.7 and 3.0 ILI cases per 1,000 consultations respectively.

Among the 945 ILI cases reported by GPs, 50 per cent were in females, 47 per cent in males and the remainder unknown. The median age was 28 years (range one to 88 years). Fourteen per cent of ILI cases were reported as vaccinated in 2011.

ILI rates during the 2011 season generally fell within the range of normal seasonal activity, and were low compared to previous years (Figure 2). The overall (metropolitan and rural) ILI rate rose above baseline levels of 2.5 ILI per 1,000 consultations in week 19 (week commencing 9 May), and declined to baseline levels by week 41 (week commencing 10 October). ILI activity peaked at 10.5 ILI per 1,000 consultations in week 32 (week commencing 8 August) in metropolitan practices and at 6.2 ILI per 1,000 consultations in week 35 (week commencing 29 August) in rural practices (Figure 3).

GPs swabbed a total of 670 (71 per cent) ILI patients in 2011, of which 185 (28 per cent) tested positive to influenza. Of these, 102 (55 per cent) were type A, 82 (44 per cent) were type B and one was type C. Of the 102 type A influenza viruses detected, 26 (25 per cent) were A(H1N1)pdm09, 62 (61 per cent) were A(H3N2) and the remaining 14 (14 per cent) were not further sub-typed (Table 1).

Among the influenza positive patients, 164 (86 per cent) were reported as not vaccinated (Table 1). Twenty-five patients (four influenza positive and 21 influenza negative) had an unknown vaccination status. Overall, 14 per cent (92/645) of swabbed patients were vaccinated but significantly more influenza negative patients were

Figure 2: General Practice Sentinel Surveillance and Melbourne Medical Deputising Service influenza-like illness consultation rates, Victoria, 2003–2011

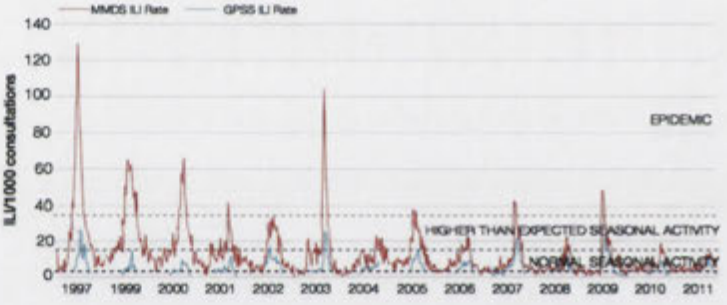


Figure 3: General Practice Sentinel Surveillance and Melbourne Medical Deputising Service influenza-like illness rates and routinely notified laboratory confirmed influenza cases by week, Victoria, 2011

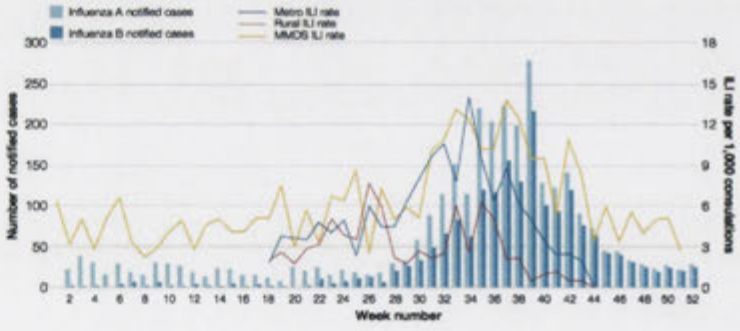


Table 1: Number (%) of General Practice Sentinel Surveillance swabs and routinely notified cases by influenza type/ subtype, vaccination status, co-morbidity and median age, Victoria, 2011

	GPSS				Routinely notified cases	
	Total swabs	Vaccinated (%)	Co-morbidity (%)	Median age	Total (%)	Median age
Influenza A						
A(H1N1)pdm09	26	0 (0)	1 (4)	32	213	33
A(H3N2)	62	6 (10)	7 (11)	27	15	44
Untyped	14	3 (21)	0 (0)		2,080	
Total influenza A	102	9 (9)	8 8)			
Influenza B	82	7 (9)	7 (9)	14	787	20
Influenza A and B co-infection					34	
Influenza C	1	1 (100)	0 (0)	NA	2	
Negative	485	75 (15)	56 (12)	30		
Grand total	**670**	**92 (14)**	**71 (11)**	**29**	**3,007**	

Figure 4a: Routinely notified cases of laboratory confirmed influenza by age group, Victoria, 2011

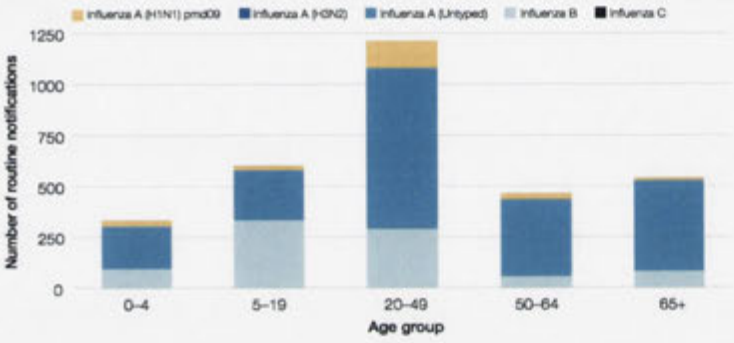
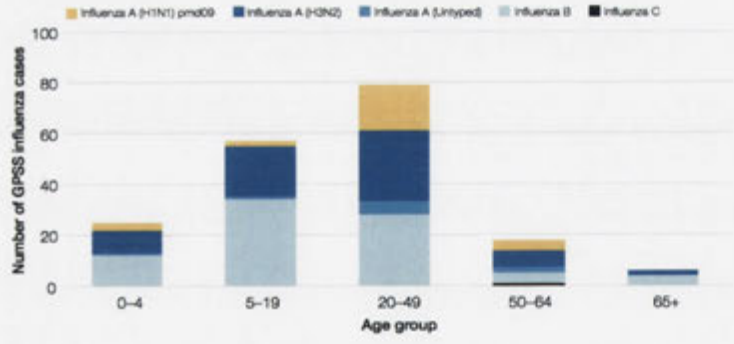


Figure 4b: GPSS cases of laboratory confirmed influenza by age group, Victoria, 2011



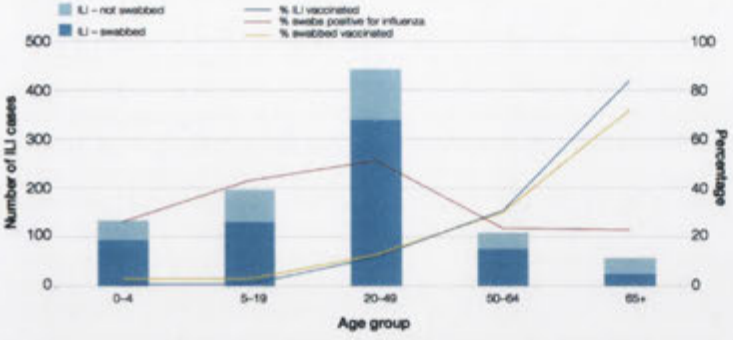
vaccinated (15 per cent) than influenza positive patients (nine per cent; p=0.01). There was no significant difference in the proportion of patients with a co-morbidity recommended for influenza vaccination between those that were positive for influenza (eight per cent) and those that were negative (12 per cent; p=0.10).

The median age of influenza A(H1N1) pdm09 cases detected from the GPSS was 32 years (range: 1–55 years), compared to 27 years for A(H3N2) (range: 1–72 years) and 14 years for type B influenza (range: 1–74 years). The one influenza C case was aged 51 years. Forty-three percent of GPSS influenza positive patients were in the 20–49 year age group (Figure 4). Fifty-six percent of influenza type B cases were younger than 20 years while 67 per cent of A(H1N1) pdm09 cases were in the 20–49 years age group. There was no statistically significant difference in the proportion of ILI patients that were swabbed across age groups (p=0.23) (Figure 5). The proportion of patients that were vaccinated increased with age, particularly those aged 65 years and older, while the proportion positive for influenza was highest in the 20–49 years age group.

Notified laboratory confirmed influenza

There were 3,007 routinely notified cases of influenza made to the department in 2011. Of these, 2,184 (73 per cent) were type A, 787 (26 per cent) were type B, 34 (1 per cent) were type A and B co-infections, and two were type C influenza (Table 1). The number of cases, particularly influenza A, increased from week

Figure 5: General Practice Sentinel Surveillance ILI and swabs by age group, vaccination status and percent positive, Victoria, 2011



28 (week commencing 18 July) in a pattern that was generally consistent with GPSS and MMDS ILI rates (Figure 3). Notified cases of both type A and type B influenza peaked in week 39 (week commencing 19 September), two weeks and four weeks after the peaks in the MMDS and the GPSS ILI rates respectively.

Of the 2,184 type A cases, 213 (10 per cent) were A(H1N1)pdm09, 15 (<1 per cent) were A(H3N2), and 2,080 (95 per cent) were untyped. The median age of routinely notified influenza A(H1N1)pdm09 cases was 33 years (range: 0–88 years), 44 years for A(H3N2) (range: 3–90 years) and 20 years for type B cases (range: 0–90 years) (Table 1). Fifty-five per cent of notified influenza A(H1N1) pdm09 cases were in the 20–49 years age group (55 per cent) (Figure 4). Females comprised 53 per cent of the routinely notified cases in 2011.

Seven cases were reported to have died as a result of their influenza infection in 2011. These cases were aged 24 to 85 years with a median of 63 years. With the exception of one case, all were due to type A infection, of which three were further subtyped: two as A(H1N1)pdm09 and one as A(H3N2). One death was due to type B.

Outbreak investigations

In 2011, a total of 25 respiratory outbreaks were notified to the department, of which 13 were confirmed as caused by influenza. Of these, one was in a prison setting, and 12 (one type B and 11 type A, of which two were subtyped as A(H3N2) and one as A(H1N1) pdm09) were in aged care facilities. The first outbreak occurred in week 3 (week commencing 17 January). The remainder of the outbreaks were notified between early August and early November, with five outbreaks notified in September.

Melbourne medical deputising service

A total of 757 patients had a recorded "flu" or "influenza" diagnosis by the MMDS during the 2011 surveillance season, corresponding to 0.6 per cent of all consultations. ILI activity rose sharply in week 31 (week commencing 18 July) and peaked in week 36 (week commencing 5 September) with 13.8 ILI per 1,000 consultations, two weeks after the peak of the GPSS ILI rate (Figure 3). Like the GPSS, the peak ILI rate from the MMDS was low compared to previous seasons (Figure 2). The peak occurred in week 36 (week commencing 5 September).

Strain typing

Of the 771 specimens and four isolates received at the WHO Collaborating Centre, 388 (50 per cent) yielded an influenza positive isolate following cell culture. Of these, 243 (63 per cent) were type A and 145 (37 per cent) were type B. Of the influenza A viruses, 89 were A(H1N1)pdm09 (A/California/7/09) strains and 154 were A(H3N2) viruses. Eighty-eight (98 per cent) of the A(H1N1) viruses were antigenically similar to the 2011 vaccine strain A/California/7/2009, while 135 (88 per cent) of the A(H3N2) strain viruses were similar to the 2011 vaccine strain A/Perth/16/2009. All influenza type B strains except one were of the B/Victoria/2/87 lineage, with 130 (90 per cent) being similar to the 2011 vaccine strain B/Brisbane/60/2008. One type B virus was from the B/Yamagata/16/88 lineage. All of the Victorian influenza positive isolates were tested for susceptibility to the neuraminidase inhibitors oseltamivir and zanamivir. One of the 89 A(H1N1)pdm09 viruses tested (one per cent) was found to be oseltamivir resistant due to a H275Y mutation in the neuraminidase gene. It is unknown if this patient was being treated with oseltamivir prior to specimen collection. None of the A(H3N2) or B viruses were resistant to oseltamivir or zanamivir.

Discussion

The 2011 influenza season in Victoria, as measured by ILI from both the MMDS and GPSS, was mild compared to previous seasons. The season overall was not dominated by any type or subtype of influenza, although type A cases tended to be more common earlier in the season and type B in the latter part. There were no detections of pre-pandemic H1N1 influenza strains, confirming

that influenza A(H1N1)pdm09 is now the seasonal influenza A(H1N1) strain. There were 13 laboratory confirmed influenza outbreaks in 2011, nearly all of which were in aged care facilities, and although this represents a considerable increase on the six reported in 2010[6] it may be indicative of the re-emergence of influenza A(H3N2) which is generally associated with older age groups.[7]

In 2011 the proportion of GPSS ILI cases that were swabbed was 71 per cent, similar to 2010 (70 per cent)[6] and 2009 (68 per cent) but significantly higher than from 2003 to 2008 in which 35–50 per cent of ILI patients were swabbed ($p<0.001$).[8] This suggests higher awareness and/or concern regarding influenza and an increase in the ease of testing since the 2009 pandemic. However, only 28 per cent of tests were positive for influenza, which was low compared to the previous years 2006 to 2010 in which the median proportion positive was 35 per cent (range: 28–45 per cent) ($p<0.001$).

The proportion of total ILI cases that were vaccinated was 14 per cent in 2011, significantly lower than the average of the years 2006–2010 (18 per cent, $p<0.001$).[6,9-11] Similarly, 14 per cent of swabbed ILI cases in 2011 were vaccinated, significantly lower than the average of the previous five years 2006–2010 (19 per cent, $p<0.001$). This suggests that while patients are being tested more, fewer are being vaccinated.

As indicated by the median ages and age distributions for both GPSS laboratory confirmed influenza and routine notifications, type B influenza cases were generally younger than type A(H3N2) cases, consistent with the typically observed age distributions for these influenza types.[7] The median age of A(H1N1)pdm09 has risen from 20 years in 2009, 26 (GPSS) and 21 (routine notifications) in 2010 to 32 (GPSS) and 33 (routine notifications) in 2011. This increase in age was also observed in the United Kingdom Severe Influenza Surveillance System where the median age of A(H1N1)pdm09 increased from 20 years in 2009 to 35 years in 2010.[12] Such a shift in the median age of cases is not unexpected following the emergence of a pandemic influenza strain in which higher attack rates in younger age groups that have no prior immunity are observed during the initial outbreak, followed by a shift to older age groups as immunity increases in the young.[13,14]

The trivalent influenza vaccine for the 2011 southern hemisphere season contained California/7/2009 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus and B/Brisbane/60/2008-like virus. Strain analysis undertaken by the WHO Collaborating Centre indicated a good antigenic match between the 2011 vaccine and circulating strains, with 88 per cent of the A(H1N1) viruses matching the vaccine strain A/California/7/2009, 88 per cent of the A(H3N2) viruses matching the vaccine strain A/Perth/16/2009 and 90 per cent of type B viruses similar to the B/Brisbane/60/2008 strain in the vaccine. We have previously shown that type- and subtype-stratified adjusted vaccine effectiveness estimates (A(H1N1)pdm09: 78 per cent; A(H3N2): 58 per cent; B: 53 per cent) were broadly consistent with a good match between vaccine and circulating strains.[15]

In previous years the ILI rate as measured by the MMDS has generally peaked prior to that of the GPSS, followed several weeks later by a peak in routine notifications. However in 2011 GPSS ILI rates peaked two weeks prior to that of the MMDS. The reasons for this are unclear, but may be an artefact of a season with low or mild ILI activity in which a peak is less well defined and exacerbated by the non-specific ILI case definition. Routine notifications, given the time taken for testing and the notification to be made to the department peaked the latest. The age distribution of laboratory confirmed influenza was consistent with previous years, with a majority of those from the GPSS comprised of working age adults, while there was a higher proportion of elderly among the cases routinely notified to the department, likely to be a reflection of hospitalised influenza patients.

The Victorian influenza surveillance system continues to provide a reliable, consistent system for monitoring the epidemiology of ILI and laboratory confirmed influenza in Victoria.

Victorian influenza surveillance system reports are available at **https://www.victorianflusurveillance.com.au/**

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Surveillance Report

Epidemiology of the 2012 influenza season in Victoria, Australia

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Objective: To assess the magnitude and severity of the 2012 influenza season in Victoria, Australia using surveillance data from five sources.

Methods: Data from influenza notifications, sentinel general practices, a sentinel hospital network, a sentinel locum service and strain typing databases for 2012 were descriptively analysed.

Results: Influenza and influenza-like illness activity was moderate compared to previous years, although a considerable increase in notified laboratory-confirmed influenza was observed. Type A influenza comprised between 83% and 87% of cases from the general practitioners, hospitals and notifiable surveillance data. Influenza A/H3 was dominant in July and August, and most tested isolates were antigenically similar to the A/Perth/16/2009 virus used in the vaccine. There was a smaller peak of influenza type B in September. No tested viruses were resistant to any neuraminidase inhibitor antivirals. Higher proportions of type A/H3, hospitalized cases and those with a comorbid condition indicated for influenza vaccination were aged 65 years or older. Influenza vaccination coverage among influenza-like illness patients was 24% in sentinel general practices and 50% in hospitals.

Discussion: The 2012 influenza season in Victoria was average compared to previous years, with an increased dominance of A/H3 accompanied by increases in older and hospitalized cases. Differences in magnitude and the epidemiological profile of cases detected by the different data sources demonstrate the importance of using a range of surveillance data to assess the relative severity of influenza seasons.

Victoria is Australia's southernmost mainland state with a population of approximately 5.5 million and a median age of 37.3 years.[1] It has a temperate climate and an influenza season that usually occurs between May and October. The Victorian influenza surveillance system consists of several surveillance data sources used to monitor seasonal influenza and influenza-like illness (ILI) activity in Victoria: notified laboratory-confirmed influenza, sentinel general practices and hospitals, a sentinel metropolitan locum service and reference laboratory typing.

Medical practitioners and laboratory personnel are required by state law to notify the Department of Health of all laboratory-confirmed cases of influenza within five days of diagnosis. Identification, demographic and diagnostic data must also accompany the notification.

The Victorian General Practice Sentinel Surveillance (GPSS) programme provides reports on ILI by sentinel general practitioners (GPs) from May to October each year. A subset of these ILI cases is swabbed for laboratory testing for influenza.[2] The Influenza Complications Alert Network (FluCAN) is a real-time sentinel hospital surveillance system for acute respiratory disease and collects surveillance data on hospitalised adults with laboratory-confirmed influenza.

The Melbourne Medical Deputising Service (MMDS) is the largest medical locum service in Australia and provides 24-hour medical services to patients at their residence in the Melbourne metropolitan area and Geelong. MMDS provides the proportion of ILI diagnoses made from all consultations.

Influenza-positive samples submitted to the World Health Organization (WHO) Collaborating Centre for Reference and Research on Influenza for strain characterization and antiviral drug sensitivity testing comprise the fifth surveillance data source.

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The objectives of the Victorian influenza surveillance system are to: monitor the epidemiology of laboratory-confirmed influenza in Victoria; identify the onset, duration and relative severity of annual influenza seasons in Victoria; provide samples for the characterization of circulating influenza strains in the community to assist in the evaluation of the current seasonal vaccine and formulation of the following season's vaccine; provide potential for early recognition of new influenza viruses and new or emerging respiratory diseases; and estimate influenza vaccine effectiveness each year.

Here we describe the epidemiology of the 2012 influenza season from the Victorian influenza surveillance system.

METHODS

Notifiable diseases surveillance (notified cases)

Records of all laboratory-confirmed influenza cases (defined as detection of influenza virus by nucleic acid testing or culture from an appropriate respiratory tract specimen) with a 2012 notification date were extracted from the Department of Health Public Health Event Surveillance System on 19 March 2013. For consistency and comparability only cases classified as "routinely notified" were used in the descriptive analyses; this excluded cases identified from outbreak investigations and GPSS but included FluCAN cases, which were unable to be separated from the data set. As this report focuses on case-based surveillance, notified institutional outbreaks were excluded.

General Practice Sentinel Surveillance programme

In 2012, 104 GPs (74 from 29 metropolitan practices and 30 from 12 rural practices) participated in GPSS, which operated from 30 April to 28 October (weeks 18 to 43) inclusive. The number of ILIs, defined as a case with fever, cough and fatigue/malaise,[3] and total consultations per week were submitted weekly by fax, e-mail or online submission. ILI rates were calculated as the number of ILI patients per 1000 consultations.

GPs collected either a nose or throat swab from a subset of patients presenting within four days of symptom onset, chosen at the discretion of the GP. Data collected on swabbed patients included: age, sex, symptoms (fever, cough, fatigue, myalgia, other), seasonal influenza vaccination status (for 2012 and the previous 2011 vaccines), date of vaccination/s and any co-morbidity for which influenza vaccination is recommended.[4]

Testing of these clinical specimens comprised extraction of ribonucleic acid and in-house validated real-time multiplex polymerase chain reaction (PCR) assays to detect type A influenza viruses (matrix gene), type B influenza viruses (nucleoprotein gene) and type C influenza viruses (matrix gene). Influenza A virus-positive samples were further subtyped using individual real-time PCR assays incorporating primers and probes specific for the haemagglutinin gene of A(H1N1)pdm09 and A(H3) strains.

Influenza Complications Alert Network

FluCAN is a hospital-based programme that collects surveillance data on hospitalized patients with laboratory-confirmed influenza in near real-time.[5] The network also aims to estimate vaccine coverage and vaccine effectiveness by comparing vaccination status in PCR-confirmed cases with a sample of test-negative controls. In Victoria, four hospitals are involved, two of which have paediatric units that collect data on hospitalized children.[6] Subtyping of influenza A virus infections is not routinely conducted in FluCAN.

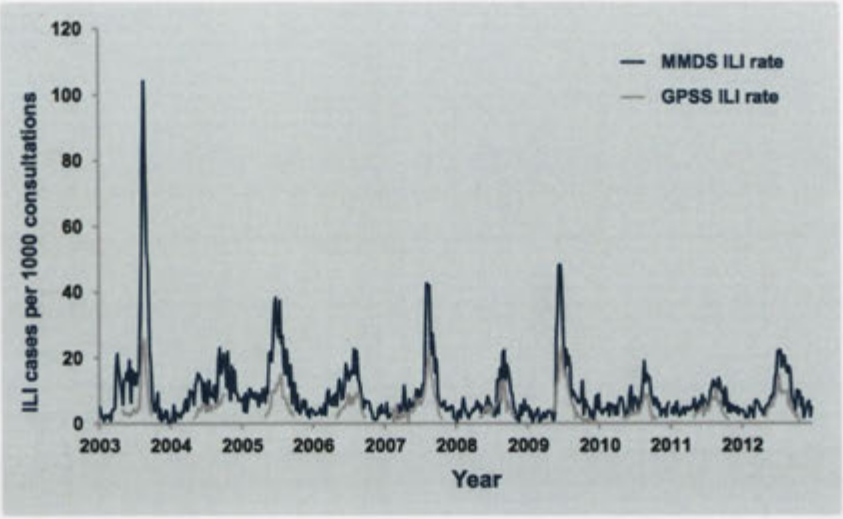
Melbourne Medical Deputising Service

Weekly rates of influenza-related diagnoses by MMDS clinicians per 1000 consultations were calculated from records returned from the MMDS clinical database using the search terms "influenza" and "flu." To avoid inclusion of those immunized prophylactically, records that contained the terms "Fluvax," "at risk" and "immunization" were excluded.

Strain characterization and antiviral resistance testing

In 2012, all influenza-positive GPSS samples tested by the Victorian Infectious Diseases Reference Laboratory (VIDRL) as well as a selection of virus specimens and isolates tested by other Victorian laboratories were forwarded to the WHO Collaborating Centre for Reference and Research on Influenza for strain characterization and antiviral drug sensitivity testing. Samples were

Figure 1. **General Practice Sentinel Surveillance (GPSS) and Melbourne Medical Deputising Service (MMDS) influenza-like illness (ILI) consultation rates, Victoria, Australia, 2003 to 2012**



first inoculated into Madin-Darby Canine Kidney cells to obtain virus isolates. Those successfully isolated were then analysed by haemagglutination inhibition assay to determine antigenic similarity to the current vaccine strains. Isolates were also tested in a neuraminidase inhibition assay to determine susceptibility to the antiviral drugs oseltamivir, zanamivir, peramivir and laninamivir.

Data analyses

Descriptive analyses of the surveillance data were conducted in Microsoft Excel. Distributions of influenza and vaccination status by type/subtype, age group and presence of a comorbid condition were compared using the chi-squared test in Stata (version 10.0; StataCorp LP, College Station, TX, USA) with $P < 0.05$ considered significant.

RESULTS

Influenza-like illness

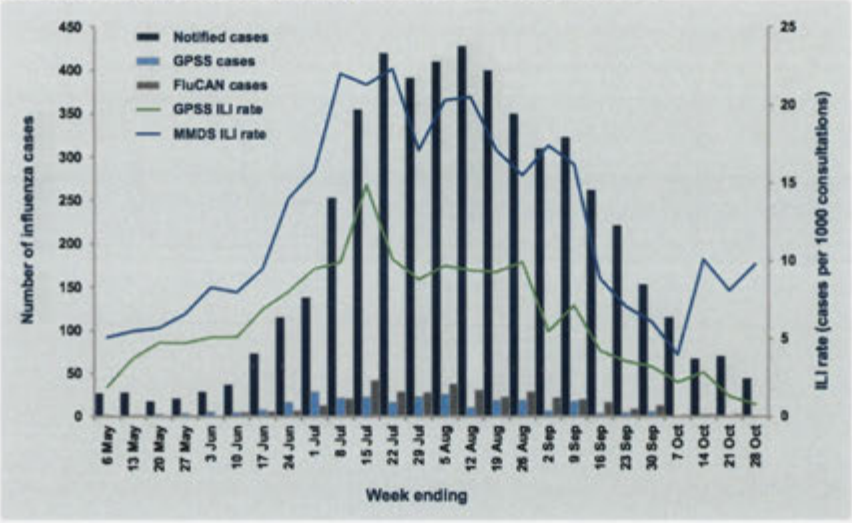
In 2012 GPPS conducted 186 375 consultations during the 26-week surveillance period, of which 1176 (six per 1000 consultations) were for patients with ILI. Consultations for ILI were significantly higher for metropolitan GPs compared to rural GPs (seven and five per 1000 consultations, respectively; $P < 0.001$). During the same period, 948 cases of ILI were diagnosed from 76 267 MMDS consultations (12 per 1000 consultations). ILI cases peaked at 14.9 and 22.3 per 1000 consultations for the GPSS and MMDS systems during the week ending 15 July and one week later, respectively; both were slightly higher than those observed in 2010 and 2011 (**Figure 1**). Elevated ILI activity was sustained in MMDS for approximately two months beginning in early July (**Figure 2**).

Laboratory-confirmed influenza

Laboratory-confirmed influenza cases were reported from three sources – notified cases (n = 5058), GPSS (n = 280) and FluCAN (n = 389) (**Table 1**). There was no clearly defined peak for notified cases in 2012, although 72% were notified in the two months between mid-July and mid-September (Figure 2). There were also no well-defined peaks for laboratory-confirmed cases of influenza from GPSS and FluCAN, although for FluCAN hospitals the highest number of cases admitted was in mid-to-late July (**Figure 2**).

Most notified cases (n = 4278; 85%) were influenza type A with subtyping reported for 223 (5%); of these, 67 (30%) were H1 and 156 (70%) were H3. H3 cases were detected throughout the peak period while H1 cases were mainly reported in July. There were also 745 cases (15%) of influenza type B notified, predominantly in the latter half of the surveillance period (**Figure 3**); 29 cases of type A and type B coinfection; and six cases of type C infections.

Figure 2. **Number of laboratory-confirmed influenza cases and influenza-like illness consultation rates by surveillance source, Victoria, Australia, 30 April to 28 October 2012**



Notified cases – cases notified to Department of Health; GPSS – General Practice Sentinel Surveillance; FluCAN – Influenza Complications Alert Network; ILI – influenza-like illness; MMDS – Melbourne Medical Deputising Service

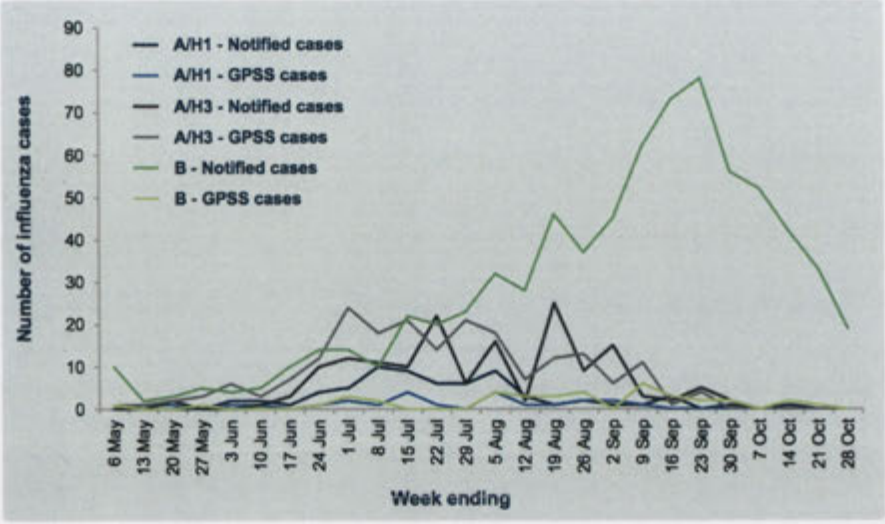
Table 1. **Laboratory-confirmed influenza cases* by surveillance source, age group and type/subtype, Victoria, Australia, 2012**

Source	Age group (years)	A/H1		A/H3		A (not subtyped)		B	
		n	%	*n*	%	*n*	%	*n*	%
Notified cases	0–4	18	27	13	8	471	12	48	6
	5–14	7	10	11	7	400	10	182	25
	15–29	14	21	21	13	543	13	149	20
	30–49	11	16	35	22	1117	28	194	26
	50–64	10	15	25	16	580	14	74	10
	≥ 65	7	10	51	33	940	23	94	13
	Not reported	–	–	–	–	4	–	4	–
	Total	**67**	**100**	**156**	**100**	**4055**	**100**	**745**	**100**
GPSS	0–4	3	13	23	11	2	22	2	5
	5–14	2	8	32	16	1	11	9	24
	15–29	5	21	28	14	3	33	11	29
	30–49	9	38	69	34	3	33	13	34
	50–64	5	21	35	17	0	0	2	5
	≥ 65	0	0	18	9	0	0	1	3
	Total	**24**	**100**	**205**	**100**	**9**	**100**	**38**	**100**
FluCAN	0–4	–	–	–	–	22	6	5	10
	5–14	–	–	–	–	7	2	4	8
	15–29	–	–	–	–	28	8	9	18
	30–49	–	–	–	–	59	17	13	26
	50–64	–	–	–	–	54	16	4	8
	≥ 65	–	–	–	–	169	50	15	30
	Total	–	–	–	–	**339**	**100**	**50**	**100**

Notified cases – cases notified to Department of Health; GPSS – General Practice Sentinel Surveillance; FluCAN – Influenza Complications Alert Network.

* Excluding 29 notified cases of type A and B coinfection and 10 cases of type C (six notified cases and four from GPSS).

Figure 3. **Number of laboratory-confirmed influenza cases by type/subtype* and surveillance source, Victoria, Australia, 30 April to 28 October 2012**



Notified cases – cases notified to Department of Health; GPSS – General Practice Sentinel Surveillance

* 4055 cases of influenza A that were not further subtyped were excluded.

Of the 1176 ILI cases identified from GPSS, 709 (60%) were swabbed and 280 (39%) were positive for influenza. The proportion of swabbed ILI cases positive for influenza ranged from 15%–25% until mid-June then quickly rose to 40%–60% until late September, and from 35% in 50–64 year-olds to 54% among those aged 5–14 years ($P = 0.06$). Of the 280 laboratory-confirmed influenza cases from GPSS, 205 (73%) were A/H3 infections, 24 (9%) were A/H1, 38 (14%) were type B and four were type C; specimens from the remaining nine influenza A cases contained insufficient virus for subtyping. Most (71%) of the type B cases were detected in August and September (**Figure 3**). The majority of the 389 FluCAN cases ($n = 339$; 87%) were type A but were not subtyped.

Sixteen notified cases were reported to have died due to influenza: one due to type B infection and the remainder type A, of which three were subtyped as H3. Twelve cases were aged 65 years or older, one was aged zero to four years, with the remaining three cases aged between five and 64 years.

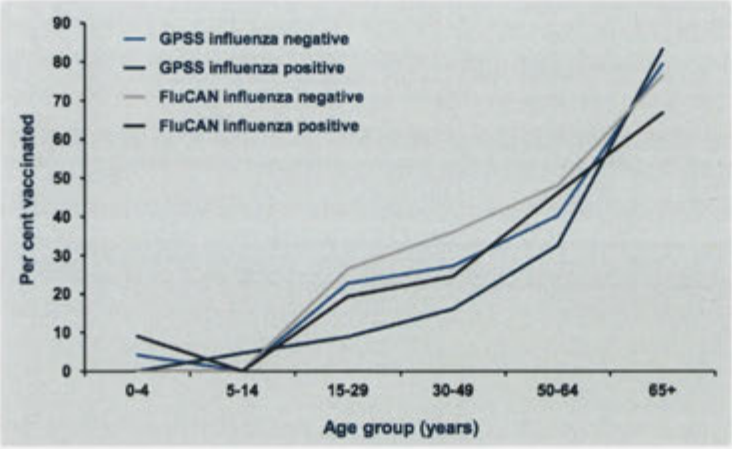
The age group with the highest proportion of laboratory-confirmed cases was those aged 30–49 years for both notified cases (27%) and GPSS (34%). There were also relatively high proportions of cases aged 65 years or older from FluCAN and notified cases (47% and 22%, respectively) but not GPSS (7%). However, the rate of notified cases was highest for those aged zero to four years and 65 years or older, with 154 and 137 notified cases per 100 000 population, respectively, compared to 61–90 per 100 000 for the other age groups.

There was a significant difference in the age distribution of notified cases by influenza type B and A subtypes (excluding influenza A cases that were not subtyped, $P < 0.001$). A higher proportion of influenza A/H1 cases were aged zero to four years, whereas for influenza A/H3 cases, a higher proportion were aged 65 years or older. There was no difference observed in GPSS ($P = 0.12$) (**Table 1**). In FluCAN, cases of influenza type A were significantly older than those with type B ($P = 0.003$).

Vaccination status

Vaccination status was recorded for 688 (97%) of 709 swabbed GPSS patients of whom 168 (24%) reported being vaccinated. FluCAN collected vaccination status from cases and influenza-negative controls and recorded vaccination status for 772 of 935 (83%) patients who had been swabbed, half of whom were

Figure 4. **Proportion of General Practice Sentinel Surveillance (GPSS) and Influenza Complications Alert Network (FluCAN) patients vaccinated* by influenza status, age group and surveillance source, Victoria, Australia, 2012**



* Includes only those patients who were swabbed and tested for influenza.

vaccinated (n = 385; 50%). There was no statistically significant difference between the proportion of influenza-positive and -negative patients with known vaccination status in either GPSS (P = 0.89) or FluCAN (P = 0.23). For both surveillance data sets the proportion of patients vaccinated increased with age (**Figure 4**). With the exception of those aged 65 years or older in GPSS, the proportion of influenza-positive patients who were vaccinated in adult age groups was lower than the proportion of influenza-negative patients who were vaccinated in each system.

Comorbidities

Data on comorbidities for which influenza vaccination is indicated were reported for 632 (89%) of the 709 swabbed patients from GPSS. The presence of a comorbid condition was reported for 111 (18%) of swabbed patients; there was no difference between influenza-positive and influenza-negative patients (17% compared with 18%; P = 0.60). However, the proportion with a reported comorbidity rose steadily with increasing age group from 3% in those aged zero to four years to 58% in the 65 years or older age group (P < 0.001). In FluCAN patients, the proportion with a reported comorbidity rose steadily with increasing age group from 31% in those aged zero to four years to 87% in the 50–64 year age group and 90% in the 65 years or older age group.

Strain characterization and antiviral resistance testing

A total of 1293 patient specimens were submitted to the WHO Collaborating Centre in 2012. Culture was attempted for 1095 of these samples, with 563 (51%) yielding an influenza virus isolate: 470 (83%) type A viruses, 92 (16%) type B viruses and one type C virus. Most of the viruses isolated were A/H3 viruses (n = 437, 93%) with most of these (82%) being antigenically similar to the A/Perth/16/2009 virus used in the seasonal influenza vaccine. A/H1 viruses comprised just 7% (n = 33), with 29 being antigenically similar to the A/California/7/2009 strain used in the vaccine; the remaining four were low reactors (haemagglutination inhibition titre ≥ 8 fold lower). Among the 92 type B viruses isolated, 54 (59%) were antigenically similar to the B/Brisbane/60/2008 (Victoria lineage) strain used in the vaccine. The remainder included 16 Victoria and 21 Yamagata lineage viruses.

Neuraminidase inhibition assays indicated that none of the 473 viruses tested was resistant to any of the antiviral drugs tested.

DISCUSSION

The magnitude of ILI activity in the 2012 influenza season in Victoria, as shown by GPSS and MMDS, was slightly higher than 2010 and 2011 but broadly average compared to the previous 10 years. Although the proportion of ILI patients identified by MMDS was higher than GPSS, both were consistent with trends observed in previous years. The number of laboratory-confirmed influenza cases from GPSS was also comparable to 2010 and 2011.[7,8] The number of patients reported through FluCAN in 2012 was considerably higher than the 146 cases reported in 2011 (the first year that all four hospitals participated in FluCAN).[9] Notified cases of laboratory-confirmed influenza increased by 68% in 2012 compared to 2011 and was also much higher than the 1914 notified cases in 2010.[7,8] This increase was disproportionate compared with that of the other data sources in the Victorian surveillance system; therefore we believe the increase in notified cases reflects an increase in testing rather than a dramatic increase in disease.[10]

Type A influenza peaked during July and August, with a much smaller peak of type B in September. Subtyping of viruses from GPSS and a subset of notified cases indicated the 2012 season was dominated by influenza A/H3, continuing the trend of seasonal dominance of A/H3 away from the emergence and almost exclusive predominance of influenza A(H1N1) pdm09 in 2009.[11] A season in which H3 is the dominant subtype followed by a smaller type B increase is a well-established pattern of influenza epidemics during the winter months of temperate zones,[12] as in Victoria in 2007,[13] New Zealand in 2012,[14] the United States of America[15] and Canada[16] during the 2012/13 northern hemisphere influenza season.

Although the type A influenza reported through FluCAN were not further characterized, it is likely that a substantial proportion were A/H3 infections, given that a high proportion of FluCAN cases were aged 65 years or older and that many cases in this age group among notified cases were A/H3. A higher median age of A/H3 cases compared to seasonal A/H1 and type B cases has recently been observed in Victoria.[17] However, the increase of H3 in older cases only partially explains the increase in all notified cases; similar proportional increases were observed across all age groups, possibly arising from increased presentation of more severe cases caused by A/H3 virus infections across all ages as well as increased testing.

The proportion of ILI patients who were swabbed in GPSS declined to 60% in 2012 from 71% in both 2010 and 2011.[7,8] As the aim of this component of GPSS is to determine what strains are circulating each season, demographic and other data are not collected on these patients. Therefore further comparison cannot be made, neither over the years nor between those that were swabbed or not. While providing flexibility to the doctors, discretionary swabbing is also a limitation of GPSS as factors that may influence a GP to differentially swab one patient over another (such as age or vaccination status) are unknown.

Vaccination coverage among patients in both GPSS and FluCAN systems increased between 2011 and 2012, possibly due to a shift in age distribution to older patients in 2012.[6,18] Higher vaccination coverage in FluCAN patients compared to GPSS in both years may be due to the older age distribution and higher prevalence of comorbid conditions indicated for influenza vaccination (groups for which influenza vaccine is provided free through the National Immunization Programme[4]) of those attending hospitals compared to general practice.

Two observations from the surveillance system suggest that the 2012 seasonal trivalent influenza vaccine (comprised of A/California/7/2009 (H1N1) pdm09-like virus, an A/Perth/16/2009 (H3N2)-like virus and a B/Brisbane/60/2008-like virus)[19] may have been moderately effective. First, the results of strain typing suggested a good antigenic match of vaccine strains – particularly the A/H1 and A/H3 subtypes – to a high proportion of Victorian isolates for which strain characterization testing was undertaken. Second, a higher proportion of swabbed patients in nearly all adult age groups of GPSS and FluCAN who were negative for influenza were vaccinated compared to those who tested positive. However, these findings should be interpreted with caution. We have previously demonstrated with Victorian data that an apparent good match of vaccine to circulating strains does not necessarily correlate with greater vaccine effectiveness.[20] It has been suggested that antibody immunity measured by haemagglutination inhibition assay may not be an optimal correlate of protection against clinical infection because it may not always detect drift in the haemagglutinin antigen.[21,22] Also, the relatively few participating institutions and

limited number of specimens forwarded for strain characterization may not necessarily be representative of all virus/es circulating in the community. The calculation of influenza vaccine effectiveness from surveillance data requires application of a more systematic methodology,[18,23] which will be reported separately.

The inclusion of hospitalized cases from FluCAN augmented the Victorian influenza surveillance system in 2012 by including cases at the severe end of the clinical spectrum. However, while FluCAN cases were reported independently, they were also included in the notified cases data set. While community surveillance suggested a relatively benign influenza season, hospital data indicated an increase in severe disease among older people, presumably associated with A/H3. This demonstrates the importance of using a range of surveillance data sources. Efforts are continuing to improve the quality and breadth of integrated influenza surveillance in Victoria by subtyping a higher proportion of type A influenza infections (especially those identified through FluCAN) and examining the feasibility of establishing ILI and influenza surveillance in hospital emergency departments.

Conflicts of interest

None declared.

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Chapter 7

Influenza vaccine effectiveness

About this chapter

The papers in this chapter used influenza laboratory testing data from a general practitioner sentinel surveillance program in a case test-negative study design to estimate influenza vaccine effectiveness (VE) against medically attended laboratory confirmed influenza. Effectiveness was calculated for annual seasonal trivalent influenza vaccines from 2007 to 2011 inclusive and monovalent pandemic (H1N1) vaccine in 2010, and published in *BMC Infectious Diseases, Vaccine, Emerging Infectious Diseases* and *Eurosurveillance.*

Overall seasonal influenza VE varied from a low of 3% in 2009 to 79% in 2010, reflecting the sudden emergence of influenza A(H1N1)pdm09 in 2009 and its establishment as the dominant strain in 2010. The monovalent pandemic (H1N1) vaccine had a considerably lower effectiveness of 47%. There was also considerable variation in type- and subtype-specific estimates of VE that could not necessarily be reconciled by whether or not vaccine and circulating strains were matched. Insufficient study power compromised the ability to generate more precise estimates for some stratified analyses, particularly by age group.

Papers in this chapter

1. **Fielding JE**, Grant KA, Papadakis G, Kelly HA. Estimation of type- and subtype-specific influenza vaccine effectiveness in Victoria, Australia using a test negative case control method, 2007–2008. *BMC Infect Dis* 2011; 17: 170.
2. Kelly HA, Grant KA, **Fielding JE**, Carville KS, Looker CO, Tran T, Jacoby P. Pandemic influenza H1N1 2009 infection in Victoria, Australia: No evidence for harm or benefit following receipt of seasonal influenza vaccine in 2009. *Vaccine* 2011; 29: 6419-6426.
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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Estimation of type- and subtype-specific influenza vaccine effectiveness in Victoria, Australia using a test negative case control method, 2007-2008

James E Fielding[1,2*], Kristina A Grant[1], Georgina Papadakis[1] and Heath A Kelly[1]

Abstract

Background: Antigenic variation of influenza virus necessitates annual reformulation of seasonal influenza vaccines, which contain two type A strains (H1N1 and H3N2) and one type B strain. We used a test negative case control design to estimate influenza vaccine effectiveness (VE) against influenza by type and subtype over two consecutive seasons in Victoria, Australia.

Methods: Patients presenting with influenza-like illness to general practitioners (GPs) in a sentinel surveillance network during 2007 and 2008 were tested for influenza. Cases tested positive for influenza by polymerase chain reaction and controls tested negative for influenza. Vaccination status was recorded by sentinel GPs. Vaccine effectiveness was calculated as [(1 - adjusted odds ratio) × 100%].

Results: There were 386 eligible study participants in 2007 of whom 50% were influenza positive and 19% were vaccinated. In 2008 there were 330 eligible study participants of whom 32% were influenza positive and 17% were vaccinated. Adjusted VE against A/H3N2 influenza in 2007 was 68% (95% CI, 32 to 85%) but VE against A/H1N1 (27%; 95% CI, -92 to 72%) and B (84%; 95% CI, -2 to 98%) were not statistically significant. In 2008, the adjusted VE estimate was positive against type B influenza (49%) but negative for A/H1N1 (-88%) and A/H3N2 (-66%); none was statistically significant.

Conclusions: Type- and subtype-specific assessment of influenza VE is needed to identify variations that cannot be differentiated from a measure of VE against all influenza. Type- and subtype-specific influenza VE estimates in Victoria in 2007 and 2008 were generally consistent with strain circulation data.

Background

Vaccination is the cornerstone of influenza morbidity and mortality prevention and many countries have implemented publicly funded influenza vaccination programs for nationally defined high-risk groups [1]. As part of its National Immunisation Program, in 2007 and 2008 the Australian Government provided free influenza vaccination to all Australians aged 65 years and over, and all Aboriginal and Torres Strait Islander people aged 50 years and over or aged 15-49 years with medical risk factors [2]. Influenza vaccination was also recommended, but not funded, for: individuals aged six months or older with conditions predisposing to severe influenza, people who may potentially transmit influenza to those at high risk of complications from influenza, people providing essential services and travellers. Individual industries are also advised to consider the benefits of offering influenza vaccine in the workplace.

Only split virus and subunit trivalent inactivated influenza vaccines are available for use in Australia against two type A strains (one of each subtype H1N1 and H3N2) and one type B strain which are frequently replaced due to antigenic drift of circulating viruses [2,3]. The World Health Organization (WHO) conducts biannual consultations to recommend which influenza virus strains should be included in the influenza vaccine for the following northern and southern hemisphere seasons [4]. The influenza virus compositions of the 2007 season vaccine were: A/New Caledonia/20/99 (H1N1)-like virus; A/Wisconsin/67/2005(H3N2)-like

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virus; and B/Malaysia/2506/2004-like virus (of the B/Victoria/2/87 lineage) [5] and in 2008 were: A/Solomon Islands/3/2006 (H1N1)-like virus; A/Brisbane/10/2007 (H3N2)-like virus; and B/Florida/4/2006-like virus (of the B/Yamagata/16/88 lineage) [6].

Regular evaluation of vaccination programs by assessment of effectiveness of vaccine to prevent disease is important, particularly for influenza where vaccines often change seasonally. Whilst clinical trials are the ideal method for establishing vaccine efficacy, properly designed observational studies provide a reliable and more practical means of calculating vaccine effectiveness (VE) under field conditions [7,8].

Victoria is Australia's second most populous state with a temperate climate and an annual influenza season that usually occurs between May and September. Here we describe assessment of the effectiveness of seasonal influenza vaccine against laboratory confirmed influenza infection over two consecutive influenza seasons (2007 and 2008) using a test negative case control study design applied to a general practitioner (GP) sentinel surveillance network. We have previously applied this method to assess seasonal influenza VE against any laboratory confirmed influenza [9] but here estimate the type- and subtype-specific protection given by each seasonal influenza vaccine. To our knowledge type and subtype VE estimates have not previously been conducted for a southern hemisphere season.

Methods

Sentinel surveillance

A sentinel general practice surveillance program for influenza-like illness (ILI) and laboratory confirmed influenza has been conducted in Victoria by the Victorian Infectious Diseases Reference Laboratory (VIDRL) and the Victorian Government Department of Health since 1998. The program is comprised of a network of GPs throughout Victoria who receive continuing professional development points from the Royal Australian College of General Practitioners and the Australian College of Rural and Remote Medicine for their participation. Each week during the influenza season, GPs report cases of ILI as a proportion of total patients seen. Consistent with established criteria, ILI was defined as history of fever, cough and fatigue/malaise [10]. The GPs were also asked to collect a nose and throat swab from patients presenting with ILI within four days of symptoms onset and forward to VIDRL for testing. Additional data on the patient's age, sex, date of symptom(s) onset, whether vaccinated and date of vaccination were collected on the test request form. In 2007, 50 GPs participated in the sentinel surveillance program which operated for 34 weeks from 12 March (week 11) to 4 November (week 44) inclusive. There were 67 GPs in the 2008 program which operated for 31 weeks from 14 April (week 16) to 16 November (week 46). The program commenced earlier in 2007 to accommodate a pilot varicella-zoster virus infection sentinel surveillance program and finished later in 2008 to enable full capture of ILI patients from a late season commencement.

Laboratory testing

All nose and throat swab samples were collected using Copan dry swabs placed into virus transport medium. Samples were tested by multiplex polymerase chain reaction (PCR) for influenza A, influenza B, respiratory syncytial virus, picornavirus, parainfluenza virus and adenovirus using a conventional gel based assay [11]. A conserved portion of the matrix gene and haemagglutinin gene were targeted to identify influenza type A and type B viruses respectively, with specific primers for influenza A haemagglutinin H1 and H3 genes used to determine subtype. Specimens were forwarded to the WHO Collaborating Centre for Reference and Research on Influenza for strain typing.

Ascertainment of cases and controls

Cases and controls were sampled prospectively throughout the study period. A person with ILI who tested positive for influenza was classified as a case whilst a patient with a negative test result, or who was positive for another respiratory virus, was classified as a control. A person selected as a control could become a case for a subsequent separate clinical presentation during the season, but not vice versa. Patients were excluded from the VE analysis if testing did not produce a result.

Data analysis and calculation of VE

Analyses were conducted using Stata (version 10.0; StataCorp LP). The chi squared test was used to compare proportions, with $p < 0.05$ considered statistically significant. Patients were excluded from the VE analysis if vaccination status was unknown, if the date of symptom(s) onset was unknown or if there was an interval of greater than four days between symptom onset and specimen collection, based on the decreased likelihood of a positive result after this time [12,13]. For the purposes of analysis, patients were considered not vaccinated if there was less than 14 days between the dates of vaccination and symptom onset.

Vaccine effectiveness was defined as [(1 - odds ratio) × 100%] where the odds ratio is the odds of laboratory confirmed cases being vaccinated divided by the odds of test negative controls being vaccinated. In the test-negative case control design, the odds ratio estimates the incidence density (rate) ratio because controls are selected longitudinally throughout the course of the study (i.e. by 'density sampling') [14,15]. The odds ratio

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in test-negative case control studies has also been shown to approximate the risk ratio under conditions of varying attack rates and test sensitivity and specificity [16]. Logistic regression was used to calculate odds ratios and 95% confidence intervals (CI) that were adjusted for the confounding variables of age (stratified into the age groups 0-4 years, 5-19 years, 20-49 years, 50-64 years and 65 years and over) and month of specimen collection. Sensitivity analyses were also conducted to determine the effect on VE estimates of: 1) not excluding study participants if more than four days had elapsed between symptom onset and specimen collection; 2) excluding those vaccinated within 14 days of symptoms onset and 3) classifying those vaccinated within 14 days of symptoms onset as vaccinated.

Ethical considerations

Data in this study were collected, used and reported under the legislative authorisation of the Victorian Health (Infectious Diseases) Regulations 2001 and thus did not require Human Research Ethics Committee approval.

Results

General practitioners in the sentinel surveillance network saw a total of 182,984 patients during the study period in 2007, of which 1,226 (0.7%) had a reported ILI. The ILI rate peaked in weeks 33 and 34 between 2.0% and 2.2% from a nadir of 0.04% in week 18. In 2008 there were 159,030 patients seen and a total of 876 (0.6%) reported to have an ILI. The weekly rate generally climbed steadily from 0.2% at the start of the 2008 study period in week 18 to a peak of 1.3% in week 35.

General practitioners collected nose and throat swabs for testing from 480 (39%) and 407 (46%) patients with ILI in 2007 and 2008 respectively. Of these, 223 (46%) in 2007 and 117 (29%) in 2008 were positive for influenza. The 2007 season was characterised by a high proportion (58%) of type A/H3N2 influenza cases for which limited strain typing data indicated a generally even split between A/Brisbane/10/2007-like and A/Wisconsin/67/2005-like viruses with a further 17% due to type B and 22% due to A/H1N1 for which all of those typed were the A/Solomon Islands/3/2006-like strain (table 1). A majority (56%) of influenza cases in 2008 were type B with a further 36% due to type A/H3N2 although like 2007, a high proportion of specimens were unable to be recovered or typed (table 1).

Following exclusion of cases for whom vaccination status was unknown, symptom onset or specimen collection dates were unknown or more than four days had elapsed between symptom onset and specimen collection, there were 386 (80%) and 330 (81%) study participants in 2007 and 2008 respectively (table 2). In 2008, a higher proportion of influenza negative patients (17%) compared to influenza positive patients (6%) were excluded because more than four days had elapsed between symptom onset and specimen collection (p = 0.004) whereas in 2007 there was no significant difference (14% and 8%; p = 0.10). There was no statistically significant difference in whether or not study participants had a specimen collected within four days of symptoms onset by age group in either 2007 (p = 0.90) or 2008 (p = 0.09).

Table 1 Influenza positive swabs by subtype, year and strain, 2007-2008

Influenza subtype and strain	2007 (%)	2008 (%)
A/H1N1		
A/Solomon Islands/3/2006-like[b]	21 (43)	0
A/New Caledonia/20/99-like[a]	0	0
Not recovered/no result	28[e] (57)	4 (100)
Total	49 (100)	4 (100)
A/H3N2		
A/Brisbane/10/2007-like[b]	12 (9)	4 (10)
A/Wisconsin/67/2005-like[a]	10 (8)	0
Not recovered/no result	108[c] (83)	38 (90)
Total	130 (100)	42 (100)
A/subtype not specified	8	6
B		
B/Florida/4/2006-like[b]	2 (5)	1 (2)
B/Malaysia/2506/2004-like[a]	3[c] (8)	1 (2)
B/Shanghai/361/2002-like	2[d] (5)	0
Not recovered/no result	30 (81)	63 (97)
Total	37 (100)	65 (100)

[a] 2007 vaccine strain
[b] 2008 vaccine strain
[c] includes 1 low reactor isolate
[d] includes 2 low reactor isolates
[e] 1 case positive for A/H1N1 and A/H3N2

An epidemiological curve of influenza negative and influenza positive patients eligible for inclusion in the study (designated as controls and cases respectively) shows an earlier detection of influenza in 2007 compared to 2008, although there was only two weeks' difference in the time from which influenza positive patients were reported for more than three consecutive weeks indicating the start of each season (Figure 1). In addition to a higher number of study participants, the 2007 influenza season was longer (as defined by the number of consecutive weeks in which influenza positive cases were reported) and consisted of a higher proportion of influenza positive study participants (n = 194; 50%) compared to 2008 (n = 106; 32%). The dominant circulating influenza type and subtype varied over the two seasons: 23% of cases in 2007 were A/H1N1, 60% were A/H3N2 and the remainder were type B; the respective proportions in 2008 were 4%, 36% and 57% (table 3).

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Table 2 Study inclusion and exclusion criteria by year, 2007-2008

Criteria	2007		2008	
	Excluded	Included	Excluded	Included
Inclusion				
Respiratory swabs of ILI patients submitted by GPs	0	480	0	407
Exclusion				
Influenza result unknown	0	480	0	407
Vaccination status unknown	8	472	4	403
Symptom onset to specimen collection interval unknown	41[a]	434	22[a]	384
> 4 days between symptom onset and specimen collection	50[b]	386	54	330

[a] includes 3 patients with unknown vaccination status
[b] includes 2 patients with unknown vaccination status

Age group, sex and month of swab collection distributions for controls and cases (including type and subtype strata) are shown in table 3. There was no statistically significant difference in the sex distribution between controls and cases in either 2007 or 2008. In both years, the numbers and proportions of controls and cases were highest in the 20-49 years age group. Influenza type B cases were significantly younger than controls in 2008 ($p < 0.001$); there were no other statistically significant differences in age distribution between controls and cases. With the exception of subtype A/H1N1 in 2008 for which there were only four cases, stratification by month of swab collection revealed statistically significant differences between cases and controls (range: $p < 0.001$ to $p = 0.02$) because of the higher proportion of type A and type B cases identified in August and October 2007 respectively, and subtype A/H3N2 and type B in August/September 2008.

A similar percentage of total study participants were vaccinated in 2007 (19%) and 2008 (17%), although the difference between vaccinated controls and vaccinated cases was generally higher in 2007 (table 4). In 2008 a higher proportion of cases of subtypes A/H1N1 and A/H3N2 were vaccinated compared to controls. In both years the proportion of cases and controls that were vaccinated generally increased with age group. Among

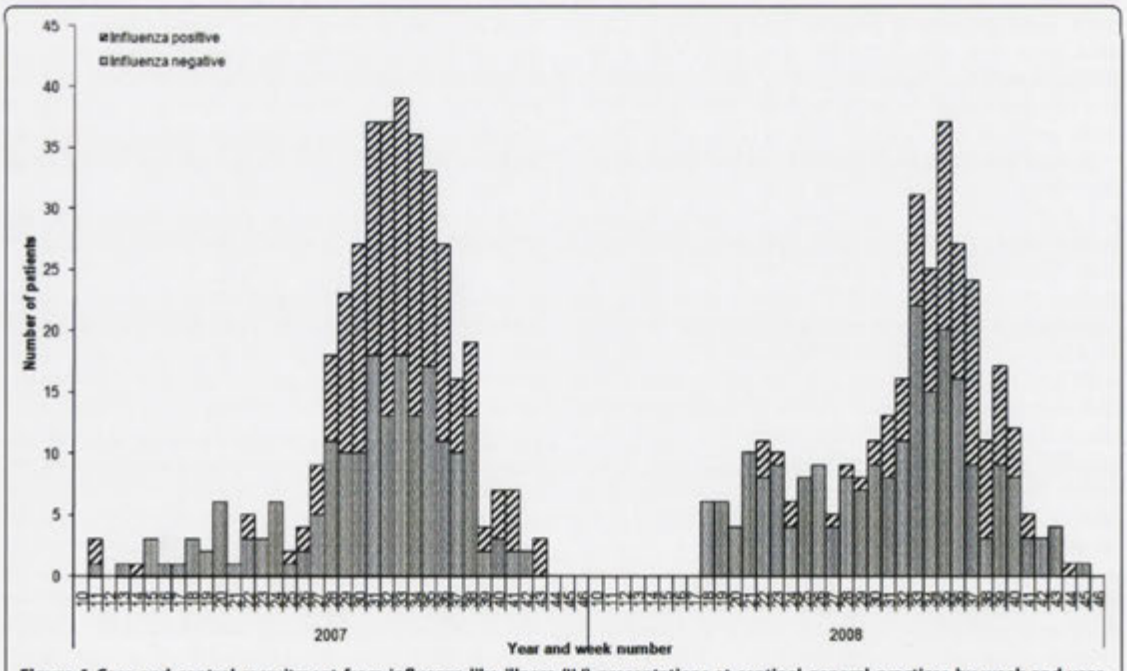

Figure 1 Case and control recruitment from influenza-like illness (ILI) presentations at sentinel general practices by week and year, 2007-2008.

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Table 3 Cases and controls by age group, sex, month of swab collection, year and type/subtype, 2007-2008

	2007					2008				
	Controls	Influenza cases (%)				Controls	Influenza cases (%)			
	(%)	All	A/H1	A/H3	B	(%)	All	A/H1	A/H3	B
Age group (years)										
0-4	7 (4)	7 (4)	3 (7)	4 (3)	0	4 (2)	5 (5)	0	1 (3)	3 (5)
5-19	22 (11)	42 (22)	12 (27)	24 (21)	6 (23)	37 (17)	28 (27)	0	6 (16)	22 (37)
20-49	126 (66)	113 (58)	25 (56)	68 (58)	17 (65)	140 (63)	57 (54)	3 (75)	18 (47)	33 (56)
50-64	28 (15)	22 (11)	4 (9)	14 (12)	2 (8)	30 (13)	11 (10)	1 (25)	9 (24)	1 (2)
≥ 65	9 (5)	10 (5)	1 (2)	7 (6)	1 (4)	13 (6)	4 (4)	0	4 (11)	0
Sex										
Female	89 (46)	96 (49)	20 (44)	62 (53)	12 (46)	105 (47)	55 (52)	1 (25)	19 (50)	34 (57)
Male	103 (54)	98 (51)	25 (56)	55 (47)	14 (54)	119 (53)	51 (48)	3 (75)	19 (50)	26 (43)
Month of swab collection										
March	2 (1)	2 (1)	0	1 (< 1)	1 (4)	0	0	0	0	0
April	5 (3)	1 (< 1)	0	1 (< 1)	0	6 (3)	0	0	0	0
May	14 (7)	1 (< 1)	1 (2)	0	0	28 (13)	3 (3)	0	0	3 (5)
June	13 (7)	4 (2)	1 (2)	3 (3)	0	33 (15)	3 (3)	0	0	3 (5)
July	48 (25)	50 (26)	10 (22)	31 (27)	7 (27)	32 (14)	9 (8)	0	3 (8)	5 (8)
August	66 (34)	94 (48)	30 (67)	56 (48)	4 (15)	69 (31)	42 (40)	4 (100)	17 (45)	21 (35)
September	37 (19)	30 (15)	3 (7)	23 (20)	4 (15)	42 (19)	43 (41)	0	14 (37)	27 (45)
October	7 (4)	12 (6)	0	2 (2)	10 (38)	13 (6)	6 (6)	0	4 (11)	1 (2)
November	0	0	0	0	0	1 (< 1)	0	0	0	0
Total	192	194	45	117	26	224	106[a]	4	38	60[a]

[a] Age unknown for one case

the study participants reported as vaccinated, only one control in each year (0.5% in 2007 and 0.4% in 2008) and no cases were vaccinated within 14 days of symptoms onset, for which there was no statistically significant difference.

Following adjustment for month of swab collection and age, there was a statistically significant protective effect of influenza vaccine against all influenza in 2007 (VE = 59%; 95% CI, 25 to 78%) (table 5). The absence of vaccinated cases and controls (table 4) meant VE was unable to be estimated for several of the five age groups so age was collapsed into three variables: children (0-19 years); working age adults (20-64 years); and the elderly (65 years or older). When stratified by age group, the

Table 4 Cases and controls by year, age group, vaccination status and type/subtype, 2007-2008

	Total study participants	Total vaccinated (%)	Controls vaccinated (%)	Influenza cases vaccinated (%)			
				All	A/H1	A/H3	B
2007							
0-4	14	0	0	0	0	0	0
5-19	64	4 (6)	1 (5)	3 (7)	2 (17)	1 (4)	0
20-49	239	35 (15)	27 (21)	8 (7)	2 (8)	6 (9)	0
50-64	50	20 (40)	13 (46)	7 (32)	2 (50)	2 (14)	1 (50)
≥ 65	19	15 (79)	8 (89)	7 (70)	1 (100)	4 (57)	1 (100)
Total	386	74 (19)	49 (26)	25 (13)	7 (16)	13 (11)	2 (8)
2008							
0-4	9	1 (11)	0	1 (20)	0	1 (100)	0
5-19	65	4 (6)	2 (5)	2 (7)	0	0	2 (9)
20-49	197	23 (12)	17 (12)	6 (11)	1 (33)	4 (22)	1 (3)
50-64	41	14 (34)	12 (40)	2 (18)	0	1 (11)	1 (100)
≥ 65	17	14 (82)	10 (77)	4 (100)	0	4 (100)	0
Total	330[a]	56 (17)	41 (18)	15 (14)	1 (25)	10 (26)	4 (7)

[a] Age unknown for one case

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Table 5 Crude and adjusted vaccine effectiveness of seasonal vaccine against influenza by year, age group and type/subtype, 2007-2008

	Influenza vaccine effectiveness (95% CI)			
	All	A/H1	A/H3	B
2007				
Crude	57 (27, 75)	46 (-28, 77)	64 (29, 81)	76 (-7, 94)
Adjusted[a]				
0-19	-98 (-1906, 80)	-333 (-5401, 66)	-7 (-1850, 94)	Not defined
20-64	64 (29, 82)	48 (-65, 84)	69 (29, 87)	85 (-19, 98)
≥ 65	74 (-283, 98)	Not defined	84 (-156, 99)	Not defined
All ages	59 (25, 78)	27 (-92, 72)	68 (32, 85)	84 (-2, 98)
2008				
Crude	26 (-40, 61)	-49 (-1367, 85)	-59 (-254, 28)	68 (7, 89)
Adjusted[a]				
0-19	-441 (-7774, 63)	Not defined	Not defined	-314 (-6713, 75)
20-64	35 (-56, 73)	-88 (-1936, 83)	-17 (-255, 62)	71 (-32, 93)
≥ 65	Not defined	Not defined	Not defined	Not defined
All ages	9 (-96, 58)	-88 (-1936, 83)	-66 (-349, 39)	49 (-58, 84)

[a] adjusted for month of swab collection

statistically significant association in 2007 was restricted to the 20-64 years age group. Furthermore, when examined by influenza type and subtype, and after adjusting for age group and month of swab collection, the vaccine was found to only be protective at a significant level against the influenza A/H3N2 subtype (VE = 68%; 95% CI, 32 to 85%), for which a statistically significant protective effect was maintained among the working age adults age group only. In 2008, only the unadjusted measure of VE against type B influenza was statistically significant. Receiving vaccine was positively associated with influenza illness for both A/H1N1 and A/H3N2 subtypes after adjustment for age and month of swab collection in 2008 but neither of these associations was statistically significant.

Sensitivity analyses were conducted to determine the possible effect of assumptions about timing of swab collection and vaccination status on the VE estimates. The effect of not excluding study participants if more than four days had elapsed between symptom onset and specimen collection was a reduction of the adjusted VE point estimates between 7% and 15% in 2007 and between 5% and 35% in 2008. Study participants who were known to be vaccinated within 14 days of symptom onset (one control each in 2007 and 2008) were classified as not vaccinated in the primary analysis. The effect of excluding these cases or classifying them as vaccinated resulted in variations of 0% to 7% around the VE point estimates, but no changes in their relative statistical significance. However, collection of the 'date of vaccination' field only commenced in 2008, in which it was completed for 86 (91%) of the 94 vaccinated study participants. In 2007, only 16 (22%) of the 73 study participants reported as vaccinated had a recorded date of vaccination.

Discussion

Although there was a low proportion of influenza cases in this study for which strain typing results were available, the statistically significant estimate of 59% effectiveness of influenza vaccine against all influenza in 2007 was generally consistent with Victorian state-wide strain typing data which indicated a partial match of circulating strains to those contained within the vaccine. These data showed A/H3N2 to be the predominant circulating subtype in 2007 (accounting for 56% of the characterised isolates) of which 42% were the A/Wisconsin/67/2005-like (vaccine) strain and the other 58% were the A/Brisbane/10/2007-like strain [17]. When stratified by subtype, the 2007 vaccine was 68% effective (95% CI, 32 to 85%) against A/H3N2 infection and although the A/Brisbane/10/2007-like strain appeared to be the most dominant A/H3N2 strain, the relatively high VE estimate is likely to be explained by the antigenic similarity between the A/Brisbane/10/2007-like and A/Wisconsin/67/2005-like strains [18]. However, stratified analysis did not indicate a significant protective effect of the vaccine against type A/H1N1 or type B infection in 2007, a finding which is supported by apparent mismatch of circulating strains to vaccine strains: 96% of the characterised A/H1N1 isolates were the (non-vaccine) A/Solomon Islands/3/2006-like strain whilst the characterised type B isolates were split between B/Florida/4/2006-like (41%), B/Shanghai/361/2002-like (35%) and B/Malaysia/2506/2004-like (24%) [18].

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With a non-significant point estimate of 9%, the adjusted effectiveness of influenza vaccine against all influenza in 2008 was considerably lower than in 2007. The 2008 influenza season in both Victoria and across Australia was of lower magnitude than 2007 and characterised by a higher proportion of cases from influenza type B virus [19,20]. This contrasts with a Western Australian study of the 2008 influenza season, which like Victoria was dominated by type B influenza virus with a late peak, that found a much higher and statistically significant VE point estimate of 58% (95% CI, 9 to 81%) against all influenza [21]. Although this study was restricted to children aged 6-59 months, for whom there is a funded vaccination program in Western Australia, the reason for such a large difference is unclear. Both the sentinel general practice surveillance and other state-wide subtyping data indicated an approximately equal predominance of type A/H3N2 and type B viruses in 2008 [20], although few cases from the sentinel surveillance were able to be strain typed. Crude analysis suggested that the vaccine was 68% effective at a statistically significant level against type B infection, although after adjustment was 49% and not significant. This finding is generally consistent with strain typing data for isolates from across Victoria in which 42% were the vaccine B/Florida/4/2006-like strain and 58% were B/Malaysia/2506/2004-like, between which there was little antigenic similarity given their different lineages (B/Yamagata/16/88 and B/Victoria/2/87 respectively) [19,20]. Strain typing of isolates sourced from elsewhere in Victoria indicated that circulating A/H3N2 was exclusively the A/Brisbane/10/2007-like strain and there was very little circulation of any A/H1N1 strains.

This study demonstrates the importance of conducting type- and subtype-specific assessment of influenza VE given the considerable variation that cannot be differentiated from a measure of VE against all influenza, despite what strain typing of circulating isolates may suggest about vaccine match/mismatch. A Canadian study that measured influenza VE at the trivalent component level during the 2006-2007 northern hemisphere season also observed wide variation between type- and subtype-specific adjusted VE point estimates from 12% to 92% [22], whilst two other observational studies in Wisconsin, United States of America (USA) and Canada also found type-specific variation of VE point estimates from -35% to 58% and 58% to 70% respectively [23,24]. However, stratification of cases to assess type- and subtype-specific influenza VE compromises power as evidenced in this and the Canadian and USA studies. Insufficient power also compromised the ability of our study to generate more precise age group-specific estimates of VE, particularly in 2008 despite the collapse of five age groups into three. This was especially evident for those aged ≥ 65 years (the main risk group eligible for vaccination) in which a protective - but not statistically significant - effect against A/H3N2 influenza was demonstrated in 2007 but had too few cases to generate any VE estimates in 2008, highlighting a previously recognised limitation that the system is best suited to estimating VE amongst working age adults who comprise the majority of the surveillance population [9]. Thus, whilst the program functions well as a representative surveillance system in assessing magnitude and duration of influenza seasons, further recruitment of sentinel GPs may be required to sufficiently power VE calculations, particularly during seasons of low magnitude or a dominant subtype.

A further limitation of this study is that the analysis has not controlled for the potential confounding effect of chronic or co-morbid conditions that are indicated for influenza vaccination. Several Canadian observational studies for which the specific confounding effect of co-morbid conditions was reported resulted in variations of the adjusted type- and subtype-specific VE estimates against seasonal influenza about the crude estimate of -23% to 7% [22,24], and an increase of 15% on the crude seasonal VE against pandemic (H1N1) 2009 influenza [25]. Whilst the confounding effect of co-existing chronic medical conditions on VE estimates may be modest and variable, these data will be included in the patient questionnaire and analysis in future seasons as a single variable. Pooling of confounders has been shown as unlikely to result in residual confounding [26].

Although clinical trials are the ideal method to assess vaccine efficacy, ethical, practical and financial considerations have lead to the emergence of observational studies - in particular case control studies such as this one - to routinely assess influenza VE [22,24,27-29]. However, inherent in observational study designs are biases that should be considered when interpreting and generalising the results to other populations. This study used test-negative control subjects which modelling, assuming no bias, has shown generally slightly underestimates the true VE under most conditions of sensitivity, specificity and influenza to non-influenza ILI attack rates [16] but was higher than traditional control subjects when assessed over three consecutive seasons [27]. Another consideration is the sampling frame of attendees of general practices, for which a high proportion are working-age adults probably representing the mid-range of the clinical spectrum of influenza. More severe presentations (particularly among children and the elderly) are more likely to present to hospitals whilst asymptomatic or mild infections, estimated to be 34% [12], will not present to any medical facility. It is difficult to speculate how exclusion of cases from the peripheries of the clinical spectrum might affect the VE estimates, but highlights the importance of interpreting

these results in the context of medically attended ILI in the general practice setting.

Ascertainment bias of influenza status within the study has been minimised by laboratory testing of all study participants with an assay that is at least 90% sensitive and 100% specific for influenza [11], and censoring of observations for which there was greater than four days between onset and specimen collection. Other factors, such as consistency of respiratory specimen collection, are difficult to quantify but may influence VE estimates. Furthermore, participants' illness and vaccination status are only known for the current season and don't account for cross-protection or prior immunity provided by previous vaccination or influenza infection.

Conclusion

We have applied a test negative case control study design to an established sentinel surveillance system to assess type- and subtype-specific effectiveness of influenza vaccine, which as yet is not routinely undertaken elsewhere in Australia. We found that VE differed by year, influenza type and subtype. Our analysis supplements existing epidemiological and immunological data about seasonal influenza and vaccination to assist with evaluation of the influenza vaccination program.

Abbreviations

(VE): vaccine effectiveness; (GPs): general practitioners; (PCR): polymerase chain reaction; (WHO): World Health Organization; (ILI): Influenza-like illness; (VIDRL): Victorian Infectious Diseases Reference Laboratory; (CI): confidence interval; (USA): United States of America

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Authors' contributions

JF conducted the data analysis and wrote the paper. KG coordinated recruitment, operation and data management of the surveillance system, undertook data analysis and reviewed and approved the final draft. GP undertook the laboratory testing and reviewed and approved the final draft. HK conceived and designed the study and reviewed and approved the final draft. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Pandemic influenza H1N1 2009 infection in Victoria, Australia: No evidence for harm or benefit following receipt of seasonal influenza vaccine in 2009

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ABSTRACT

Conflicting findings regarding the level of protection offered by seasonal influenza vaccination against pandemic influenza H1N1 have been reported. We performed a test-negative case control study using sentinel patients from general practices in Victoria to estimate seasonal influenza vaccine effectiveness against laboratory proven infection with pandemic influenza. Cases were defined as patients with an influenza-like illness who tested positive for influenza while controls had an influenza-like illness but tested negative. We found no evidence of significant protection from seasonal vaccine against pandemic influenza virus infection in any age group. Age-stratified point estimates, adjusted for pandemic phase, ranged from 44% in persons aged less than 5 years to −103% (odds ratio = 2.03) in persons aged 50–64 years. Vaccine effectiveness, adjusted for age group and pandemic phase, was 3% (95% CI −48 to 37) for all patients. Our study confirms the results from our previous interim report, and other studies, that failed to demonstrate benefit or harm from receipt of seasonal influenza vaccine in patients with confirmed infection with pandemic influenza H1N1 2009.

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1. Introduction

The first influenza pandemic of the 21st century was unexpected. Most pandemic preparedness plans had assumed a pandemic would originate somewhere in Asia and be caused by a novel sub-type. However the pandemic virus of 2009 was first recognised in North America in March and, although novel, was not a new subtype, being a reassortant of the influenza A (H1N1) subtype [1]. In accordance with established national policies in countries where influenza vaccine was available, eligible people had been vaccinated against the expected seasonal influenza strains in 2008 or early 2009 in countries of the northern hemisphere or early 2009 in countries of the southern hemisphere. In the northern hemisphere the vaccine for 2008/9 contained an A/Brisbane/59/2007-like virus as the H1N1 component and the same virus was recommended for the southern hemisphere vaccine for 2009. Although pandemic vaccines were subsequently manufactured and distributed, there was interest at the time in the effectiveness of the seasonal vaccine against pandemic influenza, since this was the vaccine that had been widely administered prior to the circulation of the pandemic virus.

Conflicting contemporary reports of the effect of seasonal vaccine on laboratory proven infection with pandemic influenza increased interest in what should have been an otherwise academic question. Unless there was significant cross-protection from previously circulating influenza strains, unexpected with a novel quadruple reassortant virus, seasonal vaccine that aimed to protect against these strains should have offered little protection against infection with the pandemic strain. This expectation was supported in interim analyses from Australia [2] and the United States [3,4]. However a case control study from Mexico reported that seasonal vaccine prevented 73% (95% CI 34–89) of laboratory confirmed infections due to pandemic influenza [5] and four studies from Canada indicated that seasonal vaccine may have increased the risk of infection with pandemic influenza [6].

Pandemic virus was first confirmed by laboratory testing in Australia on 9 May 2009 and in the state of Victoria on 20 May. The approach to management of the pandemic virus differed from the approach taken for seasonal influenza. Adapted from the Australian Management Plan for Pandemic Influenza [7], pandemic management in Victoria was characterised by different approaches in four different phases. The *delay phase* (26 April–22 May) aimed to delay entry of the virus into Australia, the *contain phase* (23 May–2 June) aimed to contain circulation of the virus once it had entered

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the country, the *modified sustain phase* (3 June–22 June) aimed to develop an approach to pandemic management that was sustainable and the *protect phase* (23 June onwards) aimed to protect the vulnerable. The *modified sustain phase* was implemented only in Victoria, with the other phases common to the other Australian states [8].

Public health and clinical responses changed with pandemic phase and impacted on the approach to laboratory testing. In the *delay* and *contain* phases, laboratory testing was authorised by the state health department and was restricted to people with a travel history or exposure to travellers. This strategy was based on the assumption, in retrospect probably not well founded, that the virus had not yet entered Victoria [9]. In these two phases, all pandemic influenza (pH1N1) cases confirmed by laboratory testing were followed up by officers from the state health department and attempts were made to identify all close contacts of confirmed cases. Antiviral prophylaxis was recommended for close contacts. During the *modified sustain* and *protect* phases, testing was recommended only for those assessed as having moderate or severe disease and those in particular risk groups. No confirmed cases were followed up in these two phases [8].

At the completion of the influenza season dominated by pandemic influenza in Victoria in 2009, we aimed to estimate the effectiveness of seasonal influenza vaccination against laboratory confirmed infection with pandemic influenza.

2. Methods

We recruited patients through sentinel general practices in Victoria to estimate the protection afforded by seasonal influenza vaccination against general practice attendance for an influenza-like illness (ILI) due to laboratory confirmed infection with pH1N1. We used a test-negative case control design with cases and controls recruited prospectively at the time of presentation to their sentinel general practitioner, although their case/control status was not determined until laboratory testing had been completed. Cases were defined as patients with an influenza-like illness who tested positive for influenza, while controls had an influenza-like illness but tested negative. This novel control selection gives the study design the title of 'test negative' [10]. With prospective recruitment, the odds ratio from the case control study is an unbiased estimate of the risk ratio without the need for the rare disease assumption required for the retrospective cumulative incidence case control design [11]. In temperate Victoria, the influenza season typically occurs in winter (June to August) and often extends into the early months of spring (September and October). We included all patients ascertained from sentinel general practices between the weeks beginning 27 April 2009, when surveillance commenced, and 20 December 2009. The last sentinel patient with confirmed pandemic influenza infection was detected on 14 December 2009.

2.1. The Victorian sentinel general practice network

Victoria's population is approximately 5.5 million, with 4.0 million people living in the state capital, Melbourne. Sentinel surveillance, usually conducted during the nominal 'influenza season' between May and September, was extended to December 24 in 2009. In 2009 sentinel surveillance comprised a network of 87 sentinel general practitioners (GPs), 60 in Melbourne and 27 in regional Victoria. GPs reported weekly on the total number of consultations and any patients presenting with ILI, defined as fever (reported or observed), cough and fatigue/malaise [12]. GPs were contacted regularly throughout the season in an attempt to ensure the quality and completeness of data.

We also conducted a survey of 342 sentinel patients with confirmed pandemic H1N1 infection diagnosed up to August 2009 and received responses from 132 (39%) [13]. Among many other questions in this survey, we included questions on date of symptom onset and vaccination status. We used responses from these two questions to update and validate information from the sentinel general practice database.

Laboratory-confirmed influenza has been a gazetted notifiable disease in Victoria since 2001. Formal ethics approval is not required for the surveillance program because of the legal requirement for the laboratory to notify positive cases. However written consent is obtained from sentinel patients, indicating that aggregate anonymous data will be used for surveillance purposes and influenza positive results will be notified to the Victorian Government Department of Health. After consent was obtained, GPs collected data on the age, sex, date of onset, symptoms and vaccination status (recording the date the vaccine was administered) of the sentinel patients. All vaccinations were with a trivalent inactivated vaccine formulation. GPs also collected a combined nose and throat swab from consenting patients, with the choice of which patients to swab at the discretion of the GP. The swab was couriered to the Victorian Infectious Diseases Reference Laboratory (VIDRL), a WHO National Influenza Centre, for laboratory testing.

2.2. Laboratory testing

Testing for influenza A viruses involved extraction of RNA from nose/throat swabs using a Qiagen DX Reagent Pack and QIA extractor extraction robot. cDNA was derived by reverse transcription using random hexamers and amplified using an ABI-7500 Fast Real-Time PCR System incorporating primers and probes targeting the matrix gene of influenza type A viruses including the pandemic virus. Samples testing positive in this screening assay were confirmed as positive or negative for the pandemic strain in a second real-time PCR assay incorporating primers and probes specific for the HA gene of that virus. All primer and probe sequences are available on request. Subtyping of non-pandemic influenza A viruses was undertaken using a gel-based PCR assay as previously reported [14]. This assay reliably sub-typed viruses detected in the matrix real-time assay when the cycle threshold was less than 36.

2.3. Estimating influenza vaccine effectiveness

Analysis was restricted to patients who presented with an ILI to any of the sentinel surveillance practices and who subsequently had a swab taken for the identification of influenza virus by real time PCR. Patients whose PCR tests were inhibited were excluded from the analysis, as were patients whose vaccine status or age was unknown, patients for whom subtyping was not possible and patients who had non-pandemic influenza detected. We calculated the number of days between symptom onset and the date the combined nose/throat swab was taken and restricted our analysis to a maximum of four days between these dates, since PCR positivity decreases with time following symptom onset due to decreasing viral excretion [15]. We counted a patient as vaccinated if the patient's sentinel GP had recorded receipt of the seasonal vaccine at least 14 days prior to symptom onset. Patients who had received vaccine less than 14 days prior to symptom and onset, and those who had received no vaccine, were classified as not vaccinated. Vaccines from three manufacturers were licensed for us in Australia in 2009. All were trivalent inactivated vaccines. We did not collect information on the specific vaccine administered to sentinel patients. In Victoria vaccination with seasonal vaccine commenced in March 2009.

Subsequent to recruitment and testing, a case was defined as a patient with ILI in whom pandemic H1N1 2009 influenza virus was

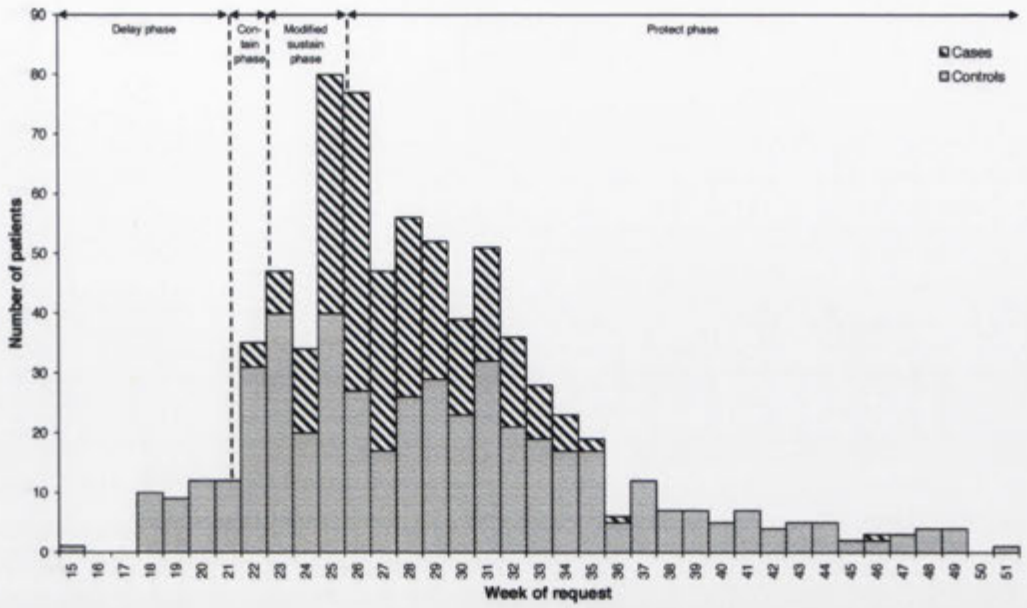

Fig. 1. Case and control detection from patients with influenza-like illness recruited through sentinel general practices in Victoria, by week and pandemic phase, 2009.

detected and a control was a patient in whom pandemic influenza was not detected. We estimated the VE (%) = (1 − OR) × 100, where OR, the odds ratio, was the odds of being a vaccinated case divided by the odds of being a vaccinated control. We compared covariates among cases and controls using the chi-squared test for categorical variables and the Mann–Whitney test for age. We used logistic regression models to estimate age-stratified VE for the following age groups: 0–4 years, 5–19 years, 20–49 years, 50–64 years and 65 years and above. To account for differences in testing patterns throughout the pandemic, we adjusted for pandemic phase using swab collection date to define the pandemic phase to which the patient was assigned. We estimated VE, adjusting for age group and pandemic phase, and performed a range of sensitivity analyses. Sentinel data were stored on a purpose written database and were imported to STATA [16] for analysis.

3. Results

3.1. The 2009 influenza season in Victoria

As reported previously, the influenza season of 2009 in Victoria started unusually early, with circulation of pandemic virus established by the time routine surveillance had commenced at the end of April [2]. The season was almost completely dominated by pandemic influenza H1N1 2009, with strain replacement virtually complete by the week beginning 25 May and 97% of all influenza viruses that could be subtyped confirmed as pandemic influenza [2]. The proportion of sentinel patients with ILI confirmed as pandemic influenza increased from 6% in the first week of surveillance, beginning 27 April, and reached a maximum of 67% in the week beginning 29 June. Case and control recruitment are shown by week and pandemic phase in Fig. 1.

Between the weeks beginning 27 April and 20 December sentinel practitioners had seen 236,448 patients, had notified 1608 (0.7%) of these patients with ILI and had taken a nose and throat swab from 1101 (69%) of them. No result was available for two cases, influenza subtyping was not possible for 42 patients and seasonal influenza was detected in 10 patients, leaving 1047 patients with pandemic influenza detected or excluded, all with age recorded (Fig. 2). Vaccine status was unknown for 42 (4.0%) patients but with no difference by pandemic influenza positive/negative status ($p = 0.42$) or age group ($p = 0.72$).

3.2. Patients included in the analysis

Between 37% and 42% of patients with ILI in each age group were swabbed with no significant difference by age group ($p = 0.39$). GPs were asked to collect a nose/throat swab only from patients whose symptoms had developed within the preceding four days. They complied with this request in 759 (89%) of all 854 notified patients for whom an onset date was reported, but patients that were pandemic influenza positive (267/280, 95%) were more likely than those that were pandemic influenza negative (476/553, 86%) to have had a swab collected within this period ($p < 0.001$) and this did not vary by vaccination status (Table 1). There was no difference in the time from symptom onset to specimen collection by vaccine status for controls alone ($p = 0.17$) or for cases alone ($p = 0.37$) (Table 1). The proportion of patients whose swab was collected within four days decreased with increasing age, from more than 90% in all patients aged less than 50 years to 80% in patients aged 50–64 years and 59% in patients aged 65 years and above ($p < 0.001$) (Table 1).

There were 743 patients available for analysis of vaccine effectiveness after further exclusion of patients whose nose and throat swabs were collected more than four days after symptom onset and for whom vaccination status was unknown (Fig. 2). Two cases (0.75%) and four controls (0.84%) had been vaccinated within 14 days of symptom onset ($p = 0.89$). Eight of 132 respondents to the case series survey reported being vaccinated at a workplace and three reported being vaccinated elsewhere. All 11 patients had been recorded as vaccinated by their sentinel GP. One patient aged 5–19 years reported not being vaccinated but had been recorded by the

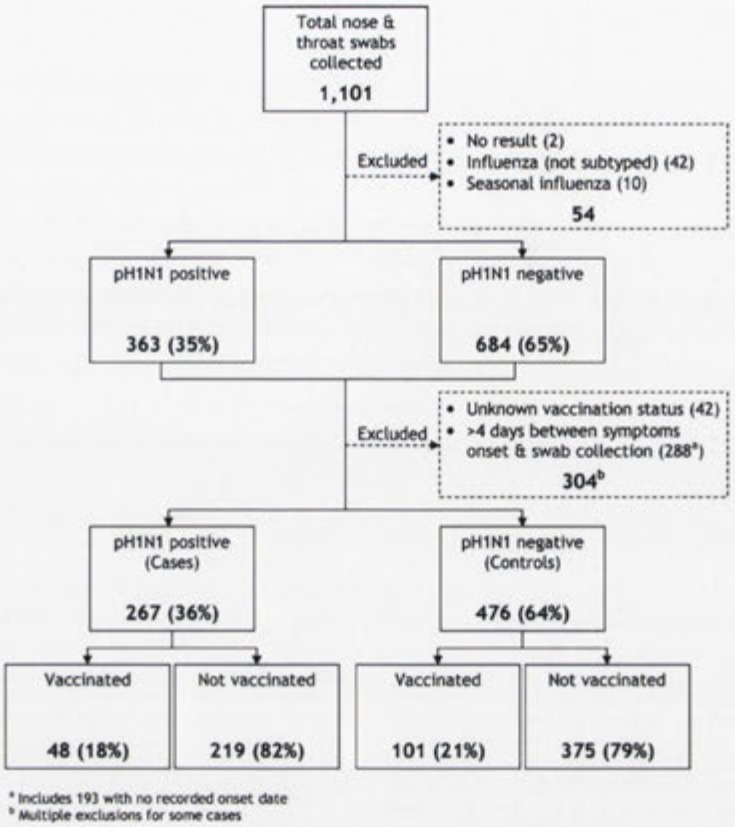

Fig. 2. Sentinel patients in the weeks beginning 27 April–20 December 2009.

GP as vaccinated and one patient aged 50–64 had vaccine status recorded as 'yes' by the GP but reported as 'no' by the patient. We used the GP data for vaccination status for both patients, the first because we were not sure whether the mother completed the survey about her own vaccination status or her child's and the second because the GP had recorded a date of vaccination for the patient.

Of the 743 patients included in the final analysis, 267 (36%) had pandemic influenza virus detected and were designated as cases, while pandemic influenza virus was not detected in the 476 patients designated as controls. The proportion of patients in whom influenza was detected increased by pandemic phase as testing requirements became more focused on those at risk. In the *delay phase*, influenza virus was detected in none of the 43 notified sentinel patients. The proportion increased to 7/58 (12%) for the *contain phase* and to 70/161 (43%) the modified *sustain phase* but decreased to 190/481 (40%) during the *protect phase* (Table 2). The median age for all patients was 25 years (range 0–86) years but was 21 years for cases and 29 years for controls (Table 2).

Only 19% of patients were vaccinated against influenza, with people aged at least 50 years more likely to have been vaccinated than younger people ($p < 0.001$, Table 3). Detection of pandemic influenza also differed by age group, with people aged 5–19 years most likely to have influenza virus detected (100/204, 49%), compared with 14/44 (32%) people aged 0–4 years and none of the 18 people aged at least 65 years ($p < 0.001$, Table 3).

Table 1
Cases and controls by age group, vaccination status and days from symptoms onset to swab collection.

Age group	Controls				Cases			
	Vaccinated		Not vaccinated		Vaccinated		Not vaccinated	
	0–4 days	>4 days	0–4 days	>4 days	0–4 days	>4 days	0–4 days	>4 days
0–4	5	2	25	3	2	0	12	0
5–19	13	0	91	9	8	0	92	5
20–49	44	7	227	27	24	0	109	6
50–64	19	4	34	13	12	1	8	1
≥65	16	8	2	4	0	0	0	0
Total	97	21	379	56	46	1	221	12

Table 2
Covariates for case and control analysis for sentinel patients with complete data available.

Covariate	Cases n = 267	Controls n = 476	p-value
Median age, years	21	29	$p < 0.001$
Age group (years)			
0–4	14	30	$p < 0.001$
5–19	100	104	
20–49	133	271	
50–64	20	53	
65+	0	18	
Swab collected within 4 days of symptom onset (n = 854 with result and onset date known, see Fig. 2)	267/280 (95%)	476/553 (86%)	$p < 0.001$
Vaccinated >14 days prior to symptom onset	46/48 (96%)	97/101 (96%)	$p = 0.99$
Swab taken during pandemic phase			
Delay	0	43	$p < 0.001$
Contain	7	51	
Modified sustain	70	91	
Protect	190	291	

3.3. Estimation of vaccine effectiveness

We found no evidence of significant protection or significant harm from seasonal vaccine against pandemic influenza virus infection in any age group, with point estimates, adjusted for pandemic phase, ranging from 45% in children aged 0–4 years to −103% (OR = 2.03) in persons aged 50–64 years (Table 3). VE, adjusted for age and pandemic phase, was 3% (95% CI −48 to 37) for all patients. Pandemic influenza was detected in only one patient aged at least 65 years but this patient was not included in the analysis because the patient's onset date was not stated and the time from onset to specimen collection was thus unknown.

Prior to adjustment for any covariates, and including swabs collected at any time post symptom onset, it appeared as if seasonal vaccine was effective in decreasing the risk of infection with pandemic influenza, with an estimated OR = 0.70 (95% CI, 0.51–0.99), corresponding to a VE of 30% (95% CI, 1–49) (Table 4). However the apparent significant effect disappeared after exclusion of swabs collected more than 4 days from symptom onset and after adjusting for age-group or pandemic phase (Table 4). After these adjustments had been made, there were only minor changes in the estimated OR for any of the uncertainties we investigated, specifically including patients as vaccinated or excluded if vaccination had occurred within 14 days of symptom onset and dealing with the two patients for whom we had only the month of vaccination recorded as vaccinated or not vaccinated. When we restricted our analysis to the 14 weeks of the peak season, the age and pandemic phase adjusted OR was 0.93 (95% CI, 0.60–1.45) (Table 4). We extended the reference model to include a vaccination status × continuous age interaction term. The interaction OR was 1.016 (95% CI 0.99–1.04, $p = 0.18$), which can be interpreted as the proportional change in vaccination OR per year of age, implying that the fitted vaccination OR increased from 0.62 (VE = 38%) at birth to 1.74 (0.62 times 1.01^{65}) (VE = −74%) at age 65. However this heterogeneity was not significant at $p < 0.05$.

4. Discussion

We found no evidence that receipt of the southern hemisphere seasonal influenza vaccine for 2009 resulted in either significant protection or increased risk from laboratory confirmed infection with pandemic influenza H1N1 2009 among Victorian patients attending a sentinel GP with an ILI, although age specific point estimates suggested some non-significant degree of protection from seasonal vaccine for younger patients and increased risk for patients aged 50–64 years. These findings corroborate our interim analysis [2], with the current analysis differing by the inclusion of more patients, adjustment for pandemic phase, censoring of data at four days between symptom onset and the collection of a nose and throat swab, and strict application of vaccination status. A novel observation from this analysis was the relatively high proportion of people aged at least 65 years who presented to their sentinel GP more than four days after symptom onset. This might suggest that symptom manifestation was milder in older people. Patients with confirmed pandemic influenza infection were a median of eight years younger than patients with an ILI not due to pandemic influenza.

4.1. Study limitations

Our sample size was determined ultimately by sentinel GP testing patterns during the pandemic in Victoria. With the observed vaccination coverage in the controls and the proportion of ILI patients who tested positive for pH1N1, we estimated our study had 99% power to detect a VE of 60% but only 21% power to detect a VE of 20%. Conversely the power to detect an OR of 2.5, correspond-

Table 3
Vaccine effectiveness of seasonal influenza vaccine against pandemic influenza H1N1 2009 by age group, Victoria, Australia, 2009.

Age group (years)	Patients tested (age and vaccine status known)	Number (%) positive for pandemic influenza (cases)	Number (%) negative for influenza (controls)	Number (%) vaccinated	Cases (%) vaccinated	Controls (%) vaccinated	Vaccine effectiveness (%) (adjusted for pandemic phase)	95% confidence interval
0–4	44	14 (32%)	30 (68%)	7 (16%)	2 (14%)	5 (17%)	45%	−259 to 92
5–19	204	100 (49%)	104 (51%)	21 (10%)	8 (8%)	13 (13%)	44%	−46 to 78
20–49	404	133 (33%)	271 (67%)	68 (17%)	24 (18%)	44 (16%)	5%	−67 to 46
50–64	73	20 (27%)	53 (73%)	31 (42%)	12 (60%)	19 (36%)	−103%	−504 to 32
≥65	18	0 (0%)	18 (100%)	16 (89%)	0	16 (89%)	Not defined	
All	743	267 (36%)	476 (64%)	143 (19%)	46 (17%)	97 (20%)	3%[a]	−48 to 37

[a] Adjusted for age-group and pandemic phase for swabs collected from patients with ILI within 4 days of symptom onset.

Table 4
Estimated odds ratios (odds of being a vaccinated case/odds of being a vaccinated control) adjusted for various covariates for combined nose/throat swabs collected within four days of symptom onset.

Covariate	Assumption	Odds ratio (95% confidence interval) [n in model]			
		Crude	Adjusted for		
			Age	Phase	Age and phase
Reference[a]		0.81 (0.55–1.20) [743]	1.12 (0.74–1.70) [725]	0.69 (0.47–1.03) [743]	0.97 (0.63–1.48) [725]
Days between onset and swab collection	No observations censored	0.70 (0.51–0.99) [1005]	1.00 (0.70–1.44) [1005]	0.64 (0.46–0.91) [1005]	0.89 (0.61–1.29) [1005]
Vaccination status	Patient excluded if <14 days between vaccination and symptom onset	0.82 (0.55–1.20) [736]	1.12 (0.74–1.70) [718]	0.70 (0.47–1.04) [736]	0.97 (0.64–1.49) [718]
	Patient considered vaccinated if <14 days between vaccination and symptom onset	0.81 (0.56–1.19) [743]	1.10 (0.74–1.66) [725]	0.71 (0.48–1.05) [743]	0.98 (0.64–1.48) [725]
	Patient considered not vaccinated if month only vaccination date given and onset in same or following month	0.82 (0.56–1.20) [744]	1.10 (0.74–1.66) [726]	0.71 (0.48–1.05) [744]	0.98 (0.64–1.48) [726]
	Patient considered vaccinated if month only vaccination date given and onset in same or following month	0.81 (0.55–1.18) [744]	1.09 (0.73–1.64) [726]	0.71 (0.48–1.04) [744]	0.97 (0.64–1.47) [726]
Swab collection date	Observation censored if swab not collected during peak of season (weeks 22–35)	0.75 (0.50–1.13) [624]	1.04 (0.67–1.61) [611]	0.67 (0.44–1.02) [624]	0.93 (0.60–1.45) [611]

[a] Observations censored if: >4 days from symptom onset to nose/throat swab collection; only a month of vaccination is provided and for which there is potentially <14 days from vaccination to symptom onset. Patient is considered not vaccinated if <14 days between vaccination and symptom onset.

ing to an apparently harmful effect of vaccination, was 99.9%, while power to detect an OR = 1.4 was only 49%. Our study would probably therefore have detected a large protective or harmful effect of vaccination, had either been present, but would have been less likely to detect more modest effects. Our study can therefore not exclude a harmful or protective effect of seasonal influenza vaccination on the risk of laboratory confirmed pandemic influenza in sentinel general practice patients. Moreover the estimate of VE from this study cannot be generalized from sentinel patients to the wider community.

The study has other limitations. Patients with ILI had not been randomised to receive vaccine. Because we collect data as part of routine surveillance, with the intention of minimising the GP's workload, we did not collect data on patients' co-morbidities and could not adjust for this in our analysis. The absence of data on co-morbidities also prevents us making inferences about possible selection bias in the controls related to co-morbidities. However coarse adjustment for co-morbidities (yes/no) made no significant difference to the estimation of risk in the Canadian studies [6]. We were also unable to test for selection bias by comparing vaccine coverage in our patients with population estimates of vaccine coverage because the latter are not collected routinely in Victoria for people aged less than 65 years. The test-negative case control design accounts for the propensity to consult with an ILI, since all patients who consult and have a swab taken are included in the study. There was no difference by age group in the proportion of patients with an ILI from whom a swab was taken. However GPs may be more or less likely to have swabbed a vaccinated patient. Study patients will not be representative of all patients with an ILI if patients with an ILI due to influenza are more or less likely to consult than a patient with an ILI due to another respiratory virus. We cannot test this assumption and residual confounding may bias our results.

4.2. Comparison with other studies

As indicated previously, two other studies failed to demonstrate protection from trivalent inactivated seasonal vaccine against infection with pandemic influenza. A preliminary report compared 541 US military personnel who had laboratory confirmed pandemic influenza infection diagnosed between April and August 2009 with date-matched controls. VE estimates were adjusted for age, number of prior vaccinations and length of military service. Interim analysis suggested that, although live attenuated influenza vaccine prevented 42% (95% CI 18–59) of laboratory confirmed infections, inactivated vaccine provided no significant protection with the estimated VE = 23% (95% CI −9 to 46). Increasing age was independently associated with protection [3].

A second preliminary study, described as case-cohort design but essentially a variation of the screening method, estimated protection from seasonal vaccine in people aged at least 18 years with laboratory confirmed pandemic influenza diagnosed between May and June 2009 in eight US states [4]. Influenza vaccination status of the population in each state was estimated from surveys. After adjusting for age and co-morbidities in the 356 cases for whom data were complete, VE was estimated as −10% (95% CI −43 to 15). The weaknesses of this interim analysis are discussed in an accompanying editorial note [4].

Perhaps more surprising was the VE estimate of 73% (95% CI 34–89) from seasonal vaccination against pandemic influenza derived from a case control study using 240 patients, 60 cases with laboratory confirmed influenza and 180 frequency matched controls, admitted to a specialist respiratory diseases hospital in Mexico between 29 March and 20 May, 2009 [5]. This level of protection is expected from a well-matched seasonal vaccine against seasonal influenza [17], but seemed unreasonably high for protection against pandemic influenza. A commentary on the study suggested the unexpected result could be explained by selection bias, with cases and controls ascertained from different populations having different opportunities for receipt of influenza vaccine. More controls (65%) than cases (25%) had co-morbidities that increased their chance of receiving influenza vaccination [18].

Another unexpected finding, reported from four Canadian studies, was an apparent 40–150% increase in the risk of medically attended infection with pandemic influenza following receipt of

seasonal vaccine, mostly seen among people aged less than 50 years [6]. A number of the studies were based on the test-negative case control design previously used in Canada [19] and in the Victorian study reported here. Similar to the findings in Canada, a study in the US military found active duty members with ILI and proven pH1N1 infection were more likely to have received influenza vaccination than those with ILI not due to pH1N1 (66% vs. 40%, $p < 0.01$), although the authors believed this was unlikely to be a true association [20].

4.3. Significance of findings

The finding of neither significant risk nor significant benefit is biologically plausible, although evidence from cross-reactive antibody studies suggest that some cross-protection may be expected, especially in older people [21]. Indeed, benefit of seasonal vaccination has been reported in two further studies, one in the US military [22] and another among hospitalised patients in Argentina [23]. However time between symptom onset and laboratory testing was not considered in either of these studies. We found that, compared with cases, a significantly decreased proportion of controls (that is, influenza negative ILI patients) were tested within 4 days of symptom onset, suggesting possible differential misclassification of controls in both these studies. This could have increased VE estimates.

An increase in risk of pH1N1 infection following seasonal vaccination is more difficult to explain, but a plausible hypothesis can be developed based on modelling and animal studies. We have previously suggested that prior infection with seasonal influenza, but not prior vaccination against seasonal influenza, provides some protection against infection with pandemic influenza. We base this hypothesis on the concept of non-specific temporary heterosubtypic immunity that provides a host with immunity to any strain of influenza for a period of perhaps 3–6 months following any influenza infection. This implies that seasonal influenza infection would decrease the risk of pandemic influenza infection [24].

In Victoria, there was no significant prior seasonal influenza circulation in 2009, with the most recent significant circulation of seasonal influenza having occurred in late August to September, 2008 [25] and we found no evidence of protection from seasonal vaccine against pandemic influenza infection in 2009. However in Canada seasonal influenza circulation preceded pandemic influenza circulation. Seasonal vaccine was found to protect against seasonal infection. Vaccinated people were therefore less likely to be infected with seasonal influenza than unvaccinated people and subsequently less likely to be protected from infection with pandemic influenza, since seasonal influenza infection provided some protection against pandemic influenza infection. It could therefore appear as if receipt of seasonal influenza vaccine increased the risk of infection with pandemic influenza [24].

The conflicting findings from observational studies on the effectiveness of seasonal influenza vaccination against infection with pandemic influenza highlight general problems with the estimation of influenza vaccine effectiveness. While most vaccines are licensed based on results from randomised controlled trials, influenza vaccines are licensed annually based only on immunogenicity studies and immunogenicity may not correspond with protection [26]. It is therefore important to estimate VE post-marketing. This has been acknowledged recently in Canada, Europe and the US with the emergence of studies aimed at estimating influenza VE from existing data sources [19,27,28]. However study designs need to adapt to the use of data not collected specifically to estimate influenza VE. For instance, a recent elegant analysis has demonstrated that a protective effect of influenza vaccination can be shown to be entirely due to bias when using administrative, rather than research, data to estimate influenza VE against non-specific outcomes in older people [29]. It seems biologically plausible that seasonal influenza vaccine may provide some limited protection against infection with pandemic influenza and, while we did not demonstrate this, it has been shown in other studies. Conflicting findings in other published studies suggesting no effect of vaccination, or increased risk of infection associated with vaccination, may be due to design issues in observational studies, including power of the studies, but, as we have previously argued, might also be explained by the hypothesis of non-specific temporary immunity following infection [30].

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Effectiveness of Seasonal Influenza Vaccine against Pandemic (H1N1) 2009 Virus, Australia, 2010

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To estimate effectiveness of seasonal trivalent and monovalent influenza vaccines against pandemic influenza A (H1N1) 2009 virus, we conducted a test-negative case–control study in Victoria, Australia, in 2010. Patients seen for influenza-like illness by general practitioners in a sentinel surveillance network during 2010 were tested for influenza; vaccination status was recorded. Case-patients had positive PCRs for pandemic (H1N1) 2009 virus, and controls had negative influenza test results. Of 319 eligible patients, test results for 139 (44%) were pandemic (H1N1) 2009 virus positive. Adjusted effectiveness of seasonal vaccine against pandemic (H1N1) 2009 virus was 79% (95% confidence interval 33%–93%); effectiveness of monovalent vaccine was 47% and not statistically significant. Vaccine effectiveness was higher among adults. Despite some limitations, this study indicates that the first seasonal trivalent influenza vaccine to include the pandemic (H1N1) 2009 virus strain provided significant protection against laboratory-confirmed pandemic (H1N1) 2009 infection.

After the emergence and rapid global spread of pandemic influenza A (H1N1) 2009 virus, development of a pandemic (H1N1) 2009–specific vaccine began (*1*). A candidate reassortant vaccine virus, derived from the A/California/7/2009 (H1N1)v virus as recommended by the World Health Organization, was used to produce a monovalent, unadjuvanted, inactivated, split-virus vaccine for Australia (*2,3*). The national monovalent pandemic (H1N1) 2009 vaccination program in Australia ran from September 30, 2009, through December 31, 2010, and vaccination was publicly funded for all persons in Australia ≥6 months of age (*4,5*).

In September 2009, the World Health Organization recommended that trivalent influenza vaccines for use in the 2010 influenza season (Southern Hemisphere winter) contain A/California/7/2009 (H1N1)–like virus, A/Perth/16/2009 (H3N2)–like virus, and B/Brisbane/60/2008 (of the B/Victoria/2/87 lineage) virus (*6*). Since March 2010, the Australian Government has provided free seasonal influenza vaccination to all Australia residents ≥65 years of age, all Aboriginal and Torres Strait Islander persons ≥50 years, all Aboriginal and Torres Strait Islander persons 15–49 years with medical risk factors, persons ≥6 months with conditions that predispose them to severe influenza, and pregnant women (*7*). Influenza vaccination is also recommended, but not funded, for persons who might transmit influenza to those at high risk for complications from influenza, persons who provide essential services, travelers, and anyone ≥6 months of age for whom reducing the likelihood of becoming ill with influenza is desired. Individual industries are also advised to consider the benefits of offering influenza vaccine in the workplace (*8*). Because pandemic (H1N1) 2009 was expected to be the dominant strain in 2010, the monovalent vaccine continued to be used despite the availability of the seasonal vaccine, particularly by persons who were not eligible for funded vaccine (M. Batchelor, pers. comm.). However, in 2010, there were no published data on the relative use of monovalent and seasonal vaccines at that time.

The need for rapid implementation of programs results in initial studies using immunogenicity, rather than efficacy, to assess performance of influenza vaccines. After 1 dose of monovalent pandemic (H1N1) 2009 vaccine containing 15 μg hemagglutinin without adjuvant, seroprotection was

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estimated to be 94%–97% in working-age adults (*3,9,10*) and 75% in children (*10*). Observational studies provide a practical way to calculate vaccine effectiveness under field conditions (*11,12*). Effectiveness of monovalent pandemic (H1N1) 2009 was estimated to be 72%–97% by 3 studies in general practice and community-based settings in Europe (*13–15*), 90% in a hospital-based study in Spain (*16*), and 100% in a community-based study of children in Canada (*17*). These studies were conducted in populations for which the respective local or national pandemic vaccination program primarily used vaccine without adjuvant.

We assessed effectiveness of the 2010 seasonal influenza vaccine against laboratory-confirmed pandemic (H1N1) 2009 influenza infection in Victoria, Australia. Data came from an established test-negative case–control study in a general practitioner sentinel surveillance network (*18,19*).

Methods

Sentinel Surveillance

Victoria is the second most populous state in Australia; it has a temperate climate, and the annual influenza season usually occurs during May–September. Each season, on behalf of the Victorian Government Department of Health, the Victorian Infectious Diseases Reference Laboratory conducts surveillance for influenza-like illness (ILI; defined as history of fever, cough, and fatigue/malaise) and laboratory-confirmed influenza. General practitioners within the network provide weekly reports on case-patients with ILI as a proportion of total patients seen and send swabs from patients with ILI to the laboratory for testing. In 2010, a total of 87 practitioners participated in the program, which operated for 25 weeks, from May 3 (week 19) through October 24 (week 43). Practitioners were asked to collect nose and throat swabs from patients with an ILI (*20*) within 4 days after onset of the patient's symptoms. Samples were collected by using Copan dry swabs (Copan Italia, Brescia, Italy) and were placed in virus transport medium. Practitioners were also asked to provide data on the patient's age, sex, date of symptom onset, vaccination status, type of influenza vaccine (monovalent or trivalent/seasonal) received, and date of vaccination. Type of vaccine and date of vaccination were ascertained from medical records and patient report.

Laboratory Testing

RNA was extracted from clinical specimens by using a Corbett extraction robot (Corbett Robotics, Brisbane, Australia), followed by reverse transcription to cDNA by using random hexamers. PCR amplification and detection selective for the type A influenza virus matrix gene was performed by using primers and a Taqman probe on an ABI-7500 Fast Real-Time PCR system (Applied Biosystems, Foster City, CA, USA). Samples determined to be positive by this assay were confirmed as positive or negative for pandemic (H1N1) 2009 in a second real-time PCR that incorporated primers and probes specific for the hemagglutinin gene of the pandemic (H1N1) 2009 virus. Influenza B viruses were identified by a separate PCR. One practitioner chose to send samples to the state reference laboratory in South Australia for testing with equivalent diagnostic assays.

Ascertainment of Case-patients and Controls

Case-patients and controls were sampled prospectively throughout the study period. A case-patient was defined as a person with ILI for whom test results for pandemic (H1N1) 2009 were positive; a control was defined as a person with negative test results for influenza virus. Analysis of vaccine effectiveness against other influenza subtypes was not undertaken because of the almost exclusive circulation of pandemic (H1N1) 2009 virus during the season; therefore, patients with positive test results for other influenza viruses were excluded. A control could become a case-patient if another illness developed during the season, but a case-patient was no longer at risk and could not be included again.

Data Analysis and Calculation of Vaccine Effectiveness

All analyses were conducted by using Stata version 10.0 (StataCorp LP, College Station, TX, USA). The χ^2 test was used to compare proportions, and the Mann-Whitney U test was used to compare time from vaccination to time seen by practitioner; $p<0.05$ was considered significant. Patients were excluded from the vaccine effectiveness analysis if vaccination status was unknown, if the date of symptom onset was unknown, or if the interval between symptom onset and specimen collection was >4 days (because of decreased likelihood of a positive result after this time) (*21,22*). Patients were considered not vaccinated if time between date of vaccination and symptom onset was <14 days. If only the month of vaccination was reported, the date of vaccination was conservatively estimated to be the last day of the month. To avoid overestimation of vaccine effectiveness arising from recruitment of controls when influenza was not circulating in the population, analysis was restricted to case-patients and controls detected within the influenza season, defined as the period during which influenza-positive case-patients were detected (weeks 26–40).

Vaccine effectiveness was defined as (1–odds ratio) × 100%; the odds ratio is the odds of laboratory-confirmed pandemic (H1N1) 2009 case-patients having been vaccinated divided by the odds of controls having been vaccinated. In the test-negative case–control design,

the odds ratio estimates the incidence density (rate) ratio because controls are selected longitudinally throughout the course of the study (i.e., by density sampling) (*23,24*). The odds ratio in test-negative case–control studies has also been shown to approximate the risk ratio under conditions of varying attack rates and test sensitivity and specificity (*25*). Logistic regression was used to calculate odds ratios and 95% confidence intervals (CIs) for having laboratory-confirmed pandemic (H1N1) 2009, which were adjusted for the variables of age group and month of specimen collection against the following: seasonal vaccine, monovalent vaccine, both vaccines, and any (either or both the seasonal and monovalent) vaccine. Sensitivity analyses were conducted to determine the effects of the following on vaccine effectiveness: not censoring for specimens collected from ILI patients >4 days after symptom onset, including controls recruited outside the defined influenza season, and assuming that patients with unspecified type A influenza had pandemic (H1N1) 2009.

Ethical Considerations

Data in this study were collected, used and reported under the legislative authorization of the Victorian Public Health and Wellbeing Act 2008 and Public Health and Wellbeing Regulations 2009. Thus, the study did not require Human Research Ethics Committee approval.

Results

A total of 172,411 patients were seen by participating practitioners during the study period, of whom 678 (0.4%) had ILI. After a nadir ILI rate of 0.2% in week 21, the rate gradually increased to 0.4% in week 31 before increasing more sharply to a peak of 0.9% in week 36. Swabs were collected from 478 (71%) ILI patients, among whom 170 (36%) had positive influenza test results and the remainder were negative. Influenza-positive patients were detected during weeks 26–40, which was defined as the influenza season (Figure). A total of 142 patients were excluded from further analysis because vaccination status was unknown (n = 11), symptom onset date was unknown (n = 33), time between symptom onset and specimen collection was >4 days (n = 43), or the specimen was collected outside the influenza season (n = 82). A significantly higher proportion of influenza-negative patients (13%) than influenza-positive patients (4%) were excluded because >4 days had elapsed between symptom onset and specimen collection (p = 0.001). No significant difference was found by age group for whether study participants had a specimen collected within 4 days after symptom onset (p = 0.10).

Of the remaining 336 patients, 156 (46%) had positive influenza test results. Most (89%) influenza case-patients had pandemic (H1N1) 2009, 6% had unspecified type A influenza, 4% had influenza A (H3N2), and 1% had influenza type B (Figure). After exclusion of the other influenza patients, 139 pandemic (H1N1) 2009 case-patients and 180 controls were included in the study analysis. Most (57%) participants were 20–49 years of age, and case-patients were significantly younger than controls (p = 0.001); no case-patient was ≥65 years of age (Table 1). No statistically significant difference was found between male and female study participants by case or control status (p = 0.60) or by vaccination status (p = 0.09). The high proportion of case-patients detected in August resulted in a significant difference between case-patients and controls by month of swab collection (p<0.001).

Overall, 59 (18%) study participants were reported as vaccinated with any vaccine, but the proportion was higher among controls (26%) than among case-patients (9%; p<0.001). The proportion of controls, who were mostly older, who had received the trivalent seasonal vaccine was higher than the proportion of controls who had received the monovalent vaccine (Table 1). Similarly, controls who had received both vaccines were all ≥20 years of age. Only case-patients who were 5–19 and 20–49 years of age were

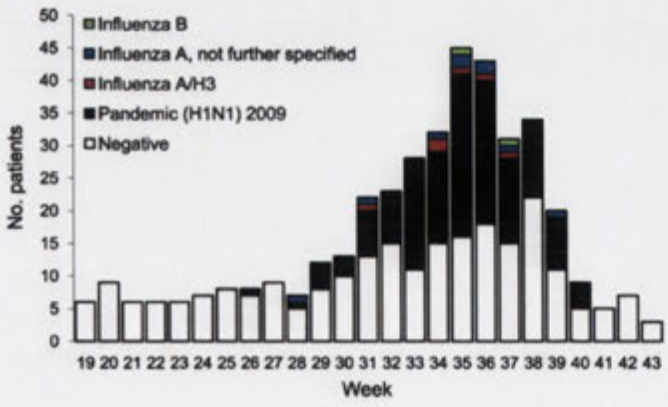

Figure. Influenza status of patients seen at sentinel general practices, Victoria, Australia, May 3 (week 19) through October 24 (week 43), 2010.

reported as vaccinated. Influenza vaccine type was not specified for 1 case-patient and 1 control, each of whom was reported as vaccinated.

Reflecting the availability of each vaccine, the median period between vaccination and visit to a general practitioner was significantly shorter for those who received seasonal vaccine (114 days) than for those who received monovalent vaccine (223 days; p<0.0001). No significant difference in the time from vaccination to practitioner visit was found between case-patients and controls for seasonal (p = 0.70) or monovalent vaccine (p = 0.95).

In general, point estimates of vaccine effectiveness adjusted for patient age and month of specimen collection differed little from crude estimates (Table 2). A significant protective effect was observed for seasonal vaccine only (adjusted vaccine effectiveness 79%; 95% CI 33%–93%) and seasonal and monovalent vaccines (adjusted vaccine effectiveness 81%; 95% CI 7%–96%). The adjusted vaccine effectiveness for receipt of any (either or both the seasonal and monovalent) vaccine was lower at 67% because of the 47% vaccine effectiveness for monovalent vaccine. The absence of vaccinated case-patients and controls meant vaccine effectiveness could not be estimated for several of the 5 age groups (Table 1); therefore, age was collapsed into 3 variables: children (0–19 years), working-age adults (20–64 years), and elderly persons (≥65 years). Estimates of vaccine effectiveness for working adults were 0%–14% higher than the overall adjusted estimates; estimates for children were either undefined because no controls were vaccinated or were without a significant protective effect. Vaccine effectiveness could not be calculated for elderly persons because there were no case-patients in this age group.

Sensitivity analyses to determine the effects of certain assumptions resulted in variations in the adjusted vaccine effectiveness point estimates of 0%–3% and no changes to their relative significance. The effects considered were as follows: assumption that those patients with unspecified influenza type A had pandemic (H1N1) 2009, no exclusion of patients if >4 days had elapsed between symptom onset and specimen collection, and no exclusion of patients if they were identified outside the defined influenza season.

Discussion

Our results indicate that the 2010 seasonal trivalent influenza vaccine is >80% effective against pandemic (H1N1) 2009 virus, regardless whether given by itself or in addition to monovalent vaccine. Groups in Europe and Canada have estimated the effectiveness of monovalent seasonal influenza vaccine against pandemic (H1N1) 2009 virus to be 72%–100% (*13–17*). However, the effectiveness of any vaccine (monovalent, seasonal, or both) against pandemic (H1N1) 2009 virus was lower (67%, 95% CI 33%–84%) because effectiveness for monovalent vaccine only was 47% (95% CI –62% to 82%). The lower effectiveness of monovalent influenza vaccine against pandemic (H1N1) 2009 virus compared with seasonal trivalent influenza vaccine is difficult to explain. Both vaccines contain the same quantities (15 μg) of hemagglutinin; and although the monovalent vaccine does not contain adjuvant and was available ≈6 months before the seasonal vaccine, it has been shown to be strongly immunogenic (*3,9,10*). Immunogenicity does not necessarily correlate directly with vaccine effectiveness, and we cannot exclude waning immunity as an explanation for the lower effectiveness of monovalent vaccine in our study. Waning immunity after receipt of monovalent vaccine has been suggested after an interim study from the United Kingdom for the 2010–11 influenza season (*26*). The finding could also be a product of the relatively small number of case-patients and controls who received only the monovalent vaccine, given that vaccine effectiveness estimates can change considerably by the inclusion or exclusion of 1–2 vaccinated study participants.

When stratified by age, estimates of vaccine effectiveness for working-age adults were higher and

Table 1. Participants in negative-test case–control study of efficacy of seasonal influenza vaccine for preventing pandemic (H1N1) 2009, Australia, 2010

Participants	Age group, y					Total, n = 319
	0–4, n = 19	5–19, n = 73	20–49, n = 181	50–64, n = 41	≥65, n = 5	
Controls						
Total*	13 (68)	27 (37)	107 (59)	28 (68)	5 (100)	180 (56)
Vaccinated with monovalent vaccine†	0	3 (11)	7 (7)	1 (4)	0	11 (6)
Vaccinated with seasonal vaccine†	0	0	9 (8)	10 (36)	2 (40)	21 (12)
Vaccinated with both vaccines†	0	0	7 (7)	4 (14)	2 (40)	13 (7)
Pandemic (H1N1) 2009 case-patients						
Total*	6 (32)	46 (63)	74 (41)	13 (32)	0	139 (44)
Vaccinated with monovalent vaccine†	0	3 (7)	3 (4)	0	0	6 (4)
Vaccinated with seasonal vaccine†	0	2 (4)	2 (3)	0	0	4 (3)
Vaccinated with both vaccines†	0	0	2 (3)	0	0	2 (1)

*No. (%) study participants.
†No. (%) controls/pandemic (H1N1) 2009 case-patients.

Table 2. Crude and adjusted vaccine effectiveness against pandemic (H1N1) 2009 virus, Australia, 2010

Effectiveness	Influenza vaccine effectiveness, % (95% confidence interval)			
	Seasonal	Monovalent	Both	Any
Crude	80 (39–93)	42 (–62 to 79)	84 (26 to 96)	70 (42 to 84)
Adjusted*				
0–19 y	Undefined†	44 (–231 to 91)	Undefined‡	–41 (–549 to 69)
20–64 y	89 (50 to 98)	56 (–88 to 90)	81 (7 to 96)	81 (52 to 92)
All ages	79 (33 to 93)	47 (–62 to 82)	81 (7 to 96)	67 (33 to 84)

*Adjusted for month of swab collection.
†No controls vaccinated.
‡No controls or case-patients vaccinated.

more precise than those for children. We previously demonstrated that the sentinel practitioner surveillance program in Victoria is well suited for estimating vaccine effectiveness among working-age adults, who account for most of the surveillance population (*18*), and the 2010 results were consistent with this observation. The relatively few participants in the young (childhood) age groups meant the study had insufficient power to produce defined or significant estimates of vaccine effectiveness. At the other end of the age spectrum, 2% of study participants (5 controls and 0 case-patients) in 2010 were ≥65 years of age compared with an average of 7% in this age group during 2003–07 (*18*). Although the absence of pandemic (H1N1) 2009 case-patients ≥65 years of age is not surprising, given that older adults have been shown to have relatively higher levels of cross-reactive antibodies to pandemic (H1N1) 2009 virus (*27–29*), the reason for the low proportion of controls in this age group remains unclear. Among the several explanations are a true lower rate of ILI in older persons during 2010, a lower rate of visits to practitioners for ILI by persons in this age group (or treatment at other health services such as hospitals), or preferential sampling of younger persons by practitioners (and perhaps awareness that pandemic [H1N1] 2009 was the predominant circulating influenza virus subtype).

In addition to having a sample size large enough to provide vaccine effectiveness estimates by age group and influenza type, several other considerations with regard to design of case–control studies of influenza vaccine effectiveness have been proposed: 1) whether the control group best represents the vaccination coverage of the source population and 2) whether collection and confounding variables have been adjusted for, particularly underlying chronic conditions for which vaccine is recommended and previous influenza vaccination history (*30*). A 2010 survey of pandemic vaccination suggests that monovalent vaccine coverage in the control group was generally consistent with that in the general population and that use of monovalent vaccine was ≈17% among those from Victoria, compared with 13% among controls (*31*). No equivalent survey of 2010 seasonal vaccine usage was available for comparison.

Data about concurrent conditions of study participants that would indicate need for influenza vaccination were not collected during the 2010 influenza season; thus, adjustment of the vaccine effectiveness estimates for this potentially confounding variable could not be conducted. Such confounding by indication (or negative confounding), in which persons at higher risk for influenza are more likely to be vaccinated, underestimates effectiveness of influenza vaccine but may be counteracted by healthy vaccinee bias (or positive confounding), which overestimates effectiveness (*30,32*). The extent to which these biases occur is likely to vary and may explain the positive and negative variation of crude influenza vaccine effectiveness estimates after adjustment for chronic conditions in several similar test-negative case–control studies (*33–35*). Speculation about the relative effects of these biases on how many received monovalent vaccine is also difficult; vaccination was funded for the entire population of Australia, but at the end of February 2010, only 18% had been vaccinated (*31*).

Similar methods using test-negative controls to assess seasonal and pandemic vaccine effectiveness against both seasonal and pandemic influenza viruses have been applied in North America and Europe (*13,16,17,33–39*). Observational studies provide a convenient and timely way to assess influenza vaccine effectiveness without the ethical, practical, and financial stringencies associated with clinical trials for vaccine efficacy, but they also have limitations. Modeling suggests that the test-negative case–control design generally underestimates true vaccine effectiveness under most conditions of test sensitivity, specificity, and the ratio of influenza to noninfluenza attack rates (*25*), although quantifying the extent of this effect in this study is difficult because the precise sensitivity and specificity of the test are not known. We attempted to limit ascertainment bias by censoring records that indicated specimen collection >4 days after symptom onset and restricting the analysis to case-patients and controls tested within the influenza season only, although sensitivity analyses indicated little effect if these restrictions were relaxed. Of note, these findings apply predominantly to working-age adults receiving medical care in the general practice setting; the study did not include those who did not seek medical care for ILI.

Thus, the study measured effectiveness of vaccine against illness severe enough to require a visit to a practitioner; the results cannot necessarily be generalized to other parts of the population, in particular young children and elderly persons. We were also unable to determine whether participants had previously been infected with pandemic (H1N1) 2009 virus, which may result in overestimation of vaccine effectiveness.

In conclusion, we applied a test-negative case–control study design to an established sentinel surveillance system to estimate effectiveness of a trivalent seasonal influenza vaccine, which included an A/California/7/2009 (H1N1)–like virus, the pandemic (H1N1) 2009 influenza virus strain. This strain is also a component of the trivalent influenza vaccine for the 2010–11 Northern Hemisphere influenza season (*40*). The trivalent vaccine provided significant protection against laboratory-confirmed pandemic (H1N1) 2009 virus infection.

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SURVEILLANCE AND OUTBREAK REPORTS

Moderate influenza vaccine effectiveness in Victoria, Australia, 2011

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We used a sentinel general practitioner (GP) network to conduct surveillance for laboratory-confirmed influenza amongst patients presenting with influenza-like illness (ILI) in Victoria, Australia in 2011. The test-negative variation of the case control study design was used to estimate effectiveness for seasonal trivalent influenza vaccine. Cases and controls were ILI patients that tested positive and negative for influenza, respectively. Vaccination status was recorded by GPs and vaccine effectiveness (VE) was calculated as (1-adjusted odds ratio)x100%. There were 529 patients included in the study, of which 29% were influenza-positive. Twelve percent of study participants were reported as vaccinated, 6% of cases and 15% of controls. Adjusted VE against all influenza was 56%, but not statistically significant. There was generally little variation in VE estimates when stratified by virus type and subtype, which is consistent with good matches between circulating strains and the vaccine strains. The VE was higher among adults of working age than among children.

Introduction

Victoria accounts for approximately 25% of Australia's population of 23 million people. It has a temperate climate, and the influenza season usually occurs between June and October. Each season, the Victorian Infectious Diseases Reference Laboratory uses a network of sentinel general practitioners (GPs) to conduct surveillance for influenza-like illness (ILI) and laboratory-confirmed influenza. The system has been operational since 1998, with an average of 60 GPs participating each year. This surveillance system is used to estimate vaccine effectiveness (VE) of the seasonal influenza vaccine.

Seasonal influenza vaccination in Australia is a publicly funded programme. The Australian government provides free influenza vaccination to all Australians aged 65 years and older, Aboriginal and Torres Strait Islander people over 15 years of age, pregnant women and individuals aged six months and older with medical conditions predisposing to severe influenza [1]. Individuals may also be vaccinated outside the funded programme, such as through workplaces. The influenza virus composition of the seasonal trivalent influenza vaccine (TIV) in Australia in 2011 was A/California/7/2009 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus (of the B/Victoria/2/87 lineage) [2].

Here we use the results from laboratory-confirmed influenza surveillance in Victoria to estimate TIV effectiveness in 2011 using the prospective test-negative variation of the case control study. This design has been used in Europe, North America and Australia [3-6]. We aimed to calculate type- and subtype-specific VE estimates and used them in combination with surveillance data to make inferences how well the 2011 seasonal TIV matched circulating strains. The strain composition recommended for use in the 2011 southern hemisphere influenza vaccine was the same as the one subsequently used in the 2011/12 northern hemisphere seasonal vaccine [7].

Methods

In 2011, 97 GPs participated in the surveillance system which operated from 2 May to 30 October inclusive. Advertising in GP circulars was used to encourage GPs to participate in the programme and targeted recruitment was undertaken in geographical areas considered to be poorly represented. A relatively even and widespread distribution suggested adequate representation of the 97 GPs throughout the metropolitan and most rural areas of the state. GPs reported the total number of consultations per week from which proportions were calculated as the number of ILI patients per 1,000 consultations. ILI was defined as fever (or history of fever), cough, and either fatigue or malaise [8]. GPs were asked to collect a nose and/or throat swab from patients with an ILI within four days of the onset of the patient's symptoms and provide data on the patient's age, sex, date of symptoms onset, influenza vaccination status in 2011 and 2010, date of vaccination and presence of comorbid conditions for which influenza

vaccination is indicated. Patients were chosen for swabbing at the discretion of the GP.

To test for influenza viruses, RNA was extracted from clinical specimens using a Corbett extraction robot followed by reverse transcription using random hexamers. cDNA was amplified using an ABI-7500 Fast Real-Time PCR System incorporating primers and probes specific for the detection of type A, B and C influenza viruses. Samples that tested positive for influenza type A in this assay were subtyped in a second real-time PCR assay incorporating primers and probe specific for influenza A(H1N1)pdm09, A(H1) (non-pandemic) and A(H3) haemagglutinin genes.

VE was defined as (1-adjusted odds ratio)x100%, where the odds ratio is the ratio of odds of laboratory-confirmed influenza cases being vaccinated to the odds of controls (those that tested negative for influenza) being vaccinated. Logistic regression was used to calculate odds ratios and 95% confidence intervals that were adjusted for the variables of age group, month of specimen collection and comorbidity. There was not sufficient statistical power to generate age-specific VE estimates for the age group ≥65 years or to further stratify the age group of 0–19 year-olds. Patients were excluded from the VE analysis if vaccination status was unknown, if the date of symptom onset was unknown or if there was an interval greater than four days between symptom onset and specimen collection, based on the decreased likelihood of a positive result after this time [9,10]. Patients were considered not vaccinated if there was less than 14 days between the date of vaccination and symptom onset. All analyses were conducted using Stata (version 10.0; StataCorp LP). The chi-squared test was used to compare proportions, with $p<0.05$ considered statistically significant.

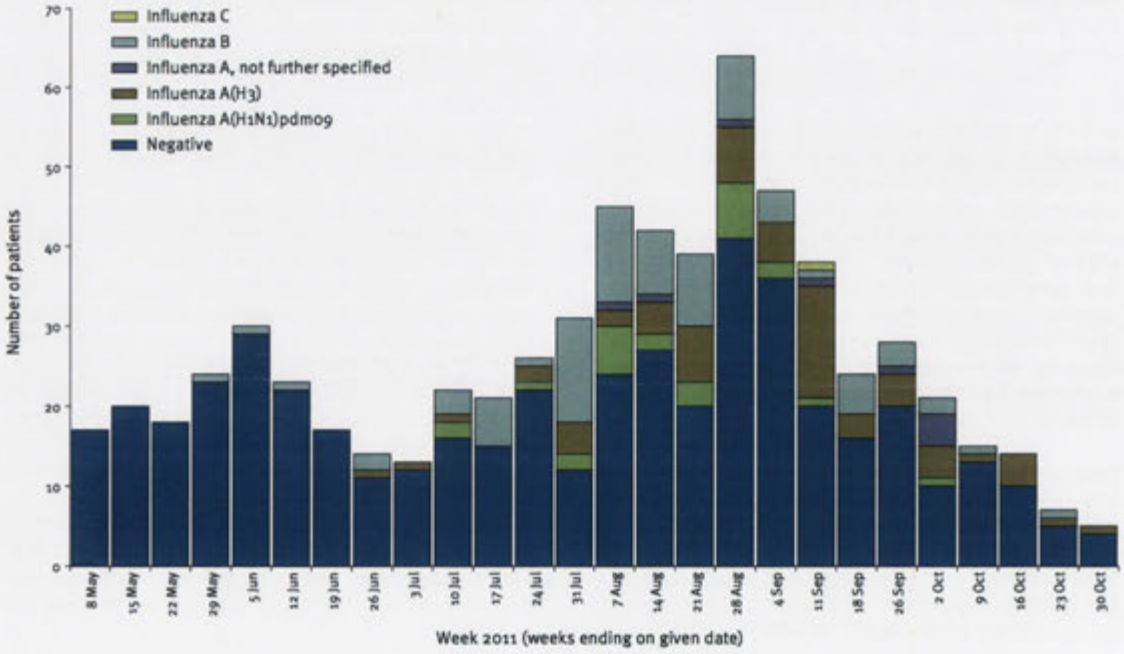
Results

Participating GPs reported seeing a total of 194,295 patients during the reporting period, of whom 945 (0.5%) met the ILI case definition, a proportion that was consistent with previous years. As the reporting of ILI cases is not identifiable and separate to those who are swabbed (for whom data are recorded on a laboratory test request form), we are unable to assess any demographic or vaccination status differences between those who were swabbed and those who were not. Of the 945 ILI cases, 665 (70%) were swabbed and 185 (28%) tested positive for influenza. In general, influenza A(H1N1)pdm09 predominated during the first half of the season, A(H3) during the middle to latter part, whilst cases of influenza B were detected throughout (Figure). One case of influenza type C infection was also detected.

We excluded 136 swabbed patients (20%) from the VE analysis due to unknown vaccination status (n=25), unknown date of symptom onset (n=44) or more than four days between symptom onset and specimen

Figure

Influenza-positive and -negative patients at sentinel general practices by week, Victoria, 2 May to 30 October (n=665)



collection (n=80); some were excluded for more than one reason. The case of influenza type C infection was also excluded. There was no statistically significant difference between the swabbed patients that were included and those that were excluded from the study by vaccination status (p=0.11), influenza positivity (p=0.07), age group (p=0.72), presence of a comorbid condition (p=0.21) or vaccination in 2010 (p=0.10).

Of the 529 patients included in the study, 155 (29%) were cases and 374 (71%) were controls. Cases were significantly younger than controls (p=0.004) and more common in August and September (p<0.001), but there was no statistically significant difference between cases and controls by sex (p=0.31) (Table 1). There was no statistically significant difference between cases and controls with respect to presence of a comorbidity recommended for influenza vaccination (p=0.15), although those with a comorbid condition were more likely to be older (p<0.001) and to be vaccinated (p<0.001). Being vaccinated in 2010 was not associated with testing positive for influenza (p=0.21), but was associated with older age (p<0.001) and with vaccination in 2011 (p<0.001).

Of the 529 patients eligible for the VE analysis, 65 (12%) were reported as vaccinated, with a statistically significant difference between cases (6%) and controls (15%) (p=0.008) (Table 2). No cases of influenza A(H1N1)pdm09 were reported as vaccinated. The proportion vaccinated was significantly higher in older age groups (p<0.001), but there was no statistically significant difference between those vaccinated and not vaccinated by month of testing (p=0.63).

There was little difference in the overall crude (60%) and adjusted (56%) point estimates for VE against all influenza, although only the crude estimate was statistically significant (Table 3). Although slightly higher against influenza A(H1N1)pdm09, age-adjusted VE estimates were generally consistent when stratified by type and subtype, however, 95% confidence intervals for estimates in the age group of 0–19 year-olds were very wide. Crude VE against influenza A(H1N1)pdm09 was 100% because none of 24 cases with confirmed influenza A(H1N1)pdm09 were vaccinated, but the VE was reduced after adjustment.

A sensitivity analysis conducted by restricting inclusion of cases and controls to the influenza season in 2011 when cases are more likely to be detected (the period from 20 June to 30 October when at least one influenza case was detected in consecutive weeks) resulted in changes to the point estimates from 0% to 1%. Not censoring patients for whom there were more than four days between symptom onset and specimen collection reduced the crude and overall adjusted VE estimates from 0% to 25% and from 2% to 14%, respectively.

Discussion

Using a population of patients with ILI who consulted sentinel GPs in Victoria, Australia, we have estimated a moderate effectiveness of 56% for the 2011 seasonal TIV against all influenza, although this was not statistically significant. VE estimates for the age group of 0-19 year-olds (childhood) were lower and considerably less precise than those for the age group of 20-64 year-olds. This is consistent with our observations in previous years which have highlighted the utility of this GP surveillance programme for estimating VE among working age adults who comprise most of the surveillance population [11,12].

TABLE 1

Characteristics of cases and controls, vaccine effectiveness study, Victoria, 2 May to 30 October (n=529)

	Number of controls (%)	Number of cases (%)	p value
Sex			
Female[a]	189 (51)	86 (55)	0.31
Age			
0–19 years	108 (29)	67 (43)	0.004
20–64 years	249 (67)	85 (55)	
≥65 years	17 (5)	3 (2)	
Month of swab collection			
May	71 (19)	2 (1)	<0.001
June	64 (17)	1 (<1)	
July	59 (16)	30 (19)	
August	107 (29)	74 (48)	
September	49 (13)	39 (25)	
October	24 (6)	9 (6)	
Comorbid condition[b]	43 (13)	12 (9)	0.15
Previously vaccinated[c]	76 (22)	25 (17)	0.21
Total	374	155	

[a] No data for one control.
[b] No data for 50 controls and 15 cases.
[c] No data for 27 controls and seven cases.

TABLE 2

Number and vaccination status of cases and controls by age group, vaccine effectiveness study, Victoria, 2 May to 30 October (n=529)

		Age group (years)			
		0–19	20–64	≥65	Total
Controls	n	108	249	17	374
	Vaccinated (%)	2 (2)	43 (17)	10 (59)	55 (15)
All influenza cases	n	67	85	3	155
	Vaccinated (%)	1 (1)	6 (7)	3 (100)	10 (6)
Influenza A(H1N1)pdm09 cases	n	4	20	0	24
	Vaccinated (%)	0 (0)	0 (0)	0 (0)	0 (0)
Influenza A(H3) cases	n	24	29	1	54
	Vaccinated (%)	0 (0)	3 (10)	1 (100)	4 (7)
Influenza B cases	n	37	30	2	69
	Vaccinated (%)	1 (3)	1 (3)	2 (100)	4 (6)

Strain typing surveillance data suggested good matches to the vaccine strains: 89% of 87 influenza A(H1N1) isolates were A/California/7/2009-like with the remainder A/California/7/2009-like (low reactor); 96% of 122 type A(H3N2) isolates were A/Perth/16/2009-like with the remainder A/Perth/16/2009-like (low reactor); 96% of 136 type B isolates were B/Brisbane/60/2008-like, 4% were B/Brisbane/60/2008-like (low reactor) and fewer than 1% were B/Florida/4/2006-like (low reactor) of the B/Yamagata/16/88 lineage (personal communication: K O'Bryan, World Health Organization Collaborating Centre for Reference and Research on Influenza, December 2011). Thus, the type- and subtype-stratified VE point estimates are broadly consistent with a good match to the circulating strains. However, none of the adjusted VE estimates was statistically significant suggesting insufficient study power. This is particularly evident in the childhood age group of the 0–19 year-olds.

To our knowledge there are no other published data for 2011 southern hemisphere seasonal influenza vaccine effectiveness. However, a point of comparison to other studies exists given the strain composition has not changed for the 2010/11 northern hemisphere and 2010 and 2011 southern hemisphere seasonal TIVs. In general the estimates obtained from our study were higher than those from other comparable studies. Using the same method we were able to demonstrate an effectiveness of 89% for the 2010 TIV against influenza A(H1N1)pdm09 among working age adults [12], compared with the 78% effectiveness observed this year. A study conducted amongst inpatients in 15 Australian hospitals in the same period in 2010 estimated a statistically significant effectiveness of 49% for TIV against hospitalisation with influenza A(H1N1) pdm09 [13]. Similarly in Europe, preliminary estimates for seasonal influenza vaccine effectiveness against all influenza using the test-negative variation of the case control study design among ILI patients seen in primary care were lower than our study, ranging from 5% to 50% [14-17]. The pooled end-of-season analysis of the European data resulted in lower adjusted estimates of VE against both influenza A(H1N1)pdm09 (27%) and type B influenza (64%) in working age adults compared to our study, although neither was statistically significant [18].

In our analysis we attempted to control for variables generally considered to be confounders [19], that is, those assumed to be associated with both exposure (vaccination) and outcome (influenza) but not on the causal pathway. These include age, month of swab collection and presence of a comorbid condition for which influenza vaccine is indicated. We observed generally little variation between crude VE estimates and those adjusted for these confounding variables. Only age was significantly associated with both vaccination and influenza. Month of swab collection and comorbidity were significantly associated with outcome and exposure respectively, but neither was significantly associated with both. Other studies using the same variation of the test-negative case control study as this one have also adjusted for receipt of influenza vaccine within a year before the study [16,18]. Whilst we collected this data field in 2011, its inclusion as a covariate in the adjusted model resulted in considerable variation from the crude and the age-, month- and comorbidity-adjusted VE estimates. However, further statistical analysis did not support inclusion of previous vaccination in the model because it assumes that previous vaccination has the same effect regardless of vaccination in the current season, and because of its high degree of correlation with current vaccination status which skews and reduces the precision of the VE estimate.

While variables may be considered to be theoretical confounders they may result in biases that could under- or over-estimate the VE. Results from influenza VE studies in Europe for the 2010/11 season included comments about the need for a cautious approach to dealing with such variables [17,20] and highlight the need for further clarification of the optimal analysis for the test-negative design when used to estimate influenza VE. Whilst relatively new, the method is administratively practical and theoretically acceptable, and

Table 3

Crude and adjusted vaccine effectiveness of seasonal vaccine against influenza by age group and type/subtype, Victoria, 2 May to 30 October (n=529)

	Influenza vaccine effectiveness (95% confidence interval)			
	Crude	Adjusted[a]		
		0–19 years	20–64 years	All ages
All	60 (19 to 80)	33 (-676 to 94)	61 (-3 to 85)	56 (-2 to 81)
Influenza A(H1N1)pdm09	100 (6 to 100)[b]	Not defined	77 (-44 to 100)[b,c]	78 (-38 to 100)[b,c]
Influenza A(H3)	54 (-34 to 84)	-44 (-1,757 to 100)[b,c]	48 (-99 to 86)	58 (-53 to 89)
Influenza B	64 (-2 to 88)	-16 (-1,298 to 90)	78 (-77 to 97)	53 (-68 to 87)

[a] Adjusted for month of swab collection and comorbidities.
[b] Calculated using exact method.
[c] Median unbiased estimates.

we will continue to refine it in collaboration with other investigators that have adopted it.

As previously discussed, other limitations of the study must also be taken into account when considering the results [6,12,21]. Briefly, the study was conducted in a general practice setting and the results are thus representative of the mid-range of the influenza clinical spectrum. Those not sick enough to attend a medical practitioner and more severe cases requiring hospitalisation were not part of the sampling frame. We were unable to quantify immunity from previous infection or healthy vaccinee bias, both of which overestimate VE. Conversely though, when conducted retrospectively, the test-negative case control design generally underestimates true VE under most conditions of test sensitivity, specificity and the ratio of influenza to non-influenza attack rates [22].

Overall, the seasonal TIV was moderately effective against medically attended influenza in Victoria, Australia during the 2011 southern hemisphere season. These VE estimates were generally consistent among working age adults when stratified by type and influenza A subtype, and consistent with an apparent good match between TIV and circulating strains during a season which saw the re-emergence of the influenza A(H3N2) subtype [23].

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Chapter 8

Discussion and conclusions

The first influenza pandemic of the 21st century occurred in 2009 with the emergence of the influenza A(H1N1)pdm09 virus. In Australia this invoked a public health response largely based on the *Australian Health Management Plan for Pandemic Influenza* (AHMPPI) that had been developed over the course of the preceding decade [1]. The experience responding to the pandemic provided an opportunity not only to evaluate the performance of the plan in practice, but also the validity of some of the assumptions about pandemic epidemiology and its effect on post-pandemic seasonal influenza.

This thesis presented 11 studies that addressed the two aims to examine the epidemiology of influenza during the first wave of the 2009 pandemic and the following influenza seasons, and to estimate the effectiveness of trivalent seasonal and monovalent vaccines prior to, during and following the pandemic. More specifically, these aims were addressed by four research questions that investigated: how the epidemiology and application of school closure and antiviral distribution control strategies for influenza A(H1N1)pdm09 differed from expectations in pandemic planning; the role of disease severity in influenza A(H1N1)pdm09 transmission; post-pandemic influenza epidemiology; and influenza vaccine effectiveness prior to, during and following the pandemic. This chapter presents the key findings and conclusions of the 11 research papers in the context of the four research questions of the thesis. The public health implications and further investigative opportunities suggested by the studies' findings for each of the research questions are also discussed.

Expectations and reality of an influenza pandemic

The AHMPPI was largely based on the 1918-19 pandemic, with estimated symptomatic infection and case fatality risks of 40 per cent and 2.4 per cent respectively and 50 per cent of the population not going to work at the peak of the pandemic [1]. The first study in Chapter 4 showed that some epidemiological features of influenza A(H1N1)pdm09, including multiple waves, a younger age of infection and increased morbidity and mortality in younger age groups, were not inconsistent with previous pandemics [2]. However, in contrast to previous pandemics the emergence of the pandemic strain in 2009 resulted from a novel

reassortant of a circulating subtype rather than antigenic shift and did not replace all influenza A virus subtypes. Furthermore, a case fatality risk of less than 0.01% was observed and the effective reproductive number was estimated to be 1.2-1.5 compared to a mean of 2.0 (range: 1.4-2.8) in previous pandemics.

School closure and distribution of oseltamivir treatment and prophylaxis to cases and their contacts was proposed as a mitigation measure for influenza pandemics in the AHMPPI [1]. During the 'Delay' and 'Contain' phases of the public health response to influenza A(H1N1)pdm09 in Victoria, closure was only applied to specific schools and classrooms in which two or more cases had been identified, for the duration of one week [3]. The second study in Chapter 4 demonstrated that not enough schools were closed soon enough, and were closed for too short a period to have any discernible impact on the transmission of influenza A(H1N1)pdm09 [4]. Indeed, a case study of one school in which there were at least 77 laboratory confirmed cases showed transmission was well established before case detection and the need to close the school was identified. This observation was also made in the wider Victorian population by the likely establishment of community transmission several weeks before cases were identified [5]. The delay in detection of cases was probably also exacerbated by a case definition that required a history of travel to an affected area, in which it was seemingly presumed that all or most infections acquired overseas would be serious enough to warrant medical attendance and testing.

A further consequence of identifying the pandemic weeks after it was first established was the rapid increase in notified cases. This placed pressure on the centralised response team, shown by the second Chapter 4 study in which collection of complete high-quality data became difficult and antiviral medication was unable to be delivered to most cases and their close contacts within 48 hours of symptom onset [4]. In addition to volume, the centralised nature of the distribution system and time between symptom onset, presentations, testing and notification likely contributed to delay in antiviral delivery.

Implications for pandemic planning

Whilst there was considerable debate about whether influenza A(H1N1)pdm09 even constituted a pandemic at all, it nevertheless challenged some of the underlying assumptions about influenza [6], and highlighted a gap in the ability of pandemic plans to accommodate a scenario with lower morbidity and mortality.

Notwithstanding the likely limited value of large-scale population-based control measures for relatively mild pandemics even if identified early, the identification of influenza A(H1N1)pdm09 later than expected also reduced the effectiveness, or made redundant, planned interventions to contain transmission. Effectiveness of school closures is greatest if the closures are universal, made early, continue until prevalence returns to low levels and children stay at home during the closure [7]. The limited school closure policy had no impact, but provided a valuable insight into the need to act early and universally should it be considered as a control measure in a future pandemic.

Public and professional disquiet about the response to the influenza A(H1N1)pdm09 pandemic, both within Australia [8, 9] and internationally [6], undermined trust in health officials. The lessons described here, along with many others regarding other elements of the broad response have been recognised [10]. Indeed, a methodology for short-term collection of enhanced epidemiological and virological data in Australia has been developed in consultation with a broad range of stakeholders to better manage the surveillance process in the early stages of a pandemic [11]. Jurisdictions will need to ensure that milder scenarios are addressed in revised pandemic plans to restore confidence and the ability to respond effectively to future pandemics.

Mild infections drove pandemic influenza transmission

The relatively mild nature of influenza A(H1N1)pdm09 coupled with evidence suggesting that community transmission in Victoria was well established before cases were identified lead to the hypothesis that spread of the virus was largely driven by those with asymptomatic or clinically mild infections [5]. Using a deterministic mathematical model, the second study in Chapter 6 showed that those with low-level symptoms and asymptomatic infections were responsible for

most influenza A(H1N1)pdm09 transmission. The other infection severity categories of moderate symptoms and hospitalised each infected less than one individual on average, making them incapable of maintaining disease transmission in the absence of mild infections.

Whilst uncertainty around estimation of model parameters can be an important limitation of modelling studies, a strength of the study in this thesis is that parameter values were primarily drawn from observational study data. Furthermore, the robustness of the model was demonstrated by sensitivity analyses that used more conservative estimates of parameter values where there was variation in the published literature or were based on plausible assumptions. Whilst the effective reproduction numbers for each infection severity category varied, under all alternative scenarios, the broad findings of the model remained unchanged.

Determining the duration of viral shedding

The recovery rate parameters of the mathematical modelling study were drawn from a systematic review of influenza A(H1N1)pdm09 viral shedding duration that was undertaken as part of this thesis and also included in Chapter 6 [12]. As expected, the duration of viral shedding generally increased with severity of clinical presentation, which in the review was classified by the study settings of community-based, hospitalised and intensive care cases. Also observed as expected, was that viral shedding duration was shorter when antiviral treatment was administered within 48 hours of illness onset. An unexpected finding of the review was that there appeared to be little or no difference in duration of influenza A(H1N1)pdm09 virus shedding between adults and children. This is in contrast to several studies of seasonal influenza prior to 2009 that found longer shedding duration in children [13-15], and has become a widely held assumption in text books [16] and pandemic planning documents [17].

The biggest challenge in conducting the systematic review was the high degree of variability in the measurement and/or definition of viral shedding duration between shortlisted studies, and a standard definition was applied to data abstracted from each study so they could be compared. This variability was borne

out by statistical testing which identified significant heterogeneity between studies and precluded meta-analysis. To enable simple and rapid comparison between future studies, the following list of standard parameters for measurement and reporting of influenza viral shedding duration were proposed:

- Unless measuring pre-symptomatic or asymptomatic shedding, the duration of viral shedding should be defined as from the day of symptom(s) onset to the day on which the last positive specimen was collected;
- Counting of the number of days of viral shedding duration should be inclusive of (rather than the difference between) the day of symptom(s) onset and the day on which last positive specimen was collected;
- Specimen collection should continue until two consecutively collected specimens both test negative;
- Where administratively possible, specimens should be collected daily but not less than one every 2 days;
- The age threshold for classification as a child or adult should be clearly defined;
- Record the date (or day with respect to symptom onset) of the commencement of antiviral therapy, or that no antiviral therapy was administered [12].

Whilst these parameters represent the ideal standards for measurement and reporting of influenza viral shedding duration, it is recognised that financial and practical considerations will frequently limit the ability with which they can be applied.

Measurement of viral shedding duration is often used as a proxy for the period of infectiousness, however this is complicated by the test used to detect influenza virus. Most studies used reverse transcription polymerase chain reaction (RT-PCR) to measure influenza A(H1N1)pdm09 virus shedding duration, which has been shown to be more sensitive than virus culture [18]. However, virus culture measures viable/infectious virus whereas RT-PCR may also detect non-viable RNA; such an error would overestimate the duration of shedding of infectious virus, although to what extent is unclear.

Public health implications

The findings from both the viral shedding duration and role of severity in transmission studies for influenza A(H1N1)pdm09 in Chapter 6 have important public health implications for pandemic planning. Whilst estimation of the duration of infectiousness is an important parameter in mathematical modelling of influenza, and can be quite sensitive to variations as short as one day, it also has a valuable role evaluating public health policy with respect to the recommended length of time that isolation and quarantine for pandemic influenza should be applied. That there was no strong evidence of a difference in viral shedding duration between adults and children is noteworthy because this conventional wisdom formed the basis of the initial Victorian pandemic response policy to quarantine and isolate of suspected or confirmed child cases for 14 days compared to seven days for adults.

The findings of the modelling study provided further support for the hypothesis that most influenza A(H1N1)pdm09 transmission was driven by those with low-level and asymptomatic infections largely unrecognised by the health system and was thus able to become established before detection. This evidence further supports the need to update pandemic plans to incorporate milder scenarios in which quarantine, isolation and other social distancing control measures may not be as effective or even necessary.

Further investigations

Both the influenza A(H1N1)pdm09 viral shedding duration and mathematical modelling studies in Chapter 6 provide scope for further investigation. Many of the viral shedding studies included in the systematic review measured viral load and symptoms, and opportunities exist to systematically review the association between influenza A(H1N1)pdm09 viral load and symptom scores, initial viral load as a predictor of symptom scores and shedding duration, and the effect of antiviral usage on symptoms scores. The systematic review of influenza A(H1N1)pdm09 virus shedding, as well as the other study proposals, could also be extended to observational studies of seasonal influenza. Although several of these associations have already been investigated in a 2008 systematic review of experimental

studies by Carrat *et al* [19], it has been suggested that the viruses used in studies comprising the review were of moderate pathogenicity by comparison with wild-type seasonal influenza viruses.

Many studies have been conducted to understand different parameters and their role in the dynamics of influenza transmission, seasonal epidemics and pandemics. However, there are few published studies that have examined the role of clinical presentation. The study in Chapter 6 presents obvious opportunities to further develop and apply the model to other scenarios, such as seasonal influenza, subsequent waves of the influenza A(H1N1)pdm09 pandemic or other pandemics. Modelling infection severity in seasonal epidemics would require incorporation of influenza vaccination coverage and effectiveness parameters into the model, which could also be used to provide insights into the impact of vaccination in preventing natural immunity from asymptomatic or mild influenza virus infections. Given that immunity conferred by influenza vaccination is widely accepted to be not as strong, cross-protective or long-lasting as that provided by natural influenza infection [20], modelling may suggest a more efficient influenza vaccination program structure that allows for more natural infection in particular subpopulations at lower risk of moderate or severe infections and balanced against economic cost of days lost to illness.

Post-pandemic influenza epidemiology

Three successive annual studies from 2010 to 2012 inclusive were undertaken to understand how the epidemiology of seasonal influenza has changed since the emergence of influenza A(H1N1)pdm09 in 2009 [21-23]. Influenza A(H1N1)pdm09 was the dominant subtype in 2010 as it was in 2009 [24], and completely replaced the seasonal A(H1N1) subtype that circulated prior to 2009 [25, 26]. There was co-circulation of A(H1N1)pdm09, A(H3N2) and type B viruses in the 2011 influenza season but none was dominant. A higher proportion of older influenza A(H1N1)pdm09 cases was observed in 2011 compared to the previous season, consistent with observations in the northern hemisphere [27]. Such a finding would be expected following the emergence of a pandemic influenza strain in which higher attack rates in younger age groups that have no prior immunity

are observed during the initial outbreak, followed by a shift to older age groups as immunity increases in the young [28, 29]. The 2012 influenza season was characterised by dominance of the A(H3N2) subtype. There was a later and smaller peak of type B cases, which was also observed in 2011. Accompanying the increase of A(H3N2) cases in 2011 and 2012 was a higher number of laboratory confirmed influenza outbreaks in aged care facilities and an increase in severe disease requiring hospitalisation among older people, consistent with the observation that this subtype is generally associated with more severe illness in older age groups [30].

In general, the 2010, 2011 and 2012 influenza seasons, as measured by influenza-like illness (ILI) activity, were moderate in magnitude and within the thresholds of normal seasonal activity compared to the previous years. Whilst peaks in ILI activity were similar in each of the three seasons, there was an increase of more than 250% in notified cases over the same period. The disparity between ILI activity and notified cases as a measure of seasonal influenza magnitude was first observed during the 2009 pandemic [24] and appears to have continued in the following years, likely as a result of increased testing by medical practitioners. This is supported by data from the general practitioner sentinel surveillance (GPSS) program which showed that in 2010 to 2012 participating medical practitioners tested between 60 and 71% of ILI patients for influenza [21-23], compared to an average of 40% in the years 2003-2007 [31].

The Victorian influenza surveillance system is well established, and provides a reliable and consistent method for monitoring the epidemiology of ILI and laboratory confirmed influenza in Victoria. A key strength of the system is its multiple data sources that capture a wide spectrum of clinical presentations in different settings, but which have comparable metrics that provide reassurance and validation when other elements of the surveillance may be indicating a different epidemiological pattern.

Public health implications

The confidence in the Victorian influenza surveillance system, and its usefulness in understanding influenza epidemiology and guiding public health control measures, were most clearly demonstrated during the response to the pandemic in 2009. By indicating a milder disease than the number of notified cases suggested, the ILI activity measured by the general practitioner sentinel surveillance (GPSS) program and the Melbourne Medical Deputising Service in part informed the decision to scale down the intensity of the initial public health response to influenza A(H1N1)pdm09 [24]. Whilst notifiable influenza surveillance is still important for understanding the epidemiology of confirmed diagnoses, changes in testing practices have limited its utility as a measure of the magnitude of an influenza season in the post-pandemic years. To better monitor and understand testing behaviour, it has therefore been proposed that surveillance also include the collection of the number of influenza laboratory tests performed to calculate the proportion of test results that are positive [8, 32]. Whilst the GPSS already collects negative testing data to calculate the proportion of tests that are influenza positive, it is subject to wide weekly variation because of the relatively small numbers [33].

Further system improvements

Mortality and hospital emergency department (ED) surveillance data for ILI and laboratory confirmed influenza are not routinely collected and represent an obvious gap in surveillance in Victoria. Routine collection and analysis of death registrations from the Registry of Births, Deaths and Marriages, as is done in New South Wales [34], is the logical option for sourcing suspected and confirmed influenza mortality data in Victoria, but has been administratively difficult to implement. Whilst an automated, broad-based, near real-time public health surveillance system using presentations to EDs has been established in New South Wales [35], it is expensive and resource-intensive to operate. Before considering the necessity of such a system for ILI and influenza surveillance in Victoria, an analysis of retrospective data from Victorian EDs could indicate the added value that near-real time ED surveillance could provide over existing surveillance data sources.

Several options exist for the collection of denominator data for the proportion of influenza tests that are positive. This includes making influenza negative test data notifiable or the voluntary provision of the data by all or a subset of laboratories. To maximise participation, notification would need to be as low burden as possible (for example by electronic notification) and commercial sensitivities about disclosure of diagnostic testing markets would need to be addressed.

Influenza vaccine effectiveness from 2007 to 2011

Four studies in Chapter 7 examined influenza vaccine effectiveness (VE) in Victoria over five years, incorporating the first wave of the influenza A(H1N1)pdm09 pandemic in 2009, as well as the two preceding and following years [36-39]. Subtype-specific estimates by year and the dominant circulating strains for the respective years are shown in table 1.

Point estimates of influenza VE varied considerably over the 2007-2011 period, both from year to year and between types and subtypes within the same influenza season, although few differences were statistically significant. Little correlation is evident between vaccine effectiveness and the percentage match between circulating and vaccine strains, as measured by haemagglutinin inhibition (HI). For example, VE against A(H3N2) and type B influenza in 2007 were relatively high (68% and 84% respectively) despite relatively poor observed matches of circulating to vaccine strains. This contrasts with 2011 in which 96% of circulating A(H3N2) and type B influenza strains were matched to the respective vaccine strains, yet type/subtype-specific VE estimates were lower. Despite these differences, the VE point estimates against all influenza in both years were very similar.

It is likely that multiple immunological and epidemiological factors are contributing to the apparent poor correlation between influenza vaccine effectiveness and match between circulating and vaccine strains. A study conducted during the 2010-2011 influenza season in Canada, which found suboptimal VE despite vaccine antigenic similarity to circulating strains based on HI characterisation, also undertook phylogenetic analysis that revealed multiple amino acid substitutions at antigenic sites [40]. The Canadian study also showed

amino acid substitutions in the haemagglutinin of the egg-adapted vaccine strain relative to the WHO-recommended strain, resulting in further differences between the vaccine and circulating strains. The incorporation of phylogenetic analysis into assessment of VE in Victoria in 2012 also showed accumulated substitutions in the antigenic site of the circulating A(H3N2) strain compared to the vaccine strain, despite antigenic similarity as indicated by HI assay [41].

Table 1. Adjusted vaccine effectiveness against influenza by year and type (subtype), Victoria, 2007-2011.

Year	Influenza type(subtype)	Adjusted VE (95% CI)	Percent match of circulating strain to vaccine strain
2007	A(H1N1)	27 (-92, 72)	0
	A(H3N2)	68 (32, 85)	45
	B	84 (-2, 98)	29
	All	**59 (25, 78)**	
2008	A(H1N1)	-88 (-1936, 83)	0
	A(H3N2)	-66 (-349, 39)	100
	B	49 (-58, 84)	50
	All	**9 (-96, 58)**	
2009	A(H1N1)pdm09	3 (-48, 37)	0
2010	A(H1N1)pdm09	79 (33, 93)* 47 (-62, 82)^	100
2011	A(H1N1)pdm09	78 (-38, 100)	89
	A(H3N2)	58 (-53, 89)	96
	B	53 (-68, 87)	96
	All	**56 (-2, 81)**	

* seasonal trivalent influenza vaccine

^ monovalent pandemic (H1N1) vaccine

Further complicating the measurement of VE is existing immunity to influenza, either from previous infection or vaccination, in study participants. Whilst exposure to influenza virus is unknown and unable to be measured, two recent studies in the US found lower effectiveness among subjects who were vaccinated in

both the studied and prior seasons, although the findings were not statistically significant [42, 43]. In contrast, a Canadian study found that VE was higher among those who had been vaccinated in both the studied and previous seasons, although unlike the US studies the vaccine strain composition was the same for both seasons and accompanied by phylogenetic analysis of circulating and vaccine viruses [44]. Data collection on vaccination in the previous season commenced in Victoria for the GPSS in 2011, and VE estimates when comparing vaccination status in study season only, prior season only, both seasons and either season to neither season in 2011 and 2012 were inconsistent [45].

Another important limitation of the influenza VE studies undertaken using the GPSS in Victoria is that they are insufficiently powered. Few estimates showed a statistically significant protective effect, particularly the stratified analyses. This has prevented meaningful analysis and comparison of influenza VE by age group in each of the studies included in this thesis, but also comparisons of type and subtype-specific VE in years when relatively few cases were identified. This was evident in 2008, particularly the type A subtypes, for which confidence intervals around the point estimates were very wide [36]. Despite the limited power available for some analyses, in general point estimates of VE in each of the studies only varied marginally when subjected to sensitivity analyses to test assumptions and a different analytical approach [46].

As expected, the trivalent seasonal influenza vaccine conferred no protective effect against influenza A(H1N1)pdm09 in 2009 [37]. The effectiveness point estimate of the 2010 trivalent seasonal influenza vaccine against influenza A(H1N1)pdm09 (79%) was higher than the monovalent pandemic (H1N1) 2009 vaccine (47%), which was available in Australia from September 2009 as part of the national pandemic vaccination program [47]. Whilst not statistically significant, waning immunity cannot be excluded as an explanation; the monovalent vaccine did not contain adjuvant and was available approximately six months before the seasonal vaccine. Waning VE by time since vaccination was also observed in Victoria in 2012 but the effect was also not statistically significant [41].

As well as providing a practical and relatively low-cost means of calculating vaccine effectiveness, the case test-negative study design has been shown to be robust under a wide range of assumptions and circumstances, and less subject to bias than traditional case control or cohort studies [48-50]. Nevertheless, as the methodology evolves, greater scrutiny and thought are being applied to the finer details. The presence of a comorbid condition for which influenza vaccination is indicated is regarded as an important confounding variable given that persons at higher risk for influenza may be more likely to be vaccinated. This field was not collected by the GPSS until 2011 and it therefore possible that the studies of the 2007-2008 and 2010 seasons in particular underestimated VE as a result. Whilst this may have been counteracted by healthy vaccinee bias, it is difficult to speculate to what, if any, extent.

More recently, it has been suggested that influenza VE may be biased if the proportion of non-influenza viral illness differs by influenza vaccination status [50]. Underpinning this theory is the suggestion that influenza infection invokes an innate immune response that results in a temporary reduction in risk of infection with another respiratory virus. It is therefore proposed that whilst influenza vaccination would reduce the risk of influenza infection, it could increase the risk of infection with other non-influenza respiratory viruses [51, 52]. With a higher risk of non-influenza respiratory illness in vaccinated individuals than in those who are unvaccinated, the 'test-negative' group would have a higher proportion of vaccinated individuals compared to the source population, resulting in an overestimate of VE. Whilst one study reported increased risk of non-influenza respiratory virus infections associated with receipt of inactivated influenza vaccine [51], another found no evidence of an association [53].

Finally, it must also be acknowledged that annual estimates of VE in Victoria are based on general practice consultations for which the patient population is largely working age adults, thus limiting the generalisability by age. The clinical spectrum of patients is also restricted as those with severe infections that are hospitalised and those who have very mild or asymptomatic infections will not attend general practice. The latter group represent another potential source of bias in the case

test-negative study design; vaccine effectiveness will be underestimated if vaccinated cases are less severely ill and seek care less frequently than unvaccinated cases [49].

Public health implications

Ongoing assessment of influenza VE is important for several reasons: influenza vaccination is publicly funded for a large proportion of the Australian population and regular evaluation of its effectiveness is needed; it provides the only assessment of how the vaccine performs in the field; and the circulating strains and vaccine composition (usually) change every year. Measurement and reporting of VE with Victorian data collected from both the GPSS program and the Influenza Complications Alert Network is of particular importance because it is not regularly undertaken anywhere else in Australia or indeed the southern hemisphere.

Whilst timely publication of VE estimates will not change vaccine policy, given that vaccination programs will have already commenced or been completed, they can help public health officials better understand the epidemiology during an influenza season and manage expectations of the vaccine program. During a severe influenza season, a poor VE could suggest the need to prioritise resource allocation to alternative and more effective control measures.

Further investigations

The case test-negative study design is now well-established across Europe and North America. Groups utilising the methodology to measure influenza VE have formed a strong collaborative network, and efforts to improve it in the next several years are likely to focus on nuanced areas such as sources and control of bias, and better understanding the complex and interacting virological, immunological and epidemiological factors and their influence on influenza VE. The effect of prior vaccination is of particular interest but will likely require a longitudinal study to investigate properly. The cost and scope of such a study is probably beyond local capacity in the short-term, but could be pursued through international collaboration. There are also opportunities to improve the power of GPSS dataset and enable more precise and stratified VE analyses, by recruiting more GPs and/or pooling data from other Australian sentinel influenza surveillance programs.

Conclusions

Although the influenza A(H1N1)pdm09 pandemic spread rapidly around the globe and primarily affected younger age groups, it was relatively mild in terms of morbidity and mortality compared with previous pandemics. However, the intensity of the public health response, which was based on plans assuming a worst-case scenario, was not commensurate with the severity and magnitude of the disease.

Transmission of influenza A(H1N1)pdm09 was largely driven by those effectively invisible to the health system and was therefore well-established by the time it was detected. The delay in detection and high proportion of relatively mild infections meant that school closures and antiviral distribution to notified cases and their contacts were ineffective. Pandemic plans need to be revised to accommodate a range of scenarios and ensure trust from public and professionals in future pandemic responses.

Following its emergence and replacement of the previously circulating seasonal A(H1N1) in 2009, influenza A(H1N1)pdm09 remained dominant in Victoria in 2010. Higher proportions of A(H3N2) and type B influenza were observed in 2011 before dominance of A(H3N2) in 2012 that was accompanied by an increase in more severe infections, particularly in older age groups. Whilst ILI surveillance suggested influenza seasons of moderate magnitude from 2010-2012, notifiable disease data indicated a considerable increase in influenza testing by medical practitioners.

Influenza vaccine effectiveness in Victoria varied considerably in the years preceding, during and following the 2009 pandemic. With the exception of high influenza A(H1N1)pdm09-specific seasonal VE in 2010 and 2011, and no protective effect of seasonal vaccine against influenza A(H1N1)pdm09 in 2009, type and subtype-specific VE were inconsistent across seasons and had little evident correlation with the percentage match between circulating and vaccine strains as measured by HI. Further investigation of the role of previous immunity and antigenic similarity by phylogenetic analysis is needed to better understand the determinants of influenza VE.

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Appendix

Supplementary papers

About this appendix

This appendix contains papers related to aspects of influenza epidemiology and vaccine effectiveness following the 2009 pandemic in which I made a minor contribution during the course of my doctoral candidature.

The first study, published in *Emerging Infectious Diseases*, was a retrospective cross-sectional study of index case-patients and their household contacts that examined transmission of influenza A(H1N1)pdm09 in households, identified possible risk factors for intra-household secondary transmission, and assessed the effects of prevention and control measures introduced to limit transmission.

The following three studies, all published in *BMC Infectious Diseases*, were part of a research grant investigating influenza A(H1N1)pdm09-related school closures in Victoria. Each study drew on the results from a cross-sectional survey of families affected by school closures and assessed the understanding, compliance with and financial impact of home quarantine recommended to school children because they were diagnosed with influenza A(H1N1)pdm09 or were a close contact of a case.

The final study in this appendix estimated annual influenza vaccine effectiveness for the years from 2007-2011, with the exception of the pandemic year of 2009, and was published in *Influenza and Other Respiratory Viruses*. The study drew on the same data used for the influenza vaccine effectiveness studies in Chapter 7, but was restricted to adults aged 20-64 years and classified several variables differently in the analysis. In accordance with the copyright requirements of the journal publisher, the accepted version of this article – rather than a scan of the published version – is presented in this appendix.

Papers in this appendix

1. van Gemert C, McBryde ES, **Fielding J**, Spelman T, Higgins N, Lester R, Vally H, Hellard M, Bergeri I. Intrahousehold transmission of pandemic (H1N1) 2009 virus, Victoria, Australia. *Emerg Infect Dis* 2011; 17: 1599-1607.
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Intrahousehold Transmission of Pandemic (H1N1) 2009 Virus, Victoria, Australia

Caroline van Gemert, Margaret Hellard, Emma S. McBryde, James Fielding, Tim Spelman, Nasra Higgins, Rosemary Lester, Hassan Vally,[1] and Isabel Bergeri

To examine intrahousehold secondary transmission of pandemic (H1N1) 2009 virus in households in Victoria, Australia, we conducted a retrospective cross-sectional study in late 2009. We randomly selected case-patients reported during May–June 2009 and their household contacts. Information collected included household characteristics, use of prevention and control measures, and signs and symptoms. Secondary cases were defined as influenza-like illness in household contacts within the specified period. Secondary transmission was identified for 18 of 122 susceptible household contacts. To identify independent predictors of secondary transmission, we developed a model. Risk factors were concurrent quarantine with the household index case-patient, and a protective factor was antiviral prophylaxis. These findings show that timely provision of antiviral prophylaxis to household contacts, particularly when household members are concurrently quarantined during implementation of pandemic management strategies, delays or contains community transmission of pandemic (H1N1) 2009 virus.

Households play a major role in secondary transmission of pandemic influenza. Modeling estimates that household transmission has accounted for 25%–40% of all pandemic (H1N1) 2009 cases (*1*,*2*). Although understanding the effect of individual-level and household-level factors on secondary transmission of pandemic (H1N1) 2009 is paramount to informing population-level prevention strategies, few studies have evaluated household-level risk factors (*3*–*8*).

The Australian Health Management Plan for Pandemic Influenza (AHMPPI), revised in 2008, provides a framework for preparedness and response to pandemic influenza (*9*). The emergence and magnitude of pandemic (H1N1) 2009 in Melbourne, Australia (*10*–*15*), coupled with intensive follow-up and case identification data collected during the delay and contain phases of the AHMPPI (*16*), presented a unique opportunity to characterize intrahousehold transmission during a period of community transmission. Introduction of a suite of prevention and control measures in accordance with AHMPPI also provided an opportunity to measure the effects of these interventions on pandemic (H1N1) 2009 virus transmission.

We therefore conducted a retrospective cross-sectional study of index case-patients and their household contacts in Melbourne (population >3.5 million), Australia (*17*). We examined transmission of pandemic (H1N1) 2009 in households, identified possible risk factors for intrahousehold secondary transmission, and assessed the effects of prevention and control measures introduced to limit transmission.

Methods

Participants

The sample population consisted of all persons with confirmed cases of pandemic (H1N1) 2009 reported to the

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Victorian Department of Health (VDOH) during the delay and contain phases of AHMPPI (May 18–June 3, 2009) from 2 neighboring municipal regions in Melbourne with high numbers of pandemic (H1N1) 2009 notifications. To ensure that only the first reported case in a household could be randomly selected, we flagged households with >1 confirmed case. The index case-patient and household contacts were then recruited by mail and telephone (up to 5 calls were attempted). Of those who could be contacted, we assessed the household's eligibility according to the Australian Bureau of Statistics definition of a family (households of ≥2 persons residing together, including at least 1 person <18 years of age, related by blood, marriage, de facto, adoption, or fostering) (*18*).

Data Collection

During November 18–December 21, 2009, interviewers administered questionnaires to index case-patients and their household contacts. Data collected included demographics, case details, and prevention and control measures used. Participants indicated dates of symptom onset and prevention and control measures used in a retrospective diary of the period of interest (May 11–June 14, 2009). Interpreters were used as requested or needed. A parent or guardian was also interviewed when a participant was <18 years of age. If a household member was not available, a parent, guardian, or partner provided information. Written informed consent was obtained for all participants; parents or legal guardians provided written informed consent for participants <18 years of age.

Definitions

Index case-patients were defined as patients with the first laboratory-confirmed case of pandemic (H1N1) 2009 in a household reported to the VDOH. Household contacts were defined as persons residing in the same household at the time of the index case-patient's symptom onset.

Cultural and linguistic diversity was defined as speaking English only or speaking languages other than English in the home. The latter category included those households in which English was a second language.

A secondary case-patient was defined as a household contact who met the case definition for having an influenza-like illness (ILI), defined as self-described fever plus chills and/or respiratory tract signs or symptoms such as cough, sore throat, or shortness of breath with onset 1–9 days after onset for the index case-patient. This interval was based on a serial interval (the number of days between symptom onset in the index case-patient and household contacts) of up to 9 days to identify secondary cases, given that shedding of seasonal influenza virus rarely lasts >8 days (*7,19*) and a median incubation period for seasonal influenza of ≈1.4 days (*7,20*). Secondary cases were not required to be laboratory confirmed. Household contacts who met our definition for having ILI but who reported symptom onset on the same day as or before that of the index case-patient were not considered to be at risk for secondary transmission and were not included in analysis for exposures associated with secondary transmission.

Use of antiviral drugs (treatment or prophylaxis) was self-reported. VDOH provided antiviral treatment to those who met the case definition (confirmed or suspected case) and whose symptom onset was within 48 hours and provided antiviral prophylaxis to household contacts. Quarantine was self-reported and defined as separation and restriction of movement of case-patients and contacts in their homes (*21*). During the contain phase, patients with confirmed cases were advised to quarantine themselves for 7 days after symptom onset, and contacts were advised to quarantine themselves at home for 7 days after the most recent exposure to an infectious case-patient. A case-patient was considered infectious for 7 days after symptom onset or until acute respiratory symptoms resolved, whichever was longer (*21*).

Analysis

Chi-square tests were used to determine differences in clinical signs and use of prevention and control measures between index case-patients and household contacts. The Fisher exact test statistic, used to determine nonrandom associations between 2 categorical variables, was used when the expected value was <6. Secondary attack rates (SARs) were calculated by dividing the number of secondary cases by the total number of susceptible household contacts. We stratified SARs for several potential predictors, including individual-level factors, prevention and control measures, and household-level factors. Potential predictors included gender, age group (0–4, 5–19, 20–49, ≥50 years), relationship to index case-patient (parent/child, sibling, partner, other family member, or other), use of antiviral drugs (treatment or prophylaxis), number of days quarantined with index case-patient, household size (2–3, 4–5, ≥6 persons), number of children living in the household (1, 2, ≥3 children), and cultural and linguistic diversity (English only spoken at home and English and/or other languages spoken at home).

Unadjusted logistic regression was used to identify significant candidate predictors ($p<0.05$) for inclusion in the final adjusted model. The final model used reverse stepwise selection procedures in which all significant predictors of secondary transmission were included in the initial model and removed sequentially until only significant predictors ($p<0.05$) remained. We accounted for household clustering in the unadjusted and adjusted logistic regression models; that is, we adjusted for dependency of all potential predictors based on

membership in the same household by using a generalized estimated equation with robust error estimates, assuming conditional independence within each family (i.e., within the family, each member had independent probability of becoming a case-patient). Goodness of fit for both models was assessed by using the Hosmer–Lemeshow test to 0.05 significance. Statistical analyses were conducted by using Stata version 10 (StataCorp LP, College Station, TX, USA). To indicate precision of the measurement, we have reported 3 significant (i.e., nonzero) figures.

Ethical Considerations

Participants were reimbursed with $A30. Ethical approval was obtained from the Alfred Hospital Ethics Committee and Australian National University Ethics Committee.

Results

Participation and Response Rates

Data extracted on October 20, 2009, contained records for 857 confirmed cases of pandemic (H1N1) 2009, representing 772 households, reported on or before June 3, 2009, including a total of 181 cases for persons residing in the selected municipalities. We then randomly selected 72 case-patients to participate in this study, of which 12 refused, 21 could not be contacted, and 3 did not meet eligibility requirements; the remaining 36 index case-patients and their 131 household contacts participated. Participating and nonparticipating index case-patients were similar in age and student status; however, more nonparticipating (n = 4) than participating (n = 2) index case-patients required an interpreter. Among the 36 households that participated in the study, 32 (88.9%) persons were interviewed face to face and 4 (11.1%) were interviewed by telephone. Interpreters were used for interviews in 2 households.

Participant Characteristics

The analysis included 36 index case-patients and 131 household contacts (Table 1). The age range of index case-patients was 6–47 years; that of household contacts was 1–74 years. The number of persons living in each household was 2–14, median 4.5 persons. The number of children living in each household was 1–7; most (75.0%) households had 1–2 children. In half of the households (n = 18), a language other than English was spoken at home.

Prevention and Control Measures

Antiviral treatment was taken by 30.6% of index case-patients and 4.58% of all household contacts (Table 2). Just under half (45.8%) of all household contacts reported taking antiviral prophylaxis; and among those who did, 1 person reported subsequent symptoms consistent with ILI. The proportion of index case-patients and household contacts who reported being quarantined differed significantly (88.9% and 69.5%, respectively, p = 0.013).

The median number of days to initiate quarantine was 3 days for index case-patients and 4 days for household contacts. Greater than half (61.1%) of household contacts reported concurrent quarantine with the index case-patient for at least 1 day; the range of concurrent quarantine was 1–15 days, median 4 days.

The median number of days before antiviral treatment was initiated for index case-patients and household contacts was 2 days (Figure 1). The median number of days before antiviral prophylaxis was initiated among household contacts was 6 days.

Clinical Features

Among 131 household contacts, 122 (93.1%) were considered to be at risk for secondary transmission. Among these, 18 reported symptoms consistent with ILI within 1–9 days of symptom onset for the index case-patient and were thus considered secondary case-patients (Figure 2). Household contacts who reported symptom onset before the index case-patient (n = 5), on the same day as the index case-patient (n = 4), or >9 days after onset of symptoms in the index case-patient (n = 3) were not considered to be secondary case-patients and were not included in analyses. The serial interval for secondary cases included in the analysis was 1–9 days, median 2 days.

With the exception of vomiting, clinical features reported by index and secondary case-patients did not differ significantly (range p = 0.275–0.667, Table 3). The most frequent duration of symptoms for index and secondary case-patients was 4–6 days; 31.3% and 37.0% of index and secondary case-patients, respectively, reported symptom duration within this range. Approximately three fourths (77.8%) of secondary case-patients sought medical care (p = 0.01). Prevention or control measures used by index case-patients and secondary case-patients did not differ significantly (quarantine p = 0.429, antiviral prophylaxis p = 0.429, antiviral treatment p = 0.095)

Secondary Transmission

The overall SAR in this study was 14.8% (95% confidence interval [CI] 8.90%–22.3%, Table 4). The SAR varied when stratified for different individual-level and household-level factors. In unadjusted analysis, predictors of intrahousehold secondary transmission were being female, concurrent quarantine with the index case-patient, and use of antiviral prophylaxis (Table 5). We did not find a significant association between secondary case-patients and age group, relationship to the index case, household size, number of children living in the household, or cultural

Table 1. Characteristics of pandemic (H1N1) 2009 case-patients and household contacts, Victoria, Australia, May 18–June 3, 2009*

Characteristic	No. (%) index case-patients, n = 36	No. (%) household contacts, n = 131	p value
Individual level			
Sex			
M	25 (69.4)	69 (52.7)	0.07
F	11 (30.6)	62 (47.3)	
Age, y			
0–4	0	13 (9.92)	<0.001
5–19	31 (86.1)	40 (30.5)	
20–49	5 (13.9)	68 (51.9)	
≥50	0	10 (7.63)	
Household level		NA	NA
No. persons			
2–3	5 (13.9)		
4–5	22 (61.1)		
≥6	9 (25.0)		
No. children		NA	NA
1	12 (33.3)		
2	15 (41.7)		
≥3	9 (25.0)		
Cultural and linguistic diversity		NA	NA
English only spoken at home	18 (50.0)		
English and/or other language(s) spoken at home	18 (50.0)		

*NA, not applicable.

and linguistic diversity. In the adjusted analysis, p value for gender decreased from 0.037 to 0.83 and was thus removed from the final model. In the final model, the odds of a household contact who was concurrently quarantined with the index case-patient becoming a secondary case-patient increased for each additional day (adjusted odds ratio 1.25, 95% CI 1.06–1.47), and the odds of secondary transmission among household contacts who reported use of antiviral prophylaxis decreased (adjusted odds ratio 0.042, 95% CI 0.004–0.434). We did not identify a significant interaction term to include in the multivariate model.

Discussion

This study fully characterizes transmission of pandemic (H1N1) 2009 in households in Australia during implementation of pandemic management strategies to delay or contain community transmission. The findings are relevant for prevention and control strategies used at the household level indicated in the AHMPPI and for international pandemic influenza planning. Overall, 14.8% of susceptible household contacts became secondary case-patients, assumed to have been infected by the index case-patient. The SAR for ILI observed in this study is within the range of reported SARs for ILI used as a proxy for pandemic (H1N1) 2009 in similar international studies, which were 3.7%–45% (4–8,22–27).

The odds of seeking medical care were lower for secondary than for index case-patients. Although this finding was expected because of the case ascertainment methods used, other factors involved with health care–seeking behavior should be considered. For example, household contacts may have not sought care because VDOH provided antiviral treatment and prophylaxis to household contacts without requiring evidence of laboratory-confirmed disease. Furthermore, symptomatic household contacts may have reasonably assumed that they were infected with pandemic (H1N1) 2009 given their proximity to a confirmed case-patient and may not

Table 2. Prevention and control measures used by pandemic (H1N1) 2009 case-patients and household contacts, Victoria, Australia, May 18–June 3, 2009*

Reported measure	No. (%) index case-patients, n = 36	No. (%) household contacts, n = 131	p value†
Antiviral			
Treatment	11 (30.6)	6 (4.58)	<0.001
Prophylaxis	0	60 (45.8)	<0.001
Quarantine duration, d			
≥1	32 (88.9)	91 (69.5)	0.013
≥1 with index case-patient	NA	80 (61.1)	

*NA, not applicable.
†Fisher exact test statistic used when expected value <6.

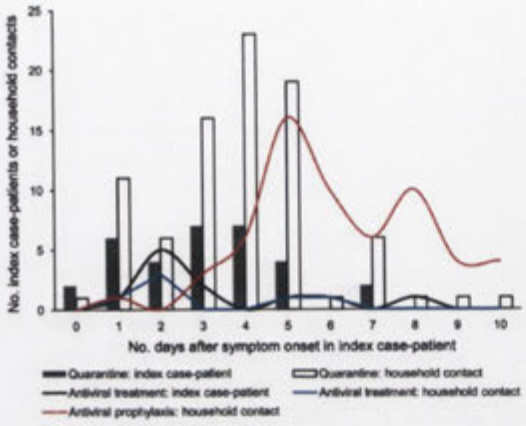

Figure 1. Timeliness of quarantine initiation and administration of antiviral (treatment and prophylaxis) by pandemic (H1N1) 2009 index case-patients and household contacts after onset of symptoms in the index case-patients, Melbourne, Victoria, Australia, May 18–June 3, 2009.

have considered confirmation necessary. The differences in health care–seeking behavior have implications for the pandemic influenza response, particularly during the phases of the AHMPPI when emphasis is on active case finding and slowing community transmission. This finding highlights the need for timely household-level, rather than individual-level, provision of treatment and prevention strategies by health care professionals, at the point of care of the index case-patient.

Several individual-level and household-level factors influenced the SAR and the odds of secondary transmission within households. The odds of becoming a secondary case-patient were almost 3× greater for female than male contacts, possibly because more women assume caregiver roles and therefore having a greater likelihood of exposure. This explanation is supported by France et al. (*4*), who reported that providing care to a case-patient was associated with a higher risk for ILI among parents. A study with greater power may be able to demonstrate this association in adjusted analyses. Other studies have also reported findings that older age was protective against secondary transmission of pandemic (H1N1) 2009, possibly as a result of prior immunity in older age groups (*4*,*5*). Although a decreasing trend of secondary transmission was observed for participants 5–19 years to 20–49 years of age, the size of this study was insufficiently powered to demonstrate a significant association between age group and rate of secondary transmission.

Our finding that antiviral prophylaxis reduced the odds of secondary transmission by 95% among at-risk household contacts was greater than that reported by France et al., who reported a 68% reduction in risk (*4*). Although this finding highlights the potential for antiviral prophylaxis to prevent secondary transmission, it should be considered along with the finding that initiation of antiviral treatment and prophylaxis for index case-patients and household contacts was considerably delayed. Current evidence highlights that rapid implementation of prevention measures such as antiviral prophylaxis is critical for control of pandemic influenza as soon as community transmission is identified; our findings identify an area for improvement in the implementation of pandemic influenza management plans. For example, the need for timely use of antiviral prophylaxis was demonstrated by Donnelly et al., who found that only 18% of pandemic influenza transmission events take place >2 days after onset of symptoms in case-patients (*28*). Ghani et al. also demonstrated this need when they reported a 3-fold increase in odds of intrahousehold secondary transmission in households that did not receive antiviral prophylaxis within 3 days of index case-patient symptom onset (*2*). Similarly, Goldstein et al. report that early antiviral treatment (on the day of or day after symptom onset) reduced the odds of household secondary transmission by 42% (*29*).

The issue of timeliness was also identified with regard to initiation of quarantine. We identified a considerable delay between onset of symptoms in the index case-patient and initiation of quarantine for index case-patients and household contacts, thus prolonging community exposure to pandemic (H1N1) 2009. Quarantine of case-patients and close contacts is considered an essential strategy for mitigating community transmission of pandemic influenza (*9*); however, to reduce the rate of community transmission, case-patients need to be quarantined as early as possible during their infectious period.

Although quarantine has been demonstrated to be effective at reducing community attack rates in pandemic influenza modeling studies, it has been hypothesized

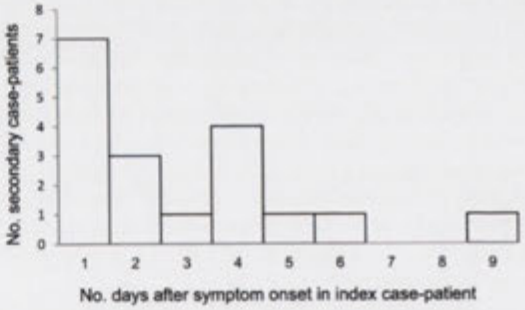

Figure 2. Serial interval for symptom onset in pandemic (H1N1) 2009 index case-patient to symptom onset in secondary case-patients, Melbourne, Victoria, Australia, May 18–June 3, 2009.

Table 3. Clinical features for pandemic (H1N1) 2009 case-patients and household contacts, Victoria, Australia, May 18–June 3, 2009

Feature	No. (%) index case-patients, n = 36	No. (%) secondary case-patients, n = 18	p value*
Sign or symptom			
Fever	35 (97.2)	18 (100)	0.67
Chills	17 (47.2)	8 (44.4)	0.54
Headache	25 (69.4)	13 (72.2)	0.55
Muscle pain	20 (55.6)	8 (44.4)	0.32
Joint pain	15 (41.7)	7 (38.9)	0.54
Fatigue	30 (83.3)	16 (88.9)	0.46
Diarrhea	8 (22.2)	2 (11.1)	0.28
Vomiting	16 (44.4)	2 (11.1)	0.01
Upper respiratory tract symptoms	32 (88.9)	17 (94.4)	0.45
Sign or symptom duration, d			
1–3	9 (25.0)	2 (11.2)	0.49
4–6	13 (36.1)	9 (50.0)	
7–9	9 (25.1)	3 (16.7)	
≥10	5 (13.8)	4 (22.2)	
Any medical care received	36 (100)	14 (77.8)	0.01
Reported prevention and control measures taken			
Quarantine	32 (88.9)	15 (83.3)	0.43
Antiviral prophylaxis	0	1 (5.56)	0.43
Antiviral treatment	11 (33.3)	2 (11.1)	0.10

*Fisher exact test statistic used when expected value was <6.

that the subsequent increase in contact rates between household members during quarantine may increase intrahousehold transmission (*30*). We found evidence supporting this hypothesis, demonstrating that the odds of secondary transmission increased >20% for each additional day of quarantine with the index case-patient. Similar effects of quarantine on intrahousehold secondary attack rates have not been reported for pandemic (H1N1) 2009; however, a study of university students in the People's Republic of China found an increased attack rate among contacts who shared a room or bathroom with confirmed pandemic (H1N1) 2009 case-patients (*31*), and a study in New York reported increased risk between siblings who interacted closely with the index case-patient (*4*). Thus, to prevent community transmission, effective communication to confirmed case-patients as well as their household contacts to ensure timely implementation of quarantine measures is needed. This finding should be considered along with previously discussed public health implications, including the recommendation for implementation of prevention and control measures at the household level rather than the individual level to ensure that messages reach household contacts. Furthermore, to counter the increased risk associated with quarantine with the index case-patient, quarantine should be implemented concurrently with distribution of antiviral prophylaxis to household contacts.

The influence of cultural and linguistic diversity on secondary transmission served as a proxy for a range of social and environmental determinants of intrahousehold transmission of pandemic (H1N1) 2009 transmission, including recognition and understanding of health promotion messages and access to antiviral treatment and prophylaxis during the containment stages of the AHMPPI. A key finding was a higher SAR among persons who spoke languages other than English at home. This finding suggests that control and prevention measures were not effectively communicated, comprehended, and adhered to by a major community subset in Victoria. Although a higher SAR was observed among persons who spoke languages other than English at home, the study had insufficient power to provide evidence for the relative contribution of cultural and linguistic diversity on secondary transmission. Nonetheless, the potential issues associated with effective communication, comprehension, and adherence to prevention and control measures by cultural and linguistically diverse communities suggest that further work should explore the social and cultural determinants of pandemic (H1N1) 2009.

This study has some limitations. First, it was subject to recall bias, which we attempted to reduce by using tools to improve accurate recall of illness (such as case notification information from VDOH and calendars of major events that occurred during the period of interest). Second, information bias may have been introduced by household members who provided information for household contacts not available at the time of interview. This bias occurred during a few interviews; however, any information bias is likely to underestimate the true association between exposures and pandemic (H1N1) 2009. Third, ILI was used as an indicator for pandemic (H1N1) 2009, and thus some misclassification may have occurred. However, because sentinel surveillance

indicated that most respiratory infections during the same period were pandemic (H1N1) 2009, misclassification was probably minimal (*32*). Fourth, recruitment of households on the basis of the confirmed status of 1 household member may introduce selection bias; however, during the study period, rates of testing of persons with mild to severe illness were high, and thus household contacts should be representative of influenza infections in the community. Fifth, the sample size was small; nonetheless, we identified several factors significantly associated with secondary transmission of pandemic (H1N1) 2009. Sixth, some ILI might be community acquired and therefore overestimate the rate of secondary transmission; we attempted to mitigate any overestimation by excluding concurrent primary cases and household contacts who reported symptom onset before that of the index case-patient.

Our study findings can aid the continued development of future pandemic influenza preparedness plans in Australia and internationally. In particular, the provision of treatment and prevention strategies at the household level, rather than at the individual level alone at the point of care of the index case-patient, should be considered. The need for engagement at the household rather than the individual level is further emphasized by the benefit of timely provision of antiviral prophylaxis to household contacts, particularly when household contacts are quarantined concurrently with the index case-patient. The integration of these practical findings in the development of pandemic influenza preparedness plans in Australia and internationally can help reduce the potential for intrahousehold transmission of influenza during future pandemics.

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Table 4. Secondary attack rates for susceptible household contacts of index case-patients with pandemic (H1N1) 2009, Victoria, Australia, May 18–June 3, 2009*

Variable	Total no. household contacts	No. with influenza-like illness	Secondary attack rate, % (95% CI)
Individual-level associations			
Sex			
M	58	5	8.62 (1.08–14.4)
F	64	13	20.3 (11.3–32.2)
Age, y			
0–4	11	1	9.09 (0.230–41.3)
5–19	35	6	17.1 (6.50–33.6)
20–49	66	10	15.2 (7.51–26.1)
≥50	10	1	10.0 (0.25–44.5)
Relationship to index case-patient			
Parent/child/partner	65	10	15.4 (7.63–26.5)
Sibling	44	8	18.2 (8.19–32.7)
Other family member	13	0	0 (0–24.7)
Prevention and control measures reported			
Antiviral prophylaxis	57	1	1.8 (0.04–9.39)
Quarantined ≥1 d with index case-patient	73	15	20.5 (12.0–31.6)
Household-level associations			
No. persons			
2–3	7	2	28.6 (3.67–71.0)
4–5	75	10	13.3 (6.58–23.2)
≥6	40	6	15.0 (5.71–29.8)
No. children			
1	31	6	19.4 (7.45–37.5)
2	47	7	14.9 (6.20–28.3)
≥3	44	5	11.4 (3.79–24.6)
Cultural and linguistic diversity			
Only English spoken at home	53	5	9.4 (3.13–20.7)
English and/or other language(s) spoken at home	69	13	18.8 (10.4–30.1)

*CI, confidence interval.

Table 5. Unadjusted associations with secondary transmission for pandemic (H1N1) 2009, Victoria, Australia, May 18–June 3, 2009*

Variable	OR (95% CI)	p value
Individual level		
Sex		
M	1.00	
F	2.70 (1.060–6.860)	0.037
Age, y		
0–4	1.00	
5–19	2.06 (0.179–23.90)	0.560
20–49	1.79 (0.228–14.00)	0.581
≥50	1.11 (0.529–23.30)	0.946
Relationship to index case-patient		
Parent/child/partner	1.00	
Sibling	1.22 (0.562–2.660)	0.613
Other family member	†	
Reported prevention and control measures		
Antiviral prophylaxis‡	0.05 (0.006–0.429)	0.006
Quarantined for ≥1 d with index case-patient§	1.22 (1.03–1.44)	0.019
Household level		
No. persons		
2–3	1.00	
4–5	0.385 (0.035–4.280)	0.437
≥6	0.441 (0.024–8.070)	0.581
No. children		
1	1.00	
2	0.729 (0.163–3.260)	0.679
≥3	0.534 (0.05–5.74)	0.605
Cultural and linguistic diversity		
Only English spoken at home	1.00	
English and/or other language(s) spoken at home	2.23 (0.448–11.100)	0.328

*Backwards stepwise selection procedures were used to develop the final adjusted model whereby predictors (p>0.05) were removed sequentially until only significant predictors (p<0.05) remained. Gender was not significant in the adjusted model (p = 0.83) and was thus removed. Goodness of fit for both models was assessed by using the Hosmer and Lemeshow test to 0.05 significance. Goodness of fit for the final model was 0.2. OR, odds ratio; CI, confidence interval.
†No secondary cases occurred in this group, and this level is not included in the unadjusted model.
‡Adjusted OR 0.042 (95% CI 0.004–0.434); p = 0.008.
§Logistic regression using number of days quarantined with index case-patient as continuous exposure. Adjusted OR 1.25 (95% CI 1.06–1.47); p = 0.008.

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Ms van Gemert was a Masters of Applied Epidemiology Scholar at the Australian National University at the time of the study. She now works as a researcher in the Centre for Population Health, Burnet Institute, Melbourne. Her primary research interest is the link between behavior and transmission of infectious diseases.

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RESEARCH ARTICLE Open Access

Sources, perceived usefulness and understanding of information disseminated to families who entered home quarantine during the H1N1 pandemic in Victoria, Australia: a cross-sectional study

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Abstract

Background: Voluntary home quarantine of cases and close contacts was the main non-pharmaceutical intervention used to limit transmission of pandemic (H1N1) 2009 influenza (pH1N1) in the initial response to the outbreak of the disease in Australia. The effectiveness of voluntary quarantine logically depends on affected families having a clear understanding of what they are being asked to do. Information may come from many sources, including the media, health officials, family and friends, schools, and health professionals. We report the extent to which families who entered home quarantine received and used information on what they were supposed to do. Specifically, we outline their sources of information; the perceived usefulness of each source; and associations between understanding of recommendations and compliance.

Methods: Cross-sectional survey administered via the internet and computer assisted telephone interview to families whose school children were recommended to go into home quarantine because they were diagnosed with H1N1 or were a close contact of a case. The sample included 314 of 1157 potentially eligible households (27% response rate) from 33 schools in metropolitan Melbourne. Adjusting for clustering within schools, we describe self-reported 'understanding of what they were meant to do during the quarantine period'; source of information (e.g. health department) and usefulness of information. Using logistic regression we examine whether compliance with quarantine recommendations was associated with understanding and the type of information source used.

Results: Ninety per cent understood what they were meant to do during the quarantine period with levels of understanding higher in households with cases (98%, 95% CI 93%-99% vs 88%, 95% CI 84%-91%, P = 0.006). Over 87% of parents received information about quarantine from the school, 63% from the health department and 44% from the media. 53% of households were fully compliant and there was increased compliance in households that reported that they understood what they were meant to do (Odds Ratio 2.27, 95% CI 1.35-3.80).

Conclusions: It is critical that public health officials work closely with other government departments and media to provide clear, consistent and simple information about what to do during quarantine as high levels of understanding will maximise compliance in the quarantined population.

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Background

In the absence of an effective vaccine, social distancing is a key strategy for preventing the spread of emerging, potentially serious, infectious respiratory diseases [1]. Voluntary home quarantine of cases and close contacts was the main non-pharmaceutical intervention used to limit transmission of pandemic (H1N1) 2009 influenza (pH1N1) in the initial response to the outbreak of the disease in Australia. The Australian Government's management plan for pandemic influenza recommended school and classroom closures to reduce the early spread of the virus [2]. School closures and home quarantine became a key strategy during the 'contain phase' of the outbreak (22 May - 2 June 2009) [3], particularly in Victoria, because the majority of Australia's HIN1 cases occurred among school-aged children in that state [4-6].

The effectiveness of voluntary quarantine logically depends on affected families having a clear understanding of what they are being asked to do. Typically, however, the conditions are not conducive to conveying clear messages. As outbreaks unfold quickly, information tends to come from many sources, including the media, health officials, family and friends, schools, employers and health professionals. In previous epidemics, the accuracy, clarity, and usefulness of this information have been shown to vary greatly [7]. Two Australian studies of quarantine compliance included a study of Western Australian school children [8] and a national study that reported intention to comply among unaffected individuals [9]; neither of these studies reported on understanding of quarantine recommendations or information sources used. In fact we could not identify any published studies that have reported the sources of information, understanding of recommendations and compliance.

We conducted a cross-sectional survey of Victorian households with children who were placed in voluntary home quarantine during the contain phase of the pH1N1 outbreak. The survey probed participants' understanding of the quarantine recommendations, the information sources used to gain this understanding, and the perceived usefulness of those sources. We also analysed whether these factors were associated with levels of compliance among families. Our goal was to inform the design and implementation of communication strategies around quarantine in future pandemics.

Methods

Study Environment

The first Australian case of pH1N1 was identified on 8 May 2009 [10]. Two weeks later, Victoria's first case was identified, a nine year-old boy who had recently returned from the United States [4]. In the 12-day contain phase that followed, cases and their immediate family members and close contacts were asked to go into home quarantine. Quarantined persons were expected to have no contact with non-household members and were treated with Oseltamivir for ten days. Cases were asked to stay in quarantine for seven days after the onset of symptoms. Contacts—defined as individuals who spent more than four hours in the same room as the confirmed case, or were within one metre of the confirmed case for more than 15 minutes—were asked to stay in home quarantine for seven days from last date of exposure to the case (Department of Health Victoria quarantine guidelines, 4 June 2009).

The trigger for closure of mainstream schools was two or more confirmed cases in separate classes. However only cases and fellow students who met the definition of contacts were placed in home quarantine; other students in closed schools were merely asked to limit their outside activities (Department of Health Victoria quarantine guidelines, 4 June 2009). The policy at special developmental schools (SDS) differed from mainstream schools: a confirmed case triggered home quarantine for the entire student body.

Sample

We identified affected households through schools. During the outbreak, the Victorian Departments of Education and Early Child Development (DEECD) and Health and the Catholic Education Office were actively involved in visiting schools, identifying cases and determining the need for quarantine. Each of these agencies held separate but incomplete information on closure and quarantine activities in schools. After pooling this information, we approached Principals at 82 schools that were known or suspected to have implemented closures and asked children to enter quarantine (Figure 1). For Catholic Schools, the DEECD information was reconciled with the information held by the Catholic Education Office before schools were approached. As a consequence of this a smaller proportion of Catholic schools were considered ineligible after schools were contacted directly (23% of Catholic Schools and 58% of government schools). We posed two eligibility questions to the Principals, namely, did the school have (1) classes closed during the contain phase of the outbreak? and (2) children who were asked to go into home quarantine?

Three Principals did not respond to our approaches, three declined to participate, and 37 schools did not meet the eligibility criteria (i.e. the Principals answered "no" to one or both of the eligibility questions). Of the rest, 33 Princpals agreed to facilitate the conduct of the survey resulting in an eligible school participation rate of 85%.

We worked with staff of these 33 schools to identify 1,188 families who experienced quarantine. School staff used a mix of information to identify these families,

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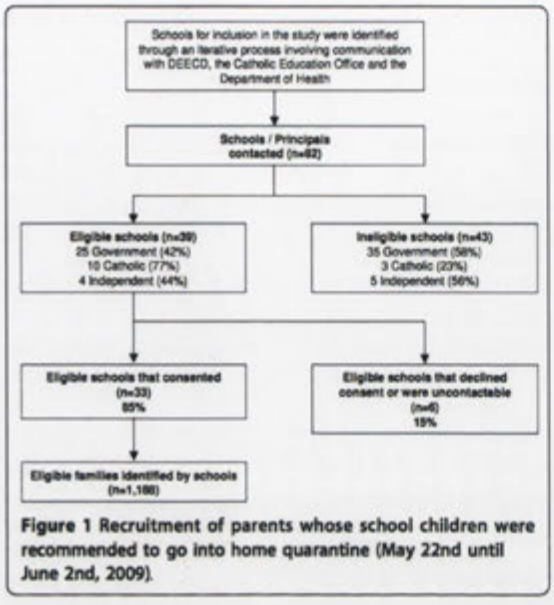

Figure 1 Recruitment of parents whose school children were recommended to go into home quarantine (May 22nd until June 2nd, 2009).

including enrolment records, class lists and documentation of which classes and students had been asked to enter quarantine. Our research team guided the school staff through the process of assembling and reviewing this information, but we did not have contact with data identifying students or families, either at this stage or during subsequent administration of the survey.

The study was approved by the ethics committee at the University of Melbourne (0932293) and the DEECD and the Catholic Education Office granted us permission to approach schools to conduct the survey.

Survey Questionnaire

The questionnaire had several modules. One module gathered demographic details about the family, including household composition, education, employment, housing and income. Another module elicited information on whether each member of the household: was a contact or case (defined as having a pH1N1 diagnosis confirmed by a laboratory or medical practitioner); received Oseltamivir for treatment or prophylaxis; and complied with quarantine.

Another module, the focus of this paper, asked participants whether they understood what their family was being asked to do during the quarantine period, where they obtained information on what to do, and how useful various sources of such information proved to be. Specifically, participants were asked to rate on a five-point scale ranging from strongly agree to strongly disagree the extent to which they agreed or disagreed with the statement *"At the time of the quarantine measures I understood what my family was being asked to do"*. Participants were also asked where they obtained *"information about what you were supposed to do in quarantine"* with the following response options: health department (which might refer to state or federal government); school; general practitioner (GP)/other health care provider; family/friends; media (newspaper/tv) and other. Multiple responses were possible. Finally, participants were asked to rate the usefulness of each information source.

For analytical purposes, we collapsed the gradations of understanding into a binary variable (strongly agree/agree vs. neither agree nor disagree/disagree/strongly disagree).

We defined a household as compliant with quarantine recommendations if they met all of the following criteria: (1) All quarantined members of the household stayed at home for most of each day; (2) No quarantined household members visited public places with lots of other people (excluding visits to health practitioners); (3) No adults from other households visited the home for ≥15 minutes; (4) Quarantined children did not mix with children from another household for ≥15 minutes; and (5) Any childcare was only provided by adults living in the household.

Survey Administration

The survey was administered during November and December 2009. School staff mailed letters to the parents in eligible families inviting them to participate. The letter presented two options: an internet address at which parents could complete the questionnaire online and a telephone number to ring to complete it via a Computer Assisted Telephone Interview (CATI). The survey was offered in English only. The letter also included a unique 8-digit identification number which enabled access to the website and CATI. This number allowed us to identify the school(s) and home class(es) of each family's child(ren), but revealed no other identifying information.

School staff mailed two reminder letters. To boost response rates and recognise the effort involved for participating families and schools we contributed $AU20 to the school for the purchase of educational resources for each completed questionnaire and all families received a movie voucher valued at AU$10.30 with the second reminder letter.

Eight letters were returned-to-sender and 23 parents responded indicating that they did not have a school-aged child who had been placed in home quarantine. This left an in-scope sample of 1,157. We received 314 responses yielding a household participation rate of 27%. Missing data on key questions related to the information sources reduced our analysable sample for this study to 297 families.

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Analysis

All analyses were conducted in Stata 11.0 (STATA Corp, College Station, TX). We calculated proportions for each of the variables of interest (household understanding of quarantine requirements, and use and perceived usefulness of information sources) and stratified these proportions by whether the households had a case or contacts only. To account for within-school clustering, we used logistic regression (using Stata's cluster command) and post-estimation commands to generate proportions, 95% confidence intervals and p-values.

We also used logistic regression, again adjusting for within-school clustering, to examine whether compliance with quarantine recommendations was associated with understanding of quarantine recommendations and the type of information source used. The types of information were grouped into official sources (health department and schools) and unofficial sources (media, family and friends and health care providers). We postulated that these relationships may be confounded by two variables—whether a household had a case or contacts only, and level of parental education—and so included these as covariates. However, because adjustment for these variables did not change the size and significance of the coefficients of interest, we report unadjusted estimates.

Results

Sample characteristics

Seventeen per cent of participants reported having had a confirmed case of pH1N1 in their household (Table 1). Seventy-six per cent of the quarantined children attended government schools, 15% attended Catholic schools and 9% attended Independent schools. Forty-one per cent of the children were in primary school, 35% were in secondary school and 24% were in Special Development Schools.

Table 1 Demographic characteristics of sample (n = 297)

	n	%
Sex of respondent		
Female	254	85.5
Age of oldest child		
Under 12	145	49.0
Number of children in home quarantine		
Two or more	46	15.5
Households with a case		
Case in household	51	17.2
School sector*		
Government	226	76.1
Catholic	45	15.2
Independent	26	8.8
School level*		
Primary	123	41.4
Primary/Secondary	1	0.3
Secondary	103	34.7
Special Development	70	23.6
Household composition		
Single parent, one child	12	4.0
Single parent, 2+ children	24	8.1
Couple, one child	40	13.5
Couple, 2+ children	221	74.4
Highest level of parental education		
Bachelor degree or higher	155	52.5

*refers to the school through which the household was contacted.

Understanding of quarantine recommendations

Ninety per cent (266/297) of participants understood what they were meant to do during the quarantine period. This proportion was significantly higher in households with cases than in households with contacts only (98%, 95% CI 93%-99% vs 88%, 95% CI 84%-91%, P < 0.001).

Information sources

Nearly 90% of parents received information about quarantine from the school and 63% obtained information from the health department (Table 2). The next most common information source was the media (44%). Overall, most families used multiple sources of information; only one household reported that they did not use any sources. 24% used only one source, 32% used two, and 44% used three or more.

A minority of participants reported using official sources only (n = 120, 40%). The majority (n = 172, 58%) used both official and unofficial sources of information. Only five households did not use any official sources.

There was some evidence that case households and contact-only households received their information from different sources. Case households were more likely to receive information from the health department (80%, 95 CI 64%-90% vs 59%, 95% CI 49%-69%, P = 0.015) and were less likely to receive their information through schools (51%, 95% CI 38%-64% vs 94% 95% CI 90%-96%, P < 0.001).

Perceptions of usefulness of information

Approximately two-thirds of participants reported that they found the information from the health department, schools and health service providers useful or extremely useful, whereas only 38% gave media sources this rating (Table 3). There were no significant differences in usefulness ratings between case households and contact-only households.

Relationship between understanding, information and compliance

Fifty-three per cent of participants reported full compliance with quarantine recommendations within their

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Table 2 Information sources used by parents whose children were placed in home quarantine

	% who obtained information from source					
	Total		Case in household		No case in household	
Information Source	n	%	%	95% CI	%	95% CI
School	257	86.5	51.0	(38.1, 63.7)	93.9	(89.8, 96.4)
Health Department	187	63.0	80.4	(64.2, 90.4)	59.3	(49.1, 68.8)
Media (newspaper/TV)	132	44.4	54.9	(42.4, 66.8)	42.3	(38.3, 46.4)
GP/other healthcare provider	84	28.3	58.8	(46.1, 70.5)	22.0	(15.6, 30.0)
Family/friends	51	17.2	13.7	(7.7, 23.1)	17.9	(14.4, 22.0)
Other	23	7.7	6.0	(2.4, 14.0)	8.1	(4.8, 13.3)

household. Of the 90% of respondents who reported understanding what they were meant to do during quarantine, 55% (n = 147) reported full compliance. In contrast, full compliance was only reported by 35% (n = 11) of the minority who did not report that they understood what they were meant to do. Compliance was higher in the households that reported understanding what they were meant to do during the quarantine period (Odds Ratio 2.27, 95% CI 1.35-3.80). There were no differences in the odds of compliance between households that used official sources of information only compared to those that used both official and unofficial sources (Odds Ratio 1.00, 95% CI 0.69-1.44). (The five households that did not use any official sources were excluded from this analysis.)

Discussion

Families with school-children who entered quarantine during Victoria's pH1N1 relied heavily on official sources of information, particularly schools and the health department. Troublingly, one third of families who used these sources did not find them useful in gaining an understanding of what they were supposed to do during quarantine. The media was the next most relied upon source although nearly 60% of families did not find this source illuminating. Our findings also suggest that the stakes associated with lack of comprehension are high, as the odds of compliance were more than twice as high among families who understood the home quarantine recommendations.

Liaising closely with a range of different media (such as print, television and internet) is critical, however media interests may not be congruent with optimal public health policy [7]. The fact that 44% of families in our study turned to the media as a source of information during the contain phase of the pandemic, but a minority found media information useful, indicates that there is much room for improvement in coordinating the messages coming from official and non-official sources. In future pandemics, which may be more severe and of longer duration than pH1N1, Australian government officials will need to work more closely with the media to provide accurate, easy-to-understand information on social distancing measures and other preventative strategies.

As most Australian cases occurred in Victorian schoolchildren, who became the chief target of preventive measures to reduce spread of pH1N1, our study provides valuable insights into information sources, understanding and compliance among families most affected by an emerging pandemic. However, the study has some limitations. Due to ethical and privacy issues the survey was not conducted until November and December 2009 (six months after the home quarantine measures had been implemented), introducing the potential for recall bias. Another potential problem relates to the way in which the question about information sources was asked, whereby we do not know how respondents who used the media to obtain information from health department would have answered. It is possible that they ticked health department,

Table 3 Usefulness of information sources in H1N1 pandemic in Victoria, Australia

	% useful or extremely useful					
	Total		Case in household		No case in household	
Information Source	n	%	%	95% CI	%	95% CI
Health Department	127	68.3	60.0	(46.1, 72.4)	70.3	(64.7, 75.5)
School	168	65.9	68.0	(49.5, 82.2)	65.9	(57.0, 73.9)
GP/other healthcare provider	51	63.0	71.4	(55.4, 83.4)	57.7	(43.9, 70.3)
Media (newspaper/TV)	51	38.6	48.1	(33.7, 62.7)	36.5	(27.8, 46.2)
Family/friends	16	32.0	42.9	(23.1, 65.2)	30.2	(18.5, 45.3)
Other	17	73.9	100.0	(29.2, 100.0)*	70.0	(50.5, 89.5)

*one-sided confidence interval.

media or both. A European study found that national and international public health authorities were by far the leading source of information in articles in the media on H1N1 influenza in the early stage of the pandemic [11]. If the same pattern was observed in Australia then it is likely that families accessed information from the health department through the media.

We had a relatively low response rate, although it is close to those achieved in similar studies that had much smaller population samples [12-14]. We had to administer the survey through schools due to privacy concerns and this is likely to have contributed to our low response rate. It also likely that response rates were low because most of the schools were located in the Northern Metropolitan region of Melbourne, an area that has higher levels of disadvantage and a greater proportion of households that speak a language other than English at home (http://www.abs.gov.au/websitedbs/D3310114.nsf/home/Census+data; accessed August 10/2010). In addition, the internet was the main mode of survey administration which may have reduced access for disadvantaged groups. To the extent that this type of response bias occurred, it is likely to make our estimates of the understanding and perceived usefulness of quarantine information among affected families higher than might be the case in all families affected by quarantine. It is possible that non-responders were less interested in H1N1 or health issues in general and that their understanding of information and the sources of information used may differ from responders. Without more information it is not possible to know how non-response bias might have affected our estimates of understanding of quarantine recommendations or the source of information.

Conclusions

Our findings reinforce the importance of providing clear messages about home quarantine and suggest that success in this area is likely to have a substantial impact on compliance. Closer attention to how government recommendations about quarantine are presented is needed, as one third of the sample reported that information obtained from these sources was not useful. Qualitative interviews with affected households might provide further insights into how the provision of this information could be improved. The quality and clarity of information from unofficial sources, particularly the media, is also important, recognising that nearly half the households in our study used media sources but two-thirds of them did not find this information useful. Coordination between the major information sources is also essential: government should work closely with the media to facilitate consistent messages, including responsible and accurate reporting of quarantine recommendations and other social distancing measures. Finally, future pandemic management may benefit from the implementation of a process to monitor in real time how communication messages are being received, thereby allowing timely analyses and amendments rather than relying on collecting information many months after the event.

The relatively benign nature of the recent pH1N1 in Australia probably prevented shortcomings in communication and outreach activities from causing serious harm. However, the next pandemic may be crueler: it may cause more serious morbidity and mortality, last longer, and necessitate the issuing of a range of recommendations over time to guide public action. Under those conditions, weaknesses in communication strategies will be exposed and may cost lives.

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Authors' contributions

AK conceived of the study and drafted the manuscript; RB contributed to the conception of the study and design and advised on analysis; KM developed the analytic plan and conducted the analyses; JM, JF, AL and DS contributed to the conception of the study and design; and SP contributed to the design of the survey and was responsible for its implementation. All authors contributed to the drafting of the manuscript and have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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RESEARCH ARTICLE Open Access

Recommendations for and compliance with social restrictions during implementation of school closures in the early phase of the influenza A (H1N1) 2009 outbreak in Melbourne, Australia

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Abstract

Background: Localized reactive school and classroom closures were implemented as part of a suite of pandemic containment measures during the initial response to influenza A (H1N1) 2009 in Melbourne, Australia. Infected individuals, and those who had been in close contact with a case, were asked to stay in voluntary home quarantine and refrain from contact with visitors for seven days from the date of symptom onset or exposure to an infected person. Oseltamivir (Tamiflu®) was available for treatment or prophylaxis.

Methods: We surveyed affected families through schools involved in the closures. Analyses of responses were descriptive. We characterized recommendations made to case and contact households and quantified adherence to guidelines and antiviral therapy.

Results: Of the 314 respondent households, 51 contained a confirmed case. The prescribed quarantine period ranged from 1-14 days, reflecting logistic difficulties in reactive implementation relative to the stated guidelines. Household-level compliance with the requirement to stay at home was high (84.5%, 95% CI 79.3,88.5) and contact with children outside the immediate family infrequent.

Conclusions: Levels of compliance with recommendations in our sample were high compared with other studies, likely due to heightened public awareness of a newly introduced virus of uncertain severity. The variability of reported recommendations highlighted the difficulties inherent in implementing a targeted reactive strategy, such as that employed in Melbourne, on a large scale during a public health emergency. This study emphasizes the need to understand how public health measures are implemented when seeking to evaluate their effectiveness.

Background

The World Health Organization declared the first influenza pandemic of the 21st Century in June 2009, following global spread of a novel swine-origin reassortant strain of influenza A (H1N1) (pH1N1) [1]. In Australia, as in many countries, initial reports were dominated by outbreaks in schools, with evidence of high rates of transmission between children [2]. Anticipating the special risks posed in the school environment, the Australian Health Management Plan for Pandemic Influenza 2008 (AHMPPI) [3] had recommended school and classroom closures as part of a suite of 'social distancing' measures aimed at limiting early spread of an imported pandemic virus. Other interventions during the initial 'Contain' phase of the pandemic response included voluntary home quarantine of cases and their close contacts, and liberal distribution of antiviral agents for treatment and prophylaxis of infection [3].

Although school closure has been widely used in the response to past pandemics [4], there is little quantitative evidence of its likely effectiveness to inform optimal implementation [5]. This absence of data is particularly

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troublesome given the estimated societal costs of school and workplace closures in the context of a pandemic response as predicted by macroeconomic models [6,7]. Mathematical models have been used to estimate the impact of school closure on epidemic dynamics, with disparate conclusions. These variations arise because of differing assumptions regarding relative age-specific attack rates [8], social mixing patterns prior to [9] and during [5] the period of school closure and the timing and extent of interventions [10,11]. Within these model frameworks, full compliance with voluntary home quarantine recommendations is often assumed, perhaps erroneously given perceived inconvenience [12]. Even where models find simulated school closures to be effective at reducing disease, their associated societal costs generally exceed savings to the health care system resulting from case prevention [13].

Localized reactive school and classroom closures were employed during the Contain phase of the response to pH1N1 in metropolitan Melbourne, Victoria, Australia, between 22nd May and 3rd June 2009 [14]. In Victoria, Department of Health guidelines recommended that schools with multiple confirmed cases in different classes should be closed for seven days from the date that the last confirmed case attended school; schools with confirmed cases in one class were instructed to close only that class. Quarantined individuals were asked to stay at home and refrain from contact with visitors for seven days from the date of symptom onset or exposure to an infected person - in the first week of measures the recommended period may have been as long as fourteen days in some cases (J Fielding, personal communication).

This questionnaire-based study aimed to characterize the implementation of this intervention across all schools that enacted closures in the Melbourne metropolitan area, representing a population of 4.1 million residents. We also sought to quantify adherence to behavioural and pharmaceutical recommendations, and define household characteristics associated with differences in compliance.

Methods

Study population

In the state of Victoria, the three main education providers are the State Government (1613 schools), Catholic Education (484 schools) and the Independent schools sector (692 schools)(http://www.australianschoolsdirectory.com.au/educationinformation.php?region=28)We obtained from the Victorian government departments of Health and Education and the Catholic Education Office lists of government and Catholic schools in which closures were implemented from the 22nd May to 3rd June 2009. From these lists, we identified a total of 82 potentially affected schools. Discussions with the principals at these schools regarding the pandemic response confirmed that only 39 had effected closures, and 33 of these agreed to participate - 6 schools did not respond to our enquiry (85% school participation rate). The reasons for differential reporting of school closure status by government agencies and principals were not clear.

On our behalf, staff at participating schools forwarded study information to the parents of 1,181 students in the closed classes or teaching groups who had been advised to go into voluntary home quarantine. An initial letter and two reminder letters were sent to each identified family during November 2009. The second reminder included a movie voucher valued at $AU10.30 to boost participation and thank families for their involvement. Participating schools received $AU20 towards the purchase of educational resources for each completed questionnaire.

In Australia, each school is characterized according to a national 'Index of Community Socio-Educational Advantage' (ICSEA), a measure that incorporates Australian Bureau of Statistics data (such as parental incomes, education and employment), Aboriginal enrolment data and community remoteness - all factors known to predict educational outcomes (http://www.myschool.edu.au). Students are allocated to quartiles of advantage relative to the national average. If a school has a disproportionate number of students in the lowest quartile, it is likely to be serving a very disadvantaged community. We looked for a relationship between the response rate at school level and the difference between the proportion of students in the lowest quartile and the national average of 25%, using univariate linear regression.

The study was approved by the University of Melbourne's Health Sciences Human Ethics Sub-Committee (0932293). The Department of Education and Early Childhood Development and the Catholic Education Office granted permission for us to approach schools to conduct the survey.

Survey

Participating parents completed an anonymous online or telephone questionnaire, which elicited a range of information, including: the compliance of all family members with behavioural recommendations and pharmaceutical interventions during the quarantine period, and factors that may have influenced compliance such as parental leave entitlements and attitudes to the intervention. This study focuses on quantitative measures of compliance. A copy of the questionnaire is available from the authors on request.

Measures of compliance

Compliance with home quarantine was calculated as a proportion, representing the number of days spent at

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home, divided by the number of recommended days of quarantine (i.e. voluntary self-quarantine beyond this period was not assessed). This measure was derived for each individual, along with the proportion of individuals who stayed at home for all of their recommended quarantine days. Compliance was further assessed at household level, representing the number of recommended quarantine days on which all family members who were asked to go into quarantine complied with recommendations. Respondents were asked to identify any trips made outside the home by quarantined individuals, whether the trips were to open or enclosed public spaces, and whether other persons were present.

Compliance with social mixing recommendations was assessed by asking whether adults or children who were not members of the households made incursions to the home environment lasting more than 15 minutes during the quarantine period. For each day nominated as being spent outside the home, the questionnaire elicited information on any mixing with children who were not family members. In any care location, participants were also asked to state whether primary child carers normally lived with the child or were from another household.

For every family member who was prescribed oseltamivir (Tamiflu®), respondents were asked whether all, half or more, less than half or none of the course was completed. Reasons for less than full completion were elicited.

Statistical analysis

Statistical analyses were performed using Stata 11.0. Analyses were performed at the level of either household or individual, depending on the outcome measure. To adjust our estimates of compliance for the clustering of responding households within schools and individuals within households, we used logistic regression modelling and post estimation commands, and reported the estimates as percentages with 95% confidence intervals (95% CIs). P-values are reported for comparisons between groups. Multilevel regression was used to investigate the extent to which the variance in household compliance was attributable to school-level versus household-level differences. Individual-level compliance estimates were adjusted only for clustering of individuals within households, as the clustering of compliance at the school level was estimated to be of minimal impact.

Results

Study population

The population of schools surveyed derived from relatively disadvantaged areas, with 16 schools reporting a larger proportion of students in the bottom quartile of advantage according to ICSEA scores than the national average (Median difference: 4, range -25, 39). Median school level response rates were 19.9% (Range: 4%, 46%). Response rates were square root transformed to approximate a normal distribution, and linear regression performed to assess the relationship between this score and the excess (or under-representation) of students in the least advantaged quartile. The two were significantly related (Coefficient (95%CI): -0.04 (-0.06, -0.01); p = 0.002), reflecting lower response rates from less advantaged schools.

We received 314 responses from 1,181 (27%) eligible households approached by the 33 participating schools. Of these, 301 primary respondents (96%) provided information regarding the presence or absence of a medically diagnosed case in the household. Reporting households ranged in size from 2 to 9 members (median 4, interquartile range 4 to 5) and contained a total of 1,330 persons (Figure 1). The total number of household members in families (n = 13) not reporting case status could not be determined due to missing data. Fifty-one families reported at least one pH1N1-infected individual. Seven of these families reported a secondary case and four reported two secondary cases, for an average secondary household attack rate of 6%. Only one of the 51 primary cases was older than 18 years.

Quarantine recommendations

Four hundred and ninety-six individuals were asked to stay in voluntary home quarantine in association with the school and classroom closures. Quarantine was more likely to be recommended for household members if a child had a confirmed case of influenza. The recommended quarantine periods varied, ranging from 1-14 days (median 7 days, IQR 5-8 days) (Figure 2).

Compliance with requirements to stay at home

Individual compliance with the recommendation to stay at home was high, with respondents reporting that individuals stayed at home for more than 94% of the days they were advised to be in quarantine (95% CI 92.8, 95.9). This figure was not associated with the length of quarantine (Figure 2) and did not fluctuate over the course of the quarantine period (data not shown). Of the 3,232 quarantined days, respondents reported that they and their family members spent most of their time outside the home during only 177 days. Of these days, 47 were spent in the homes of friends, 44 at school, 18 in the workplace and 68 at 'Other' unspecified locations. The proportion of individuals who remained at home during all days of their prescribed quarantine period was 88% - this lower figure was attributable to the variable length of the recommended quarantine period for any given individual, as shown in Figure 2.

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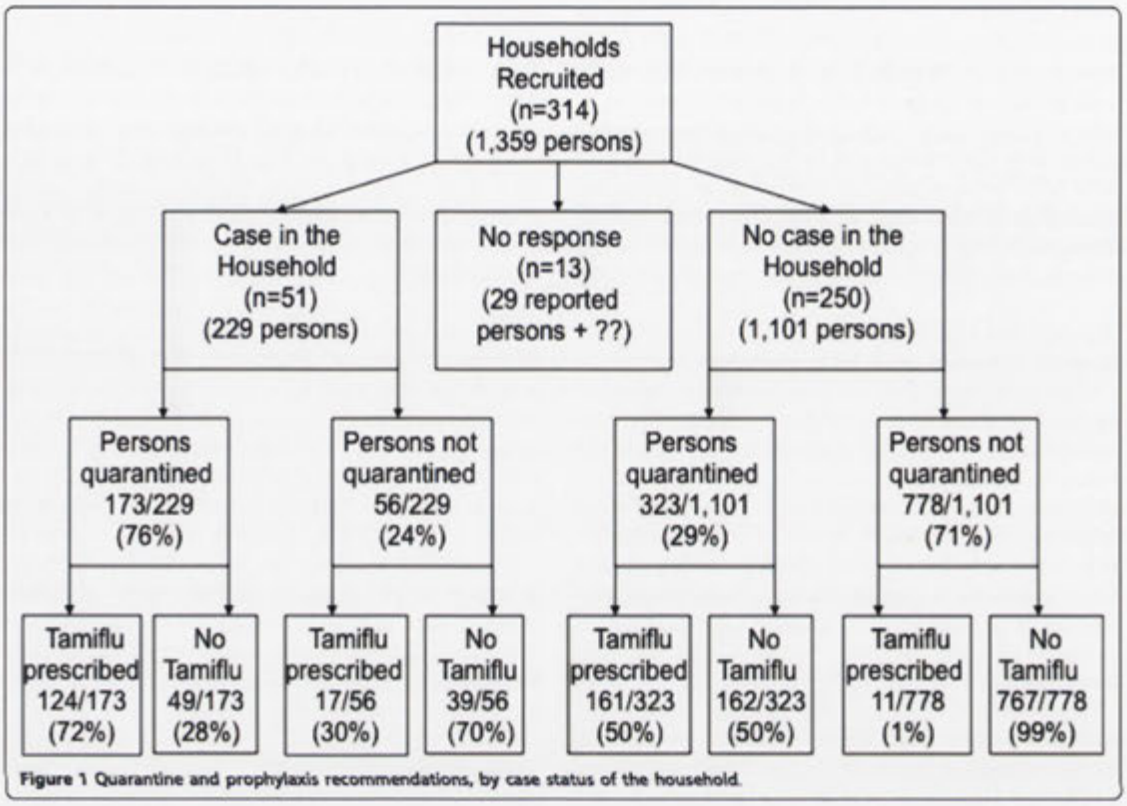

Figure 1 Quarantine and prophylaxis recommendations, by case status of the household.

When compliance was considered at household level, 250 households (84.5%; 95% CI: 79.3%, 88.5%) reported perfect compliance by all family members with quarantine recommendations throughout its duration, regardless of whether there was a case in the household (82.0% compliant) or not (85.0% compliant) (p = 0.57).

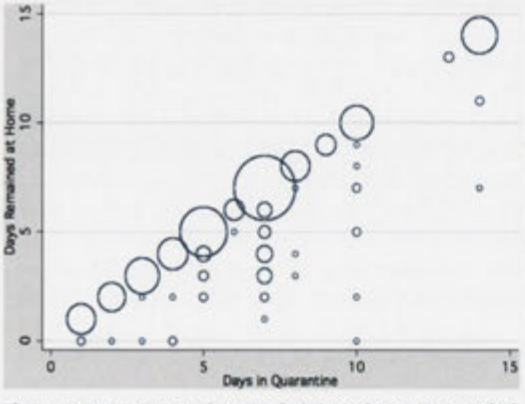

Figure 2 Days spent at home relative to the recommended duration of quarantine (size of circles reflects the frequency of reported observations).

We estimated that only one per cent of the variation in this compliance outcome was explained by differences at the school level (level 2 variance), while 99% of variation was due to differences between households (level 1 variance).

Compliance with restrictions on outings

During the quarantine period, 25 reporting households (8.4%; 95% CI: 0.05%, 12.9%) stated that at least one quarantined family member left the home to visit "an outdoor public space with lots of other people around (e.g. playground or market)". A further 36 respondents (12.0%; 95% CI: 0.08%, 17.0%) reported an excursion to an enclosed public space, other than for medical attendance. There was no significant difference in such incidents between families with or without a resident influenza case (data not shown).

Compliance with requirements to avoid social mixing

The main purpose of school closure was to restrict contact between children that may facilitate the spread of infection. Forty-three households reported that a child spent at least one day outside the family home, and mixing with other children occurred on almost half of these occasions (48.8%; 95% CI: 35.7%, 62.1%), whether

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or not there was a case in the family (p = 0.5). Contact with children who were not immediate family members was far less likely during days spent at home. No child visited a study household in which another child was ill, compared with reported child visitors in 15.9% of 226 homes without a case (p < 0.001). Adult visitors were somewhat more common (31.1%; 95% CI: 25.5%, 37.3%), and again occurred more frequently in households without (33.5%) than with (19.6%) an influenza-infected individual (p = 0.04).

Compared to children in households that complied with recommendations to stay at home, children in households that did not comply with the recommendations were more likely to have been cared for during the quarantine period by an adult from outside the home (28.3% compared with 4.0% for compliant households; p < 0.001), thus also contravening the quarantine recommendation not to mix with adults from outside the household. This distinction was especially marked for households in which there was a confirmed case of influenza, where the difference was 44.4% of children receiving outside care in non-compliant households compared with 2.4% of those that were compliant.

Compliance with antiviral medications

Oseltamivir was prescribed for 313 individuals, more often if there was a case in the household and/or for quarantined persons (Figure 1). Compliance with the medication was high, with 75% of respondents stating that the full drug course was completed (95% CI: 68.2, 80.6%). Only 7.1% refused it altogether, 9.9% took up to half, and 5.1% more than half (2.9% were unsure). The presence of a case in the household did not affect adherence to the prophylaxis or treatment regimen, nor did the age of the individual prescribed the medication. Reasons for non-completion of the course did, however, vary by age (data not shown). Where non-compliance was reported, the primary household respondent attributed this to belief that the drug was unnecessary (n = 42), particularly for individuals older than 18 years (p = 0.02). Some children refused to take the medication for unstated reasons (n = 10), but side effects, experienced (n = 12) or anticipated (n = 8), were infrequently reported.

Discussion

Despite variable recommendations for the containment of pH1N1 in Victoria (Australia), our findings suggest that compliance with both behavioural and pharmaceutical recommendations was high, particularly in case households. These closures occurred during a well-defined and relatively constricted time frame, at the very beginning of the pandemic strain's emergence in Australia, where Victoria was the first state to report person-to-person transmission. As Australia was one of the first countries to experience pH1N1 outbreaks during the Southern Hemisphere winter, local public health officials were uncertain of the likely severity of disease and acted according to the 'worst case scenario' recommendations of the AHMPPI 2008 during the initial Contain phase. Considerable media attention was focussed on school-based spread of infection and the associated public health response. Our findings may therefore be indicative of a 'best case' estimate of the public's compliance during a moderate to severe influenza pandemic.

Issues arising in the conduct of our survey highlighted the considerable logistic challenges involved in implementing this complex policy on a large scale. In seeking to quantify implementation of school closure measures in Melbourne during the 2009 pH1N1 response, it was first apparent that government records of the intervention did not accord with the level of stated school involvement. Reasons for this discrepancy were unclear, but based on discussions with principals, did not represent school refusal to comply with directives. An alternative explanation might relate to the practical challenges involved in centralized administration of a localized reactive public health intervention, applied across many sites. The highly variable quarantine duration recommended to families provides further support for this hypothesis.

Inevitable delays to response arising from the multiple steps to initiation of closure including: case diagnosis, public health reporting, contact identification and information dissemination were reflected in frequent reports of quarantine periods less than seven days. A quarantine duration of three days or less may not reliably exclude development of infection, given some variation in the length of the presymptomatic infectious period [15], particularly in children [16]. Moreover, as the period of isolation was to extend for *a total of 7 days following last contact with an infected individual*, it must be assumed that those contained for a shorter period had already spent several days post-exposure mixing freely in the community, during the time at which they were most likely to be infectious.

Strengths and limitations of the study

This is the first study to evaluate implementation of school closure on such a large scale, with our 33 schools representing an intervention conducted across the whole of metropolitan Melbourne. The low response rate from invited participants in this study is consistent with that observed in similar surveys [17-19], but does introduce potential for ascertainment bias. In particular, we received a disproportionately low level of responses from less advantaged schools, limiting our ability to represent the whole population experience and possibly

inflating estimates of compliance. Also of note, the proportion of households that contained a confirmed case (20%) was considerably higher than that in a recently published West Australian (WA) study of school closures (5%) [20]. This may suggest that not only more affluent, but also more concerned and/or compliant parents were more likely to take part in our study. Study materials were not available in languages other than English, which may also have excluded vulnerable subgroups in the population sample. Unfortunately, as invitations to participate were distributed through schools due to privacy constraints, we are not able to characterize non-respondent households in more detail. Further, conduct of the survey several months after closures took place may have reduced motivation to participate, and introduced the possibility of recall bias.

Findings in relation to other studies of quarantine compliance

Why was compliance with quarantine recommendations so high in our sample? The study of school closures in WA, implemented later than in Victoria and with greater awareness of the generally mild nature of pH1N1 disease, found greater frequency of excursions outside the home (75%) than did our survey [20]. Unlike our sample, the WA study included 'peers' as well as those children identified as actual 'contacts'. The latter were more likely to stay at home than their unexposed friends, exceeded only by cases, of whom there were relatively few [20]. Frequent socialization was reported among students sent home during pH1N1 driven closures in the United States (US) [18], in keeping with earlier observations during a large seasonal influenza B epidemic, in which individual risk perception was assessed and reported to be low [17]. Australian surveys have found a lower anticipated compliance with voluntary quarantine measures for seasonal influenza infection, compared with a pandemic virus [21].

Parental care in the home was associated with higher compliance with social restrictions. During pH1N1 associated elementary school closures in Pennsylvania, only one in five parents took time off work to care for children despite dual income earners in two thirds of households. In that study, 69% of affected children made excursions to locations outside the home during the closure period [22]. A recent contact diary study reported a 50% reduction in child socialization during school holiday periods in the United Kingdom (UK) compared with term time, suggested to be predictive of behavior during a public health intervention [23]. However, the relevance of this finding to an emergency school closure setting should be interpreted with caution, as making 'ad hoc' arrangements for child care at short notice may lead to very different patterns of child socialization, compared with periods of scheduled leave.

Oseltamivir was well accepted by respondents in this study, with almost all taking at least half of the course, and very few reporting side effects. In a 'real-time' survey from the UK, just under half of secondary school students and three quarters of primary school students completed a prescribed course of oseltamivir [19]. Non-compliance was ascribed to gastro-intestinal side-effects in half, and may have been more reliably reported than in our study due to an absence of recall bias, although questionnaires were only completed by around 40% of the sample population [19]. Similarly high rates of adverse events were seen among children receiving oseltamivir in a comprehensive school in the South-West of England, but with better compliance and a higher study participation rate (> 90%) [24].

Conclusions

High levels of compliance with quarantine and antiviral recommendations were observed in our study population, derived from families affected by school closures in Victoria during the early days of the 2009 H1N1 epidemic. These estimates likely reflect a 'best case' scenario, fuelled by high levels of public awareness and anxiety at the time the measures were imposed. However, the complex nature of the intervention was reflected in the variable directives received by families, which likely undermined its impact.

In related work, we explore the predictors of compliance at household level in further detail, including socio-economic status and parental employment arrangements, along with financial consequences of home quarantine recommendations for the family (Prof Anne Kavanagh, personal communication). At societal level, the costs associated with school closures are substantial [7], making their economic justification difficult in the absence of high case fatality, even where highly effective [13]. As implemented, the measures in Victoria were unlikely to have substantially altered the course of the epidemic. This study emphasizes the need to understand the feasibility of public health measures when considering their likely health and economic impacts in real world settings.

List of Abbreviations Used

AHMPPI: Australian Health Management Plan for Pandemic Influenza; CI: Confidence Interval; pH1N1: Pandemic Influenza A (H1N1) 2009; UK: United Kingdom; US: United States of America; WA: Western Australia

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Authors' contributions
All authors were involved in study and questionnaire design. SP and PN liased with schools that distributed study information to parents. KM and JMcV analysed the study data. JMcV led drafting of the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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RESEARCH ARTICLE Open Access

Leave entitlements, time off work and the household financial impacts of quarantine compliance during an H1N1 outbreak

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Abstract

Background: The Australian state of Victoria, with 5.2 million residents, enforced home quarantine during a H1N1 pandemic in 2009. The strategy was targeted at school children. The objective of this study was to investigate the extent to which parents' access to paid sick leave or paid carer's leave was associated with (a) time taken off work to care for quarantined children, (b) household finances, and (c) compliance with quarantine recommendations.

Methods: We conducted an online and telephone survey of households recruited through 33 schools (85% of eligible schools), received 314 responses (27%), and analysed the subsample of 133 households in which all resident parents were employed.

Results: In 52% of households, parents took time off work to care for quarantined children. Households in which no resident parent had access to leave appeared to be less likely to take time off work (42% vs 58%, p=0.08) although this difference had only borderline significance. Among parents who did take time off work, those in households without access to leave were more likely to lose pay (73% vs 21%, p<0.001). Of the 26 households in which a parent lost pay due to taking time off work, 42% experienced further financial consequences such as being unable to pay a bill. Access to leave did not predict compliance with quarantine recommendations.

Conclusions: Future pandemic plans should consider the economic costs borne by households and options for compensating quarantined families for income losses.

Background

Social distancing and quarantine measures were central to Australia's response to the outbreak of pandemic (H1N1) 2009 influenza (influenza A(H1N1)pdm09 (REF WHO)). Established community transmission of the novel virus was first confirmed in Victoria, Australia's second largest state with 5.5 million residents. The majority of infections in the early weeks of the outbreak occurred among school-aged children. This high paediatric case proportion prompted the Victorian government to close classrooms and entire schools, introduce voluntary home quarantine for many children and their families, and recommend additional social distancing.

A previous study found that non-pandemic influenza in school-aged children causes significant disruption to usual household activities, including lost work days for parents [1]. Home quarantine during the 2009 influenza outbreak in Australia may have accentuated such difficulties for two reasons. First, the length of time for which quarantine was recommended was up to seven days, which is considerably longer than usual school absences. Second, the recommendation that quarantined children not have exposure to non-household members restricted childcare options.

Paid leave entitlements are an important buffer against 'shocks' to childcare arrangements; a US study found that parents with access to paid leave are more likely to stay home to care for sick children than parents without such entitlements [2]. When presented with a hypothetical scenario of a pandemic, employees in insecure jobs that lacked leave entitlements reported that they would

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be less likely to comply with social distancing measures [3], and indeed a recent study in the US found that work-related barriers to imposing social distance was associated with increased incidence of influenza-like illness during the H1N1 outbreak [4]. One-quarter of working Australians do not have access to paid leave [5], one of the highest levels in the OECD. This raises questions about their capacity to have taken time off work during the 2009 Victorian influenza outbreak, the impact on household finances if they did, and their ability to facilitate full compliance with the quarantine restrictions imposed on their children. A study that preceded the 2009 outbreak, suggested that up to a third of Australians may experience financial difficulties if quarantined for longer than two weeks [6].

We conducted a cross-sectional survey of parents of children who were asked to go into home quarantine during the initial stages of the influenza A(H1N1)pdm09 outbreak in Victoria, which unfolded between 20 May and 3 June 2009. In earlier publications from this study we examined compliance with the quarantine measures, and the information that affected households received about these measures [7,8]. In most of the affected households, compliance with quarantine recommendations would have necessitated the children being cared for by a parent in the home. This analysis focuses on the subset of households in which all resident parents were employed during the quarantine period and no parent was him/herself quarantined. Compared to households in which one or more parents had access to paid leave, we hypothesised that households without this access would: (i) be less likely to have a parent take time off work; (ii) be at greater risk of adverse financial consequences (because some would take leave regardless); and (iii) have poorer compliance with quarantine recommendations.

Methods

Study environment

The first Australian case of influenza A(H1N1)pdm09 was identified on 8 May 2009. Two weeks later, Victoria's first case was identified – a nine-year-old boy who had recently returned from the United States [9]. In the ensuing 12-day period, 'contain' pandemic response measures [10] including case isolation, voluntary home quarantine and school closure were implemented, in an effort to prevent wider community spread of the imported virus.

During this response phase, cases and their immediate family members and close contacts were asked to go into home quarantine [11]. Quarantined persons were expected to have no contact with non-household members and were treated with oseltamivir for ten days. Cases were asked to stay in quarantine for seven days after the onset of symptoms. Contacts—defined as individuals who spent more than four hours in the same room as a confirmed case, or were within one metre of a confirmed case for more than 15 minutes—were asked to stay in home quarantine for seven days from last date of exposure to the case (Department of Health Victoria quarantine guidelines, 4 June 2009).

The trigger for closure of mainstream schools was two or more confirmed cases in separate classes. Where a single case was identified, only the class or immediate teaching group was closed. However, only cases and fellow students who met the definition of contacts were placed in home quarantine; other students were asked to limit their outside activities (Department of Health Victoria quarantine guidelines, 4 June 2009). At special developmental schools a single confirmed case triggered home quarantine for the entire student body.

Sample

The target population for this study was households in which a child had been asked to go into home quarantine during the outbreak, from schools affected by class closures during the outbreak. We identified eligible households through schools. During the outbreak, the Victorian Departments of Education and Early Child Development (DEECD) and Health (DoH) and the Catholic Education Office were actively involved in visiting schools, identifying cases and determining the need for quarantine. Each of these agencies held separate but incomplete information on quarantine activities in schools. After pooling this information, we approached principals at 82 schools and posed two eligibility questions: did the school have (i) classes closed during the 'contain' phase of the outbreak? and (ii) children who were asked to go into home quarantine?

The study's original sample size calculations were based on preliminary estimates from the Victorian Departments of Health and Education about the number of eligible schools affected by closures, the number of children in those schools and the number of households affected. Of 82 schools identified, six did not provide information to allow us to assess their eligibility, and of the schools that did provide requisite information, only 39 met the eligibility criteria. This reduced the number of in-scope households significantly below what was anticipated. Of the eligible schools, 33 agreed to facilitate the conduct of the survey (school participation rate was 85%).

We worked with staff at participating schools to identify 1,188 families with children who went into quarantine. School staff used enrolment records, class lists and documentation of which classes and students had been asked to enter quarantine in order to identify these families. We advised and guided school staff regarding the assembly and review of this information but had no contact with data identifying students or families.

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The study was approved by the University of Melbourne ethics committee (0932293) and the DEECD and the Catholic Education Office granted us permission to approach schools to conduct the survey.

Survey administration

We tested a draft version of the survey instrument for comprehension, length and ease of administration with three participants from eligible schools, and made minor modifications based on their feedback. Due to the need to administer the survey as soon as possible after the school closures occurred, so as to reduce recall bias and maximise participation, more extensive testing was not feasible. The finalised survey was administered during November and December 2009. School staff mailed letters to the parents in eligible families inviting them to participate. The letter presented two options: an internet address at which parents could complete the questionnaire online and a telephone number to ring to complete it via a Computer Assisted Telephone Interview (CATI). The survey was offered in English only. The letter also included a unique identification number which enabled access to the website and CATI. This number allowed us to identify the school(s) and home class(es) associated with each survey response, but revealed no other identifying information. A copy of the CATI questionnaire is included in an online Additional file 1: Appendix.

School staff mailed two reminder letters. To boost response rates and recognise the effort of participating families and schools we contributed $AU20 to the school for the purchase of educational resources for each completed questionnaire and all families received a movie voucher valued at AUS$10.30 with the second reminder letter.

Eight letters were returned-to-sender and 23 parents responded indicating that they did not have a school-aged child who had been placed in home quarantine. This left an in-scope sample of 1,157. We received 314 responses, yielding a household participation rate of 27% (see Figure 1).

Variables

Care arrangements during quarantine

For each child in quarantine, responding parents were asked to indicate who (e.g. parent, older sibling, grandparent, paid carer) provided any care for the child during school hours in the quarantine period. We then categorised households according to whether a parent provided any such care for any quarantined child.

Time off work and financial consequences

In households reporting that a parent had provided care for their quarantined children during school hours we asked if they took any time off work to do so and, if they did, whether this time off work was paid or unpaid. For those who took unpaid time off work, we asked them whether they had to borrow money, had difficulty paying a bill, mortgage or rent, or experienced other financial problems as a result.

Access to leave

We defined parental leave entitlements according to whether each employed parent reported having access to paid sick leave or paid carer's leave. This definition did not include annual leave. Parents who did not have paid sick or carer's leave entitlements, or were unaware of their leave entitlements, were classified as not having access to leave. Households were then classified as having access to leave if any parent had leave entitlements, or not having access to leave if no parent did.

Compliance with quarantine recommendations

A household's compliance with quarantine recommendations was assessed using the following criteria:

1. All quarantined members of the household stayed at home for most of each day.
2. Quarantined children did not mix with children from another household for 15 minutes or more.
3. No adults from other households visited the home for 15 minutes or more.
4. No quarantined household members visited public places being utilised by lots of other people (excluding visits to health practitioners).
5. Childcare was provided only by adults living in the household.

We constructed an overall measure of compliance distinguishing households that met all the criteria from those that did not.

Statistical analyses

Analysis was restricted to the 133 households in which all resident parents were employed during the quarantine period and in which no parent had been asked to stay in voluntary home quarantine (see Figure 1); for the rest of the households surveyed we assumed that non-working parents would have been able to provide childcare. According to whether a household had access to leave, we calculated the proportion of households in which (i) quarantined children were cared for by a parent during school hours; (ii) a parent took time off work to provide this care; and (iii) a parent lost pay as a consequence of taking time off work. We report p values from Pearson's χ^2 tests for differences. We also describe the financial consequences of losing pay.

We used logistic regression to quantify the association (estimating odds ratios and 95% confidence intervals)

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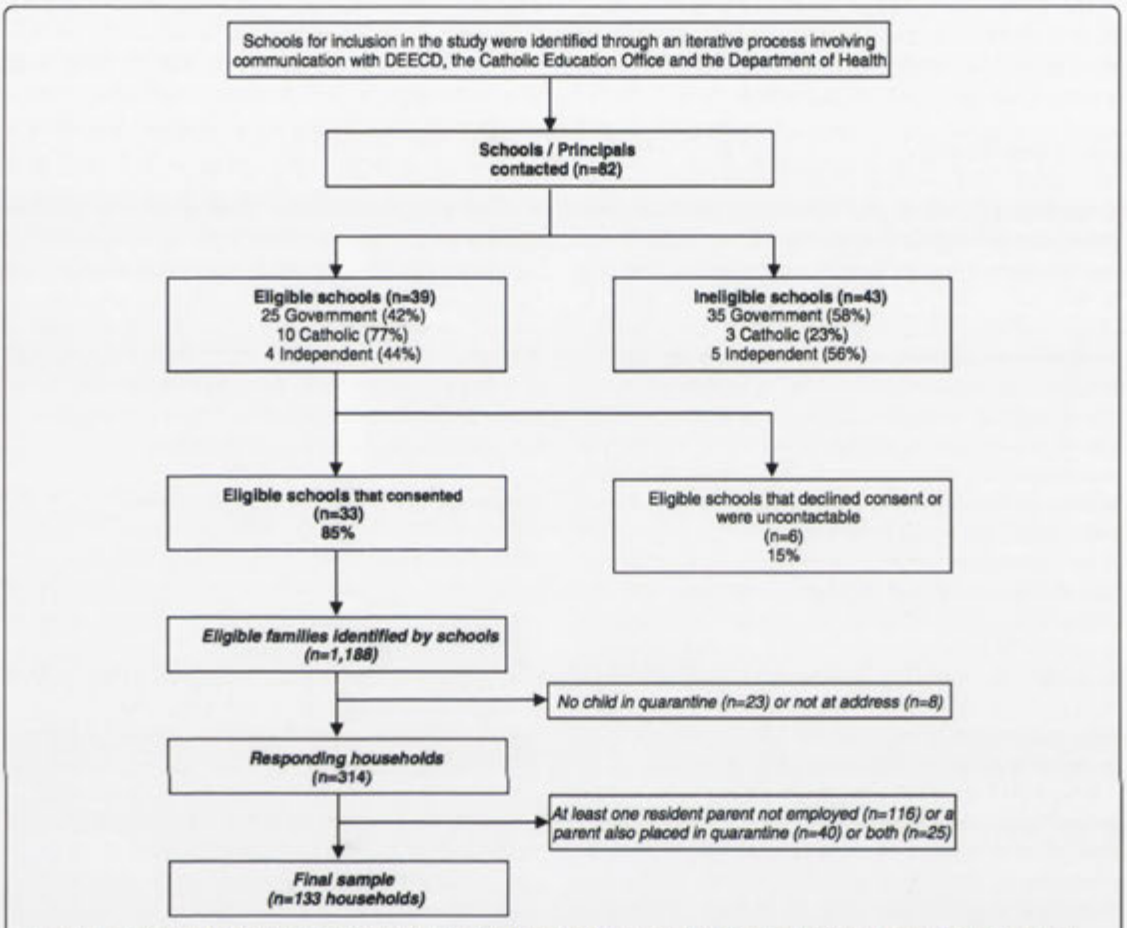

Figure 1 Recruitment of sample of parents whose school children were recommended to go into home quarantine (May 22nd until June 2nd, 2009), and restriction of final sample for this analysis to households in which all resident parents were employed during the quarantine period and in which no parent had been asked to stay in voluntary home quarantine.

between access to leave or taking time off work and compliance across all five indicators as well as the overall measure. We tested whether the estimates changed by more than 20% with the addition of two potential confounders – highest level of parent education and parental structure of household (single/couple). Addition of the covariates led to substantial attenuation of estimates (>20% change) in four of the six models assessing access to leave and compliance. Accordingly, all models reported in this paper were adjusted for these confounders. Robust standard errors were used to accommodate the fact that data from households were clustered within schools. All analyses were conducted in Stata 11.0 (College Station, TX, USA: StataCorp LP).

Results

Table 1 outlines the demographic characteristics and leave and childcare arrangements of households in the study sample. In 82% (109/133) of households a parent cared for their quarantined child during school hours and in 52% (69/133) a parent took time off work to care for their child. In 39% (52/133) of households no parent had access to paid sick or carer's leave during the quarantine period, despite the sample being restricted to only those households in which all parents were in the paid workforce.

Of the 133 households in the analysis, only eight (6%) contained somebody who had been diagnosed with influenza A(H1N1)pdm09.

Leave entitlements and care arrangements during quarantine

The proportion of households in which a parent looked after quarantined children on at least one day during the quarantine period did not differ significantly between

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Table 1 Characteristics of sample (n = 133)

	no. (%)
Parental structure in household	
Single parent	15 (11.3)
Highest level of parental education	
University bachelor degree or higher	84 (63.1)
Childcare arrangements during quarantine	
A parent cared for quarantined children during school hours on ≥1 day	109 (82.0)
Time off work	
A parent took time off work to care for quarantined children	69 (51.9)
Access to leave	
No parent in household had access to paid sick/carer's leave	52 (39.1)

households with and without access to paid leave (83% vs 81%, p=0.78).

Leave entitlements and time taken off work

A larger proportion of households with access to leave had a parent who took time off work to care for a child (58% (47/81) vs 42% (22/52) but this difference did not reach statistical significance (p=0.08). Figure 2 shows in greater detail the time taken off work and financial consequences of households in the sample, according to whether or not households had access to paid leave.

Financial consequences

Across the sample, thirty-eight per cent of households (26/69) lost pay as a result of taking time off work to care for quarantined children. Loss of pay was more frequent in households that did not have access to leave (73% vs 21%, p<0.001) (Figure 2, bottom row).

Of the 26 households in which a parent lost pay (independent of access to leave), 42% (11/26) had at least one other financial problem as a result. Twenty-three per cent (6/26) had difficulty paying a bill, 15% (4/26) had difficulty paying the mortgage or rent, 8% (2/26) had to borrow money and 19% (5/26) had other financial problems.

Compliance with quarantine recommendations

Half of all households were fully compliant with quarantine recommendations. Compared to households without access to sick leave or carer's leave, households with access to leave appeared more likely to have all quarantined members stay at home for most of the time on all days during the quarantine period (88% compared with 75%), However, the association was not statistically significant in multivariable analyses that adjusted for parental structure and parental education (OR=2.07; 95% CI 0.82 to 5.23; p=0.12). Further, there was no evidence to support associations between leave entitlements and any other of the four measures of compliance (see Table 2).

Turning to the relationship between taking time off and quarantine compliance (independent of access to leave), quarantined members of households in which a parent took time off work were less likely to make trips to populated public spaces during the quarantine period (97% vs 84%) and these households were more likely to have all quarantined members stay at home for most of the time on all days during the quarantine period (88% vs 77%). After adjustment for parental education and parental structure of households, taking time off work was associated with over double the odds of staying at

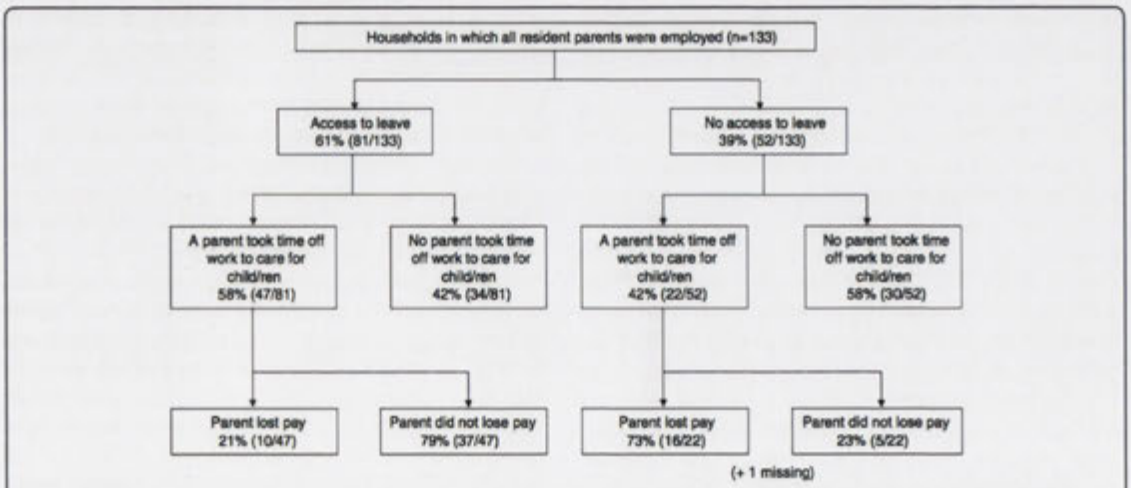

Figure 2 Diagrammatic representation of leave entitlements, time taken off work and financial consequences during the quarantine period (n = 133).

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Table 2 Logistic regression analysis of access to leave, time taken off work and compliance with quarantine recommendations (n = 133 households)*

	Stayed at home all days		No mixing with children		No mixing with adults		No trips		Childcare by household members only		Full compliance	
	%	OR (95%CI)	%	OR (95%CI)	%	OR (95%CI)	%	OR (95%CI)	%	OR (95%CI)	%	OR (95%CI)
No access to leave	75.0	1.00	75.0	1.00	61.5	1.00	88.5	1.00	88.5	1.00	46.2	1.00
Access to leave	87.7	2.07 (0.82-5.23)	80.3	1.24 (0.63- 2.45)	62.7	0.99 (0.54-1.82)	92.6	1.61 (0.49-5.28)	87.7	0.92 (0.41-2.05)	51.9	1.20 (0.62-2.34)
Did not take time off work	76.6	1.00	71.9	1.00	64.1	1.00	84.4	1.00	82.8	1.00	46.9	1.00
Took time off work	88.4	2.47 (1.17-5.22)	84.1	2.10 (0.71-6.19)	60.9	0.88 (0.32-2.40)	97.1	7.20 (1.42- 36.51)	92.8	2.69 (0.60-12.07)	52.2	1.27 (0.61-2.67)

*Adjusted for highest level of parental education and household structure (single versus two parent).

home on all days (OR 2.47, 95% CI 1.17–5.22, p=0.02) and seven times the odds of not making trips outside the home (OR 7.20, 95% CI 1.42–36.51, p=0.02). Taking time off work was not, however, associated with full compliance (see Table 2).

Discussion

During Victoria's outbreak of influenza A(H1N1)pdm09 in 2009, parents appeared to be somewhat more likely to take time off work to care for their children when a parent in the household had access to paid sick or carer's leave, compared to households without access to leave, but there is insufficient statistical evidence to reject the null hypothesis of no difference. Taking time off work was associated with two indicators of compliance with quarantine recommendations: quarantined children staying home for most of the time on all days and not making trips to populated places. However, this study found no evidence that access to leave, per se, was associated with overall compliance with quarantine recommendations. On the other hand, lack of access to leave had measurable negative impacts on families. In households without this benefit available, nearly three-quarters had a parent who lost pay, compared to one in five households with leave, and nearly 40% of households that lost pay experienced further financial difficulties as a consequence.

The chief explanation for the lack of association between access to leave and compliance with quarantine appears to be that families frequently chose to follow public health recommendations even when that meant absorbing the collateral employment-related effects due to inadequate leave entitlements: in 42% of households that did not have access to leave, a parent still took time off work to care for the quarantined child. This behavioural response is particularly selfless in light of the fact that financial consequences are borne privately whereas the benefits of home quarantine and social distancing measures accrue to the community in the form of reduced risks of transmission. While some of this behaviour may have been driven by the need to care for sick children, there were no confirmed influenza A(H1N1) pdm09 diagnoses in the vast majority (94%) of households in our sample. This suggests that, absent the strict quarantine restrictions, other childcare options may well have been attractive to parents to enable them to attend work during the period of school closure. Twenty-two per cent of households where a parent did have access to leave still lost pay as a result of taking time off work. The likely explanation is that, because leave was defined at a household level, a parent without access to leave was the one who took time off work.

Our study is the first we know of to have considered the effect of parental leave entitlements on quarantine compliance during the 2009 outbreak of influenza A (H1N1)pdm09. In Western Australian school closures during this outbreak, a parent took time off work in 45% of households [12] — a similar finding to our study. However the Western Australian study did not examine whether time taken off work influenced compliance or whether taking leave had a financial impact. Our finding contrasts with findings from studies in the US, both hypothetical and real, which have suggested a lack of access to paid sick leave is a barrier to social distancing [3,4].

The study had several limitations. First, despite beginning with a sample frame consisting of all households in Victoria affected by school closures, our relatively small analytic sample meant the study was underpowered to detect differences unless they were large. A good example of this is the relationship between parents' access to leave and their decision to take time off work to care for their children; the difference in proportions was substantial (16 percentage points) but did not attain statistical significance, likely due to the small sample size. Second, our response rate was not high, despite the use of incentives to boost participation rates. This has implications both for power and the risk of Type II errors. Nonetheless, the response rate is comparable to that

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achieved in other similar school-based studies of pandemic influenza in the US and England [13-15] and our study had the advantage of covering a larger number of affected schools than most other studies. As we showed in an earlier publication from this study, we received a disproportionately low level of response from less advantaged schools, reducing the generalisability of our findings and potentially biasing our results [8]. It could be expected that non-responding households were less likely to have access to paid leave and may have experienced greater financial consequences, resulting in the estimates presented in this paper being conservative. Unfortunately, the survey had to be administered through schools due to privacy constraints, and we are therefore not able to characterize non-respondents in more detail.

The study was also limited by the fact that the survey was administered several months after the school closures occurred, and all information was obtained via self-report, introducing the possibility of recall bias. In some cases, parents were reporting on behaviours of their children at times when parents may not have been present.

All pandemic plans must balance the likely benefits and social and economic costs of implementing social distancing measures. Characterising the costs incurred by families during quarantine and social distancing of school children during Victoria's 2009 outbreak of pandemic influenza contributes to the evidence base for future assessment of the costs and benefits of these containment strategies. Models of pandemic influenza have shown that the greatest impact of school closure on transmission is observed when closures are widespread, initiated early, and sustained beyond the epidemic peak [16-18]. In Victoria, school closure was localised, short-lived (often less than 7 days) and reactively initiated following case identification.

In households where parents are forced to take leave from work due to public health emergencies, foregoing wages is a high price to pay for honouring a public duty. Employers should be encouraged to provide flexible working arrangements, such as allowing employees to work from home or to make up hours at a later date. Setting aside the question of whether access to paid sick leave should be available to all workers, there are strong ethical arguments [19] and community support [20] for the provision of compensation to individuals who experience loss of income as a result of public health measures such as quarantine. Policy initiatives along these lines are not unprecedented: several countries affected by the SARS outbreak introduced some form of compensation for affected households [21]. In Australia, this might involve government and employers sharing the costs of compensating quarantined employees. This could operate similarly to the current legislated arrangements for jury service, whereby employers are required to release employees for jury service and pay them the difference between the set jury payment provided by the courts and what they would have received as earnings for that period had they not been on jury service [22].

Conclusions

Our findings emphasise the importance of bolstering quarantine measures that target children in public health emergencies with a supportive environment in which working parents are able to respond appropriately. We show that in the absence of this environment the social and economic costs borne by families during public health emergencies are non-trivial and unevenly distributed across the affected population. Planning for future pandemics should involve a careful weighing of these costs against the demonstrated effectiveness of any quarantine or social distancing strategies employed. Finally, if home quarantine of school children is implemented, the public and private sector should work to alleviate financial burdens that arise from loss of pay and financial hardship due to the need for affected parents to take time off work.

Additional file

Additional file 1: 0593 H1N1 Swine Flu and Schools Research Project.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AK conceived of the study and drafted the manuscript; KM developed the analytic plan and conducted the analyses; RB contributed to the conception of the study and design and advised on analysis; JM, JF, AL and DS contributed to the conception of the study and design; LG advised on the analysis and SP contributed to the design of the survey and was responsible for its implementation. All authors contributed to the drafting of the manuscript and have read and approved the final manuscript.

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Moderate influenza vaccine effectiveness with variable effectiveness by match between circulating and vaccine strains in Australian adults aged 20–64 years, 2007–2011

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Keywords

Influenza; influenza vaccine; influenza-like illness; vaccine effectiveness.

Abstract

Background

Influenza vaccines are licensed annually based on immunogenicity studies. We used five sequential years of data to estimate influenza vaccine effectiveness (VE), the critical outcome in the field.

Methods

Between 2007 and 2011, we performed annual prospective test-negative design case–control studies among adults aged 20–64 years recruited from sentinel general practices in the Australian state of Victoria. We used PCR-confirmed influenza as the endpoint to estimate influenza VE for all years. We compared annual VE estimates with the match between circulating and vaccine strains, determined by haemagglutination inhibition assays.

Results

The adjusted VE estimate for all years (excluding 2009) was 62% (95% CI 43, 75). By type and subtype, the point estimates of VE by year ranged between 31% for seasonal influenza A(H1N1) and 88% for influenza A(H1N1)pdm09. In 2007, when circulating strains were assessed as incompletely matched, the point estimate of the adjusted VE against all influenza was 58%. The point estimate was 59% in 2011 when all strains were assessed as well matched.

Conclusion

Trivalent inactivated vaccines provided moderate protection against laboratory-confirmed influenza in adults of working age, although VE estimates were sensitive to the model used. VE estimates correlated poorly with circulating strain match, as assessed by haemagglutination inhibition assays, suggesting a need for VE studies that incorporate antigenic characterization data.

Introduction

Trivalent influenza vaccines are licensed annually based on limited immunogenicity studies, most often among healthy adults.[1] Given extensive past experience with influenza vaccines among adults, this process is widely accepted. It is also the only process that is feasible, given the current vaccine production and regulation processes. Each year influenza vaccines include selected strains of influenza A(H3N2), A(H1N1) and B viruses. Because the vaccine strains may need to change, depending on the drift of the circulating viruses, there is insufficient time for large-scale vaccine efficacy and safety studies prior to vaccine licensing each year. Immunogenicity is, therefore, used as a proxy for vaccine efficacy.

Immunogenicity assesses the antibody response to the specific vaccine antigens, while vaccine efficacy estimates the proportion of influenza infections prevented by vaccination in a randomized controlled trial. Vaccine effectiveness (VE) is the same measure from an observational study.[2] Immunogenicity is not precisely correlated with VE, although effectiveness would normally be regarded as the ultimate test of a vaccine, as it assesses how well the vaccine protects against disease when delivered in routine practice.[3] In recent years, a number of investigators from Europe,[4] United States,[5] Canada[6] and Australia[7] have conducted observational studies using similar designs to monitor influenza VE.

Using methodological insights gained from these previous studies, we have studied patients recruited from an existing network of sentinel general practitioners (GP) in Victoria, Australia, to estimate influenza VE. Victoria has a temperate southern hemisphere climate and a population of approximately 5.5 million. The influenza season usually occurs between May and September. In a previous feasibility study, we suggested that the sentinel surveillance system is best suited to estimating influenza VE in adults aged 20–64 years, a group often characterized as working-age adults.[8] Moreover, this age group is most often used in vaccine trials. Confining our analysis to this group allows a comparison of results from this observational study with published trial results. This study provides summary estimates of influenza VE by type and subtype over 4 years from 2007 to 2011, years during which there were significant antigenic changes in all three types/subtypes

included in the vaccine. We compare the annual VE with the match between circulating and vaccine strains.

Methods

Study design

We used the prospective test-negative variant of the case–control study9 to estimate VE against laboratory-confirmed influenza among patients presenting to a sentinel GP in Victoria between 2007 and 2011. In this study design, patients suspected of having influenza are recruited by the GP and swabbed at recruitment. Cases are patients who subsequently test positive for influenza, and controls are those who test negative. Control selection leads to the description of this study design as 'test negative'.[9] In the prospective form of the test-negative design, patients are recruited before their case status is known, that is, before the result of their swab is available. This study design is, therefore, not strictly a case–control design in which cases and controls are recruited based on known case status. We confined our analysis to adults aged 20–64 years as younger and older patients were under-represented.

GP sentinel network

Over the 5 years of the study, sentinel GPs were recruited from metropolitan Melbourne and regional Victoria. GPs were rewarded for their participation with continuing education points from the Colleges of General Practice and Rural and Remote Medicine. GPs also received a weekly influenza surveillance report[10] and provided annual feedback by a brief survey. GP participation increased over the years from 65 in 2007 to 97 in 2011. Our GP survey data show that an average of 94.8% of GPs assessed the scheme as useful or very useful in this period.

GPs were asked to recruit patients with an ILI, defined as a combination of fever (measured or reported), cough and fatigue.[11] At the discretion of the GP, patients had a combined nose and throat swab, which was tested for influenza virus RNA at the Victorian Infectious Diseases Reference Laboratory (VIDRL) using a range of in-house reverse transcriptase and real-time PCR assays as previously reported.[7,12-14] The laboratory is designated as a National Influenza Centre by the World Health Organization. The sensitivity of an early in-house assay, which is

dependent on time from symptom onset until swabbing, was estimated as 90%, while specificity was estimated as 100%.[15] It has previously been shown that perfect specificity in the presence of imperfect, non-differential sensitivity will provide unbiased point estimates of VE from a TND study when compared with the estimate from a cohort study.[9,16]

In addition to symptoms, GPs collected data on the age and sex of patients and the date of influenza vaccination. In 2011, data on influenza vaccination in the previous year and the presence of comorbidities for which influenza vaccination is funded by the National Immunisation Program were also collected. Comorbidities were recorded as yes/no and included all those conditions that are indicated for influenza vaccination in Australia, such as immunosuppression, pre-existing respiratory disease and pre-existing cardiovascular disease.[17] Data in this study were collected, used and reported under the legislative authority of the Public Health and Wellbeing Act 2008 and the Public Health and Wellbeing Regulations 2009 and did not require approval from a Human Research Ethics Committee. Nonetheless, patients provided written informed consent for their swab to be collected, with an understanding that anonymous results may be used for surveillance purposes.

Estimating influenza VE

Vaccine status was recorded by the GP, based on GP records or patient report. As a proxy validation for accurate vaccine status, we required the GPs to provide the precise date of vaccination. In a case series in 2009, we found good concordance between GP and patient reports of vaccination, even when influenza vaccine had been administered outside the practice.[18] Patients were administered trivalent inactivated vaccines provided by a variety of manufacturers that changed by year. Vaccines from six manufacturers were licensed in Australia during the study period.[17] We did not collect data on vaccine manufacturer and assumed all vaccines were equally effective. Vaccines were analysed as potentially effective if administered at least 14 days prior to symptom onset. Patients whose vaccination occurred <14 days prior to symptom onset were excluded from the primary analysis. We also excluded any patient who had been vaccinated with only

monovalent pandemic vaccine in 2009 or 2010 or those whose vaccination status was unknown.

Differences between those who tested positive or negative for influenza, and between the vaccinated and unvaccinated, were compared by Fisher's exact test for categorical variables and t-test for continuous variables. In the primary analysis, laboratory-confirmed influenza was the outcome of interest and influenza vaccination the exposure. We estimated a crude odds ratio (OR) for vaccination comparing cases and controls for each year and each influenza type/subtype. Multivariable models were also fitted to adjust for potential confounders, including age, month of swab and time between symptom onset and swab. It is generally assumed that immunocompetency does not vary significantly in adults between the ages of 20–64 years. Age was, therefore, included as a continuous variable within this age group and recentred so that 0 represented age 20 and rescaled to decades, so that 40 years became 2 [(40–20)/10 = 2]. This allowed for variation of VE by age within the age group. To ensure valid comparisons, the same model was used for all years, but a sensitivity analysis was performed for 2011, including the extra covariates on comorbidities and previous influenza vaccination. This was the only year these covariates were collected. VE was calculated as 1-OR and reported as a percentage with a 95% confidence interval. In the model combining data for the years 2007–2011, we included year as a covariate. In this estimation, we omitted 2009 when pandemic influenza was the predominant viral strain detected, and the vaccine was completely mismatched.[19]

Our primary analysis included all patients for whom we had complete data, without censoring any variables. However, we conducted a number of sensitivity analyses on reduced data sets. When influenza infection is present, volunteer studies have shown that it is more likely to be detected within the first 4 days of infection, presumably because of decreased viral load as the infection resolves.[20] In the sensitivity analyses, we, therefore, examined the effect of excluding any patients who presented more than 4 days after symptom onset, compared with including the length of time from onset of symptoms to swabbing as a continuous variable. We also confined our analysis to the influenza season each year, with the

season identified by two consecutive weeks in which one or more detections of influenza were made from sentinel patients with ILI.[7,13,14]

All analyses were conducted in Stata version 11 (StataCorp. 2009. Stata Statistical Software: Release 11; College Station, TX, USA).

Comparison of circulating and vaccine strains

The composition of the influenza vaccine for each year was extracted from the website of the WHO Collaborating Centre for Research and Surveillance of Influenza in Melbourne.[21] The circulating strains were identified by the WHO Collaborating Centre based on specimens referred to the Centre from Victorian laboratories. Circulating and vaccine strains were compared based on the degree of cross-reaction between strains and were conventionally assessed as being incompletely matched if there was ≥8-fold difference in haemagglutination inhibition titres between the vaccine antigen and ferret-derived antibodies to the circulating strain.[1] We accepted a match as incomplete when the vaccine and predominant circulating strains differed.

Results

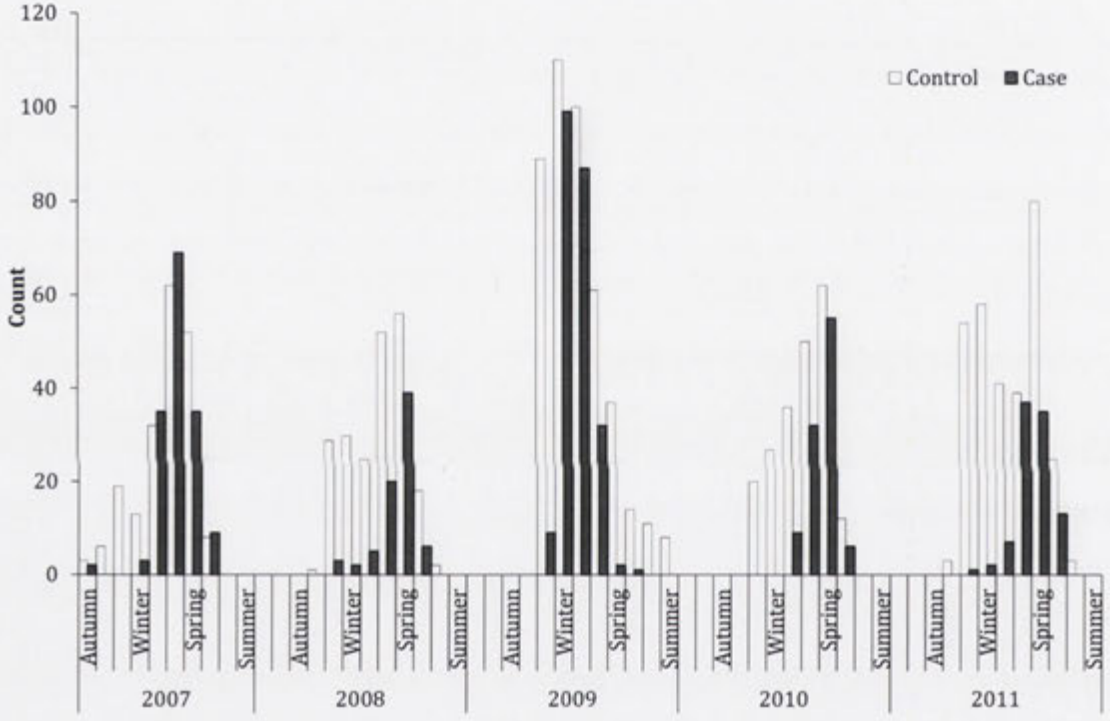
Sentinel patients

There were 3136 sentinel patients with laboratory results from the 5 years of the study, of whom 2099 (67%) were aged 20–64 years. One case of influenza C was excluded from further analysis, and two patients had no laboratory results. The vaccination status was unknown or unspecified for 64 patients, 11 were vaccinated <14 days prior to the onset of ILI symptoms and 18 were vaccinated with the monovalent H1N1 vaccine. After excluding these patients, the final sample size was 2003.

The proportion of patients with an unknown vaccination status was low, but varied by year, with 1.7% unknown in 2007, 0.7% in 2008, 4.6% in 2009, 2.8% in 2010 and 3.6% in 2011 (P = 0.008). There was no difference by case status (P = 0.6). In the 5 years combined, 368 (18%) patients were recorded as having been vaccinated, with a tendency for higher vaccine coverage (22%) in 2009, the year of the influenza A(H1N1) pandemic.

In all, 655 (33%) patients tested positive for influenza of any type or subtype (Table 1). There were 96 cases of influenza B and 559 cases of influenza A, including 36 seasonal H1N1, 313 pandemic H1N1, 160 H3N2, 1 mixed H1N1/H3N2, and 49 were not subtyped. The proportion of cases and controls ascertained by month differed by year (Figure 1).

Figure 1. Cases and controls by season[1], Victorian sentinel patients 2007–2011; [1]Autumn: March–May; Winter: June–August; Spring: September–November; Summer: December–February.



In 2011, the only year that data on comorbidities and previous vaccination were collected, 12% of 398 patients were recorded as having a comorbidity that increased their risk of an adverse outcome to infection. While more men than women recorded a comorbidity (19% versus 9%, $P = 0.005$), there was marginal difference by case status (8% cases versus 16% controls, $P = 0.08$). As expected, persons with a comorbidity were more likely to be vaccinated (33% versus 13%, $P < 0.001$). Patients who had been vaccinated in 2011 were more likely to have been vaccinated in the previous year (71% versus 17%, $P < 0.001$).

Table 1. Characteristics of 2003 adults aged 20–64 with influenza-like illness included in the analysis, by year and vaccination status. Values are n (%) unless otherwise indicated.

Characteristic	Year									
	2007		2008		2009		2010		2011	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Age in years [mean (SD)]	45.8 (11.0)	35.2 (11.6)	42.0 (12.5)	36.6 (11.0)	41.6 (12.5)	34.3 (11.7)	43.1 (12.0)	37.1 (11.2)	43.2 (12.5)	37.1 (11.2)
Gender										
F	34 (52)	124 (44)	23 (51)	117 (48)	74 (52)	249 (49)	28 (57)	108 (46)	33 (53)	158 (47)
M	32 (48)	158 (56)	22 (49)	126 (52)	68 (48)	264 (51)	21 (43)	129 (54)	29 (47)	176 (53)
Influenza PCR										
Negative	49 (74)	146 (52)	36 (80)	177 (73)	93 (65)	337 (65)	48 (92)	159 (62)	53 (85)	250 (74)
Positive	17 (26)	136 (48)	9 (20)	66 (27)	50 (35)	180 (35)	4 (8)	98 (38)	9 (15)	86 (26)
Influenza type/subtype*										
A (not subtyped)	2 (12)	4 (3)	0 (0)	5 (8)	3 (6)	20 (11)	0 (0)	8 (8)	2 (22)	5 (6)
A (H1N1)	4 (24)	26 (19)	1 (11)	3 (5)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)
A (H3N2)	9 (53)	81 (60)	6 (67)	24 (36)	0 (0)	3 (2)	0 (0)	3 (3)	5 (56)	29 (34)
A (H1N1)pdm09	0 (0)	0 (0)	0 (0)	0 (0)	47 (94)	155 (86)	4 (100)	85 (87)	0 (0)	22 (26)
A (H1|H3)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
B	2 (12)	24 (18)	2 (22)	34 (52)	0 (0)	0 (0)	0 (0)	2 (2)	2 (22)	30 (35)
Comorbid condition										
No	Data not collected in these years								37 (69)	256 (89)
Yes									17 (31)	32 (11)
Previously vaccinated										
No	Data not collected in these years								15 (27)	263 (83)
Yes									41 (73)	53 (17)

*Percents may not add up to 100 due to rounding errors

Influenza vaccine effectiveness

Overall, cases (patients with influenza) were less likely than controls (patients without influenza) to have been vaccinated (OR = 0.40), corresponding to a crude VE = 60%, 95% CI 43, 72). This was the case for 2007 and 2010 but, based on a crude analysis, cases were not significantly more likely than controls to have been vaccinated in 2008, 2009 or 2011 (Table 2).

VE was calculated for each year for all influenza cases and by influenza type and subtype (Table 2). With the exception of 2009, the adjusted VE estimates were largely similar to the crude estimates in all years when the outcome was all influenza detections. Against all influenza types and subtypes, the adjusted VE showed a statistically significant protective effect in 2007 (VE = 58%, 95% CI 17, 79), 2010 (VE = 87%, 95% CI 61, 96) and 2011 (VE = 59%, 95% CI 4, 82) and a non-significant protective effect in 2008 (VE = 29%, 95% CI −71, 71). In 2009, the year of the pandemic, the point estimate for VE was non-protective (VE = −32%, 95% CI −116, 19), but this was not statistically significant. Although crude and adjusted VE estimates were mostly similar for VE against influenza types and subtypes, estimates were variable and often not significant, likely owing to the small numbers of vaccinated cases in these categories by year (Table 2).

The adjusted VE estimate for the 4 years excluding 2009 was 62% (95% CI 43, 75). Age was not a significant predictor [OR = 0.93 (95% CI 0.83, 1.04)]. When analysed by type and subtype, the point estimates of VE ranged between 31% for seasonal influenza A(H1N1) and 88% for influenza A(H1N1)pdm09 (Table 2).

The sensitivity of the estimates was assessed when the model was modified in three ways. First, for 2011, the only year for which comorbidity and previous vaccination status were available, the adjusted VE including these variables in the model gave an estimate of 48% (95% CI −41, 81), lower than the adjusted estimate when these variables were not included (VE = 59%, 95% CI 4, 82) (Table 3). Second, among patients with information on the time between symptom onset and the collection of a nasopharyngeal swab, 151 of 1270 (12%) samples were collected after 4 days onset, but 6.4% of cases compared with 15% of controls had swabs collected after 4 days ($P < 0.001$). When these patients presenting late were

Table 2. Influenza vaccine effective estimates by year and influenza type and subtype, Victorian sentinel patients aged 20–64 years.

Year	Influenza type and subtype*	Cases n**	Vaccinated cases n (%)	Controls n	Vaccinated controls n (%)	Crude VE (95% CI)	Adjusted VE*** (95% CI)
2007	All	153	17 (11)	195	49 (25)	63 (32, 80)	58 (17, 79)
	A(H1N1)	31	4 (13)			56 (-32, 85)	49 (-70, 85)
	A(H3N2)	91	9 (10)			67 (30, 85)	63 (15, 84)
	B	26	2 (8)			75 (-9, 94)	78 (-16, 96)
2008	All	75	9 (12)	213	36 (17)	33 (-47, 69)	29 (-71, 71)
	A(H1N1)	4	1 (25)			-64 (-1521, 83)	-75 (-2065, 86)
	A(H3N2)	30	6 (20)			-23 (-222, 53)	-8 (-238, 65)
	B	36	2 (6)			71 (-26, 93)	57 (-95, 91)
2009	All	230	50 (22)	430	93 (22)	-1 (-48, 32)	-32 (-116, 19)
	A(H1N1)pdm09†	202	47 (23)			-10 (-64, 26)	-41 (-135, 16)
2010	All	102	4 (4)	207	48 (23)	86 (61, 95)	87 (61, 96)
	A(H1N1)pdm09†	89	4 (4)			84 (55, 95)	85 (56, 95)
2011‡	All	95	9 (9)	303	53 (17)	51 (-4, 77)	59 (4, 82)
	A(H3N2)	34	5 (15)			19 (-120, 70)	54 (-49, 86)
	B	32	2 (6)			69 (-36, 93)	64 (-61, 92)
Overall§	All	425	39 (9)	918	186 (20)	60 (43, 72)	62 (43, 75)
	A(H1N1)	35	5 (14)			34 (-71, 75)	31 (-107, 77)
	A(H3N2)	158	20 (13)			43 (6, 65)	52 (14, 73)
	A(H1N1)pdm09	111	4 (4)			85 (60, 95)	88 (64, 96)
	B	96	6 (6)			74 (39, 89)	65 (17, 86)

*VE is reported for subtypes where at least one vaccinated case was detected

**Cases by type and subtype will not add up to total cases because typing/subtyping was not available for all cases

***Adjusted for delay between symptom onset and swab, age and month of presentation. Model for all years, 2007-2011 also adjusted for year

†Influenza A(H1N1)pdm09 is the pandemic strain of influenza

‡None of the 22 cases of A(H1N1)pdm09 detected in 2011 were vaccinated

§2009 was not included in the overall VE estimate

excluded from the analysis, the overall, adjusted estimate of vaccine effectiveness improved to 66% (95% CI 48, 78; 2009 omitted). Finally, when only patients presenting during the influenza season were considered (n = 1230), the adjusted VE reduced slightly to 60% (95% CI 40, 73).

Table 3. Sensitivity of the VE estimates under different models.

Model	N (n*)	VE % (95% CI)
Adjusted model including comorbidity status and previous vaccination status, 2011 only	398 (274)	48 (-41, 81)
Adjusted model excluding patients who presented <4 days after symptom onset, 2007-2001 (2009 omitted)	1270 (1107)	66 (48.78)
Adjusted model excluding patients presenting outside the season, 2007-2011 (2009 omitted)	1230 (1227)	60 (40, 73)

*Numbers in parentheses are the number included in the regression model (complete case analysis)

Adjusted VE estimates by type and subtype were compared with assessments of the match between circulating and vaccine strains (Table 4). In 2007, when the majority of circulating strains were assessed as incompletely matched by the haemagglutination inhibition assay, the point estimate of the adjusted VE against all influenza was 58%. The point estimate of the VE was 87% in 2010 when vaccine and circulating strains were matched, but was 59% in 2011 when all strains were again assessed as well matched.

Table 4. Influenza vaccine effectiveness estimates. The VE for each year is provided alongside the strains included in that year's vaccine as well as the predominantly circulating strain in Victoria that year*. Strains in bold indicate an incompletely matched vaccine strain.

Year	VE, adjusted (95% CI)	Type/subtype	N*	Vaccine	Predominant strain
2007	58 (17, 79)	A/H1	65	A/New Caledonia/20/99 (H1N1)	**83% A/Solomon Islands/3/2006-like**
		A/H3	74	A/Wisconsin/67/2005 (H3N2)	**64% A/Brisbane/10/2007-like**
		B	18	B/Malaysia/2506/67/2004 (Victoria lineage)	**58% B/Florida/4/2006-like**
2008	29 (-71, 71)	A/H1	1	A/Solomon Islands/3/2006 (H1N1)	**100% A/Brisbane/59/2007-like**
		A/H3	39	A/Brisbane/10/2007 (H3N2)	81% A/Brisbane/10/2007-like
		B	19	B/Florida/4/2006 (Yamagata lineage)	38% B/Florida/4/2006-like
2009	-32 (-116, 19)	A/H1	99	A/Brisbane/59/2007 (H1N1)	**91% A/California/7/2009-like**
		A/H3	17	A/Brisbane/10/2007 (H3N2)	**59% A/Perth/16/2009-like**
		B	0	B/Florida/4/2006 (Yamagata lineage)	(No samples received from Victoria)
2010	87 (61, 96)	A/H1	233	A/California/7/2009 (H1N1)-like virus	98% A/California/7/2009-like
		A/H3	23	A/Perth/16/2009 (H3N2)-like virus	96% A/Perth/16/2009-like
		B	9	B/Brisbane/60/2008-like virus (Victoria lineage)	90% B/Brisbane/60/2008-like
2011	59 (4, 82)	A/H1	79	A/California/7/2009 (H1N1)-like virus	89% A/California/7/2009-like
		A/H3	135	A/Perth/16/2009 (H3N2)-like virus	98% A/Perth/16/2009-like
		B	128	B/Brisbane/60/2008-like virus (Victoria lineage)	95% B/Brisbane/60/2008-like

*Circulating strains are determined for a sample of viruses from Victoria by the WHO Collaborating Centre for Reference and Research on Influenza and may not be representative of the strain circulating in the community.

Discussion

Based on a prospective test-negative design variant of a case–control study, we estimated influenza VE against laboratory-confirmed influenza for adults aged 20–64 years attending a Victorian sentinel general practice in 2007–2011 as 62% (95% CI 43, 75), excluding the pandemic year of 2009. Using data for 4 years resulted in a sample size exceeding 1300 even after exclusion of 2009 when influenza A(H1N1)pdm09 was the dominant circulating strain. PCR-confirmed influenza defined the study endpoint. Relative to PCR, viral culture will miss cases, and serology will overestimate VE for trivalent inactivated vaccines.[22] For studies of inactivated influenza vaccines, such as this study, PCR is the laboratory test of choice.

Differences in VE estimates from this study and those from our previous publications resulted from restriction of our analysis to the 20- to 64-year-old age group, analysing age as a continuous variable within the group and the inclusion of the delay between symptom onset and swabbing as a continuous covariate in this analysis rather than censoring data at 4 days delay. However, comparison with previously reported results and the sensitivity analyses in this study showed the differences in approach made only marginal differences to the VE estimates by year, except for the pandemic year of 2009.[7,12-14] We did not include that year in our summary VE estimate, and an exploration of possible reasons for the differences in VE estimates will be reported separately.

In addition to limitations common to observational studies, the test-negative design has its own methodological limitations, not all of which have been completely explored. Our study was limited by the fact that we did not collect comorbidity and previous vaccination status until 2011. We had tried to keep the system as simple as possible to facilitate GP involvement, but the collection of the extra data in 2011 did not appear to burden GPs. We allow GPs discretion in determining which patients to swab, whereas other surveillance schemes use a systematic approach to swabbing, to try to limit bias.[4] All observational studies are limited by the lack of randomization of vaccination, a potential source of bias. For

example, patients with comorbidities should be more likely to be vaccinated (exposure by indication) but additionally may be more likely to be tested.

Given these potential limitations, we acknowledge that the VE estimates from this study may be biased. It is, therefore, instructive to compare our results with those from contemporary studies using the same endpoint of PCR-confirmed influenza in patient groups of similar ages. The gold standard comparator is the randomized controlled trial. Results from a large randomized controlled trial conducted in Australia and New Zealand in 2008–2009 found an efficacy of 60% (95% CI 44, 72) for matched strains and 42% (95% CI 30, 52) for all strains, which included A(H1N1)pdm 2009.[23] A meta-analysis of vaccines licensed for use in the USA estimated a pooled vaccine efficacy of 59% (95% CI 51, 67) from published trials.[24] A recent pooled test-negative design of eight studies from Europe estimated adjusted VE for all influenza in 15- to 59-year-olds as 41% (95% CI: −3, 66) in 2010–2011.[25] There are acknowledged potential biases in the test-negative design, but when comparisons from this design are limited to influenza laboratory–detected by PCR among adults of working age, efficacy (trial results) and effectiveness (observational study results) estimates are similar (Table 5).

However, our study also suggests that VE results are not directly related to the proportion of circulating strains that are matched to the vaccine. This observation may result from under-representation of viruses received by the WHO Collaborating Centre in Melbourne. The Centre receives about 15% of laboratory-confirmed influenza viruses reported by the state of Victoria each year, but it is difficult to know whether those viruses submitted represent equal proportions of the circulating strains. Even with perfect representativeness, haemagglutination inhibition assays are a blunt tool for the assessment of VE for inactivated vaccines.[22] It has also been suggested that these assays may be suboptimal for the determination of strain match, especially for more recently circulating H3N2 strains for which problems with agglutination of chicken and turkey red blood cells have been documented and assay results give sometimes discrepant results depending on whether the isolate was grown in eggs or cell culture.[1] Other options for the assessment of vaccine match have their own limitations;

Table 5. Comparison of contemporary vaccine effect measures from community-based studies using a PCR endpoint in working-age adults.

Study and setting	Design	Years	Age group	Vaccine effect measure	Participants			VE (95% CI)
					Total	With influenza	Without influenza	
Observational study, Australia (this study)	Test-negative design	2007-2008 and 2010-2011	20-64 years	Effectiveness of all strains	1343	425	918	62 (43, 75)
Pooled observational study, Europe[25]	Test-negative design from eight countries	2010-2011	15-59 years	Effectiveness of all strains	2511	1117	1394	41 (-3, 66)
Systematic review, vaccines licensed in the USA[24]	Mantel-Haenszel random effects model meta-analysis	Searched for eligible studies 1967-2011	18-64 years	Efficacy of all strains	32470	578	31892	59 (51, 67)
Vaccine licensure study, Australia and New Zealand[23]	Randomized controlled trial	2008-2009	18-64 years	Efficacy-matched strains Efficacy of non-matched strains	14859	277	14582	60 (44, 72) 42 (30, 52)

microneutralization is labour- and time-intensive and has limited accuracy,[26] and phylogenetic analysis does not reliably correlate with antigenic drift.[27]

A study from Taiwan that modelled excess seasonal pneumonia and influenza mortality in older persons showed a lower mortality when vaccine and circulating strains were matched. However, there was also a trend towards lower mortality with mismatched vaccines during the post-SARS period.[28] In an analysis from the 2007–2008 influenza season in the USA, VE was estimated as 37% with a suboptimal match for both the H3N2 and B strains.[29] The authors concluded that, in any season, assessment of the clinical effectiveness of influenza vaccines cannot be determined solely by laboratory evaluation of the degree of antigenic match between vaccine and circulation strains. This was confirmed in the 2010–2011 influenza season in Canada, when an incompletely matched H3N2 strain was identified by both reduced subtype VE estimation and phylogenetic analysis, but not by haemagglutination inhibition assay.[27]

We conclude that the trivalent influenza vaccine provides only moderate protection, of the order of 60%, against medically attended ILI due to laboratory-confirmed influenza in working-age adults. Other VE estimates for the 2010–2011 northern hemisphere season and the 2010 and 2011 southern hemisphere seasons are consistent with this conclusion.[14,27,30-32] In future seasons, we plan to continue to collect data on important confounders, such as comorbidity status and incorporate antigenic characterization data to estimate VE by strain. While it must be stressed that current influenza vaccines are proven to be effective in both trials and observational studies, it is our view that reliance on vaccines of moderate effectiveness should not be allowed to delay the development of new potentially improved vaccines.

Established and evolving observational study designs to estimate influenza vaccine effectiveness should continue to be improved. Such improvements could involve standardizing study designs internationally, as has already been done in Europe.[25] Increasing sample sizes could increase the precision of VE estimates, especially by influenza type and subtype. Improved study designs would facilitate reliable field effectiveness estimates of new-generation vaccines as they become available.

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