

Chapter 2. Investigate an acute public health problem

*Investigating COVID-19 transmission in a tertiary hospital in Hanoi, Vietnam
using social network analysis*

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List of Abbreviations – Chapter 2

CCTV	Video surveillance
CDC	Centers for Diseases Control and Prevention
COVID-19	Coronavirus 2019
MAE	Master of Applied Epidemiology
NIHE	National Institute of Hygiene and Epidemiology
PHEIC	Public Health Emergency of International Concern
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SNA	Social Network Analysis
rt-PCR	Reverse Transcription - Polymerase Chain Reaction

Prologue

Background

World Health Organization (WHO) has declared COVID-19 as a Public Health Emergency of International Concern (PHEIC) by the beginning of 2020, merely three months after its first record in Wuhan, China. COVID-19 quickly attracted many social concern due to its rapid community transmission (1).

In Vietnam, Bach Mai hospital was designated as a health facility to treat COVID-19 cases. This is a tertiary referral hospital responsible for treating mild to life-threatening illnesses in a wide range of diseases. Bach Mai hospital is known for its innovative treatments and state-of-the-art facilities. On 18 March 2020, one nurse in Bach Mai hospital confirmed SARS-CoV-2 infection, which resulted in a COVID-19 outbreak of 46 confirmed cases epidemiologically related to the hospital. This was the first COVID-19 outbreak in a healthcare setting in Vietnam. Many stakeholders were involved in the outbreak investigation, including the National Steering Committee of COVID-19 Prevention and Control, the Bach Mai Hospital, the US Centers for Disease Control and Prevention (CDC), and a team from the Field Epidemiology Teaching Program.

Standard epidemiological techniques like case investigation and contact tracing have been widely used during the COVID-19 pandemic. Additional techniques like social network analysis (SNA) are much less frequently used. The aim of SNA in outbreak investigation is to provide additional, in-depth information to elucidate detailed transmission patterns and sub-networks within the concerned populations. The identification of highly influential cases (with high out-degree and betweenness measures) and closely connected case sub-networks (components) could allow for prioritizing contact tracing activities in a more targeted way. Cases that disproportionately infect others and their networks could be identified quickly, and their contacts could be monitored more intensely to interrupt transmission faster. Nonetheless, one of the limitations of the practical use of SNA in field epidemiology is the time needed to collect the necessary data during a real-time outbreak response. Given the time-sensitive and volatile nature of infectious disease outbreaks, collecting data for network analyses alongside traditional outbreak containment activities might be complicated, especially when resources are stretched, and interfere with other response priority activities. Therefore, in a frontline setting, the use of SNA to support an outbreak investigation may have to be limited to unavoidable circumstances, e.g. contact tracing is not performed due to some reasons, e.g. rapid spread of the virus in the community and lack of human resources.

My role

The COVID-19 outbreak in the Bach Mai hospital occurred when I volunteered at the Rapid Response Team, the National Steering Committee for COVID-19 Prevention and Control. The Team included members of the General Department of Preventive Medicine, the National Institute of Hygiene and Epidemiology (NIHE), the Ministry of Science and Technology, private IT companies, Hanoi University of Public Health, Hanoi Medical University, and local Centers for Diseases Control and Prevention. For the Bach Mai outbreak, we worked with Bach Mai Hospital's staff to establish a contact tracing team to investigate the outbreak.

I was responsible for three activities during this outbreak. I conducted interviews with confirmed cases and close contacts of confirmed cases to construct the transmission chain of the outbreak and managed the outbreak's epidemiological dataset. I was also in charge of data visualization of the outbreak. This included the connection networks between COVID-19 cases and related close contacts, which helped investigate the potential source of infection and the transmission timeline of the outbreak. At first, the network was drawn by hand, then I used R and Gephi software when the inter-case connection became complicated with the higher number of cases. I also drew a 2D map of Bach Mai Hospital with related COVID-19 cases information to identify and predict high-risk areas.

Achievement

Using contact tracing data of the outbreak investigation, I did publish my article in the Tropical Medicine & International Health journal (Appendix 1). This article included the use of SNA techniques to explore COVID-19 transmission dynamics in hospital setting. Our findings highlighted the importance of non-clinical workers in the SARS-CoV-2 transmission route in the hospital, who were often neglected from the initial response to the outbreak, as well as the effectiveness of SNA in investigating the transmission dynamics in a closed setting like hospital. I also presented these results at two international conferences in 2020. The first one was the 9th Bi-Regional FETP COVID-19 Online Conference on 10-12 November 2020 (Appendix 2) and the second was the Special Edition - Australasian COVID-19 Virtual Conference on 09 December 2020 (Appendix 3).

My oral presentation was awarded Outstanding Presentation at the 9th Bi-regional TEPHINET Conference 2020 (Pictured below).

FETP Taiwan is presenting

陳學雄 and 15 more

10:10 AM

(a) degree centrality (b) betweenness centrality (c) closeness centrality

67 connections between 45 cases
C27 - ancillary support staff linked to ten cases

Among the top 10 cases of each metric combined:

- Ancillary support staff: 60%
- Caregivers: 20%
- Patients: 20%

12

Video call participants: You, NgocAnh Hoang, Martyn Kirk, Carl Reddy, FETP Taiwan, Ministry of Malay..., Tom Weiser, Ratchadaporn Pa..., 頌恩, 近頌恩

Investigating COVID-19 Transmission in a Tertiary Hospital in Hanoi, Vietnam, Using Social Network Analysis
Presenter: Ngoc-Anh Hoang Thi, MAE, Australia

Second Place Outstanding Presentation



Abstract

Background

In March 2020, a COVID-19 outbreak in a major referral hospital in Hanoi, Vietnam led to 7,664 patients and staff being sent into lockdown for two weeks, and over 52,200 persons across 49 provinces being quarantined. We assessed SARS-CoV-2 transmission patterns during this to date largest hospital outbreak in Vietnam using social network analysis (SNA).

Methods

We constructed a directed relational network and calculated network metrics for 'degree', 'betweenness', 'closeness', and 'eigenvector' centrality to understand individual-level transmission patterns. We analysed network components and modularity to identify sub-network structures with disproportionately big effects.

Results

We detected 68 connections between 46 confirmed cases, of which 27 (58.7%) were ancillary support staff, seven (15.2%) caregivers, six (13%) patients, and two (4.4%) nurses. Among the ten most important cases selected by each SNA network metric, transmission dynamics clustered in 17 cases, of which 12 (70.6%) cases were ancillary support staff. Ancillary support staff also constituted 71.1% of cases in the dominant sub-network and 68.8% of cases in the three largest sub-communities.

Conclusions

We identified non-clinical ancillary support staff, who are responsible for room service and food distribution in hospital wards in Vietnam, as a group with disproportionately big impacts on transmission dynamics during this outbreak. Our findings call for a holistic approach to nosocomial outbreak prevention and response that includes both clinical and non-clinical hospital staff. Our work also shows the potential of SNA as a complementary outbreak investigation method to better understand infection patterns in hospitals and similar settings.

Lessons learned

As a new epidemiologist, this project has brought to me many special and unforgettable memories and experiences in investigating an outbreak. This was the first time I had been involved in the whole process of an investigation, and I got to observe how to work on different hypotheses and predict an unfolding outbreak in real-time. In the process, I was very lucky to work with many experts in diverse fields, from epidemiology, and medicine to technology and computer science. My problem-solving skills and group skills improved tremendously from my experience working with people in different disciplinary and backgrounds.

Furthermore, I got a chance to sharpen my data visualization skill. From this investigation, I now have experience working with various software to illustrate the social network, namely Microbetrace; R; and Gephi. This project gave me great motivation to study SNA and its implementation in outbreak investigation.

Public health impact

Numerous COVID-19 outbreaks in hospitals have occurred since the start of the pandemic, impacting negatively on patients, staff members, and communities (2,3). Health care workers are at increased risk of infection, particularly those directly exposed to SARS-CoV-2 potential sources from patient care and patient triage. Most nosocomial outbreak investigations focus on clinical staff but less on those who are not directly involved in patient care but are also exposed to sources of infections. Our findings highlighted the importance of non-clinical

workers in driving the SARS-CoV-2 transmission in the hospital setting, namely in this outbreak are ancillary support staff who are responsible for cleaning rooms and food services. These people had a high frequency of mobility around the hospital but were often neglected from the initial response to the outbreak. Our findings addressed a concern to review the current contact tracing protocols in the hospital. During the contact tracing investigation, all people who had high frequent movement around the hospital should be considered high-risk people. Quickly identifying these people to prioritize control measures helps to prevent the wide spread of diseases. Focusing only on people involved in clinical care (e.g. doctors, nurses, patients, caregivers) might delay the response to the outbreak.

COVID-19 outbreaks in the hospital often follow network patterns, with super-spreading persons or events playing an important role in the transmission dynamics. SNA has been applied in previous outbreaks investigations such as tuberculosis (4) or the host-pathogen interactome (5), but not been seen in COVID-19 outbreaks in close settings like hospitals. Our findings highlight its value as an analysis method for field epidemiologists in response to the COVID-19 pandemic. It demonstrates the potential application of using network metrics to prevent the transmission route.

Recommendation

With the support of SNA, we detected a group of non-clinical hospital staff who were essential to the transmission dynamics in a nosocomial COVID-19 outbreak. These staffs are often overlooked during the investigation, yet they play an important part in the interconnection between wards and departments of the hospital. We recommended that all hospital staff should be considered as potential drivers of transmission during a nosocomial outbreak response. Focusing only on core clinical staff like doctors and nurses could substantially delay successful outbreak containment. Our finding of overlooking important ancillary support staff highlighted a gap in the contact tracing process. A careful review of the contact tracing protocol in the hospital is necessary to be prepared for the current COVID-19 pandemic as well as other infectious diseases in the future. Conducting simulation exercises of occurring an outbreak inside the hospital might help the review process.

Although we did not perform SNA analysis in the acute event i.e., during the hospital outbreak investigation, evidence from this project recommends a useful tool to support traditional outbreak investigation for field epidemiologists in the future. We suggested that the

value of SNA in the COVID-19 outbreak response, as well as technical skills to perform such analyses, should be improved among field epidemiologists.

Acknowledgement

I would like to acknowledge the great contribution of my academic supervisor at Master of Applied Epidemiology (MAE) program – Dr. Florian Vogt, who supported me in completing the advanced manuscript and presentations at two international conferences. I thank Dr. Pham Quang Thai – my field supervisor at NIHE, for his support and guideline in the project, and his introduction of me to the investigation in the first place. I also would like to thank Ms. Quach Ha-Linh for her great support and delicate friendship throughout the whole MAE time. I acknowledged Dr. Robyn Lucas, Dr. Philippa Binns, Dr. Samantha Colquhoun from the MAE program for their supports in my presentations. Special acknowledgement was given to healthcare staff at NIHE; Vietnam National Steering Committee for COVID-19 Prevention and Control; Bach Mai Hospital; community healthcare workers from local 49 CDCs; and the Ministry of Health, the Ministry of Science and Technology.

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Appendix 1. Journal Article

Hoang NA[#], Pham QT[#], Quach HL, Hoang VN, Nguyen CK, Dang DA & Vogt F. (2022).

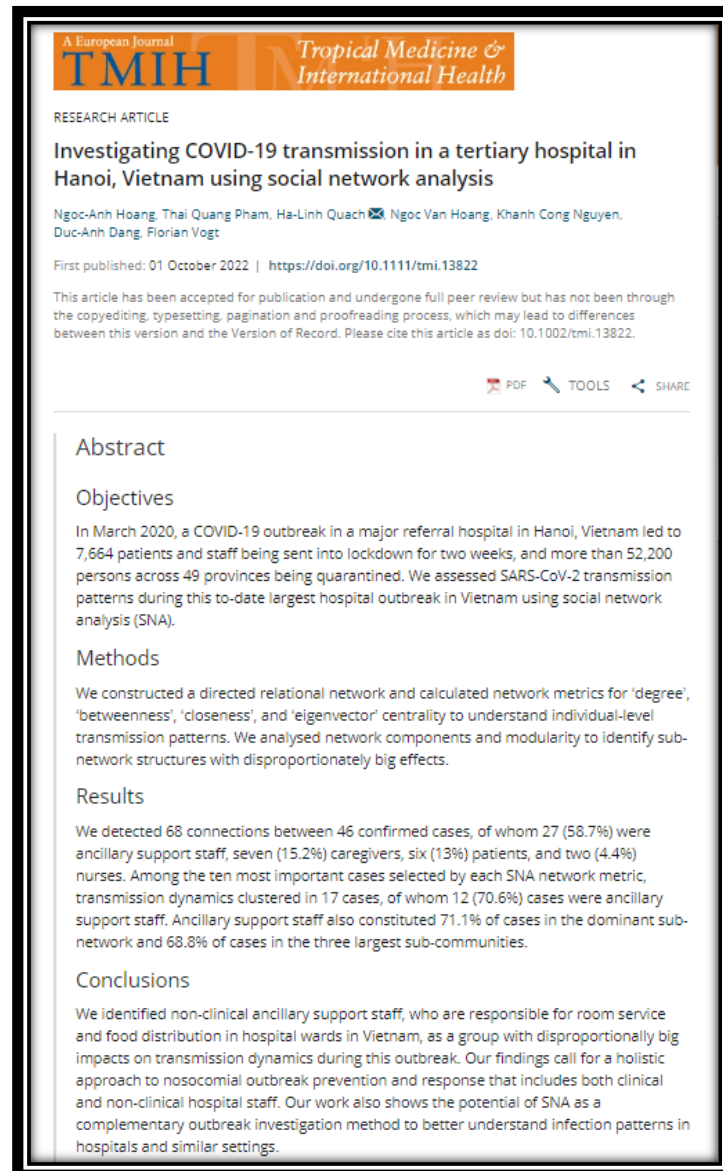
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* Shared first authorship

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**Investigating COVID-19 transmission in a tertiary hospital in Hanoi, Vietnam using
social network analysis**

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25

26 **ABSTRACT**

27 **Objectives**

28 In March 2020, a COVID-19 outbreak in a major referral hospital in Hanoi, Vietnam led to
29 7,664 patients and staff being sent into lockdown for two weeks, and over 52,200 persons
30 across 49 provinces being quarantined. We assessed SARS-CoV-2 transmission patterns
31 during this to date largest hospital outbreak in Vietnam using social network analysis (SNA).

32 **Methods**

33 We constructed a directed relational network and calculated network metrics for ‘degree’,
34 ‘betweenness’, ‘closeness’, and ‘eigenvector’ centrality to understand individual-level
35 transmission patterns. We analysed network components and modularity to identify sub-
36 network structures with disproportionately big effects.

37 **Results**

38 We detected 68 connections between 46 confirmed cases, of which 27 (58.7%) were ancillary
39 support staff, seven (15.2%) caregivers, six (13%) patients, and two (4.4%) nurses. Among the
40 ten most important cases selected by each SNA network metric, transmission dynamics
41 clustered in 17 cases, of which 12 (70.6%) cases were ancillary support staff. Ancillary support
42 staff also constituted 71.1% of cases in the dominant sub-network and 68.8% of cases in the
43 three largest sub-communities.

44 **Conclusions**

45 We identified non-clinical ancillary support staff, who are responsible for room service and
46 food distribution in hospital wards in Vietnam, as a group with disproportionately big impacts
47 on transmission dynamics during this outbreak. Our findings call for a holistic approach to
48 nosocomial outbreak prevention and response that includes both clinical and non-clinical
49 hospital staff. Our work also shows the potential of SNA as a complementary outbreak
50 investigation method to better understand infection patterns in hospitals and similar settings.

51 **Keywords:** nosocomial infection, hospital outbreak, social network analyses, COVID-19,
52 Vietnam.

53

54 **CONFLICT OF INTEREST**

55 The authors declare no conflict of interest.

56

57 **FUNDING**

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59 the Commonwealth Department of Foreign Affairs and Trade.

60

61 INTRODUCTION

62 Hospital staff and patients are at significantly higher risk of SARS-CoV-2 infection than the
63 general population, and several COVID-19 outbreaks in hospitals have been reported around
64 the world (1–3). In Vietnam, the first COVID-19 outbreak in a health care setting occurred in
65 Bach Mai Hospital (BMH), a major tertiary referral hospital in Hanoi, when one of its staff was
66 confirmed SARS-CoV-2 positive on 18 March 2020. The outbreak response gradually
67 escalated to a hard lockdown of the entire hospital, and about 52,200 persons were quarantined
68 across Vietnam as part of the containment efforts. A total of 46 cases were detected before the
69 BMH outbreak was declared over after three weeks.

70 Standard epidemiological techniques like case investigation and contact tracing have been
71 widely used during the COVID-19 pandemic. Additional techniques like social network
72 analysis (SNA) are much less frequently used. The aim of SNA in outbreak investigation is to
73 provide additional, in-depth information to elucidate detailed transmission patterns and sub-
74 networks within the concerned populations (4–6). While SNA has, where applied, proved
75 useful to explore individual-level transmission dynamics for diseases like tuberculosis, HIV,
76 and E.coli outbreaks (7–9), it is not regularly used as part of the standard epidemiological
77 outbreak investigation techniques in field epidemiology. While there have been a couple of
78 attempts during the SARS-CoV-2 pandemic to use SNA to understand super-spreader events
79 (10,11), and in a COVID-19 cluster in the community (12), the value of SNA for outbreak
80 investigations of COVID-19 has not yet been sufficiently established. In particular, SNA has
81 not yet been used to investigate SARS-CoV-2 transmission dynamics in closed settings like
82 hospitals.

83 In this study, we use SNA techniques to gain an in-depth understanding of the transmission
84 structure during the COVID-19 outbreak in the BMH, Hanoi, Vietnam in March 2020. Based
85 on our findings, we also discuss the benefits of SNA as a supplementary tool in field
86 epidemiology generally.

87

88 METHODS

89 Design

90 This study was a retrospective outbreak investigation using SNA. We calculated key network
91 centrality metrics, in particular for ‘degree’, ‘betweenness’, ‘closeness’, and ‘eigenvector’
92 centrality, and constructed sociograms using contact tracing data collected during the BMH
93 outbreak response to identify the transmission dynamics at the individual level. See Appendix
94 1 for detailed definitions and further explanations of SNA metrics used in this manuscript.

95

96 **Setting**

97 BMH is a major tertiary hospital in Hanoi, Vietnam. The Tropical Disease Centre of BMH was
98 designated as one of the reference units to treat COVID-19 patients. On 18 March 2020, a nurse
99 working at the COVID-19 screening office in this centre tested positive for SARS-CoV-2,
100 thereby triggering the first nosocomial COVID-19 outbreak in Vietnam. Outbreak response
101 was quickly escalated after active case finding and extensive testing discovered several cases
102 in other departments, ultimately leading to a hard lockdown of BMH on 28 March 2020 for
103 7,664 persons, among them 6,258 staff, 793 patients, and 613 caregivers, within the hospital
104 premises for two weeks. More than 52,200 persons were quarantined for 14 days across 49
105 provinces in Vietnam. About 15,000 tests were done among persons quarantined in the hospital
106 and a further 30,000 in the community. A total of 46 laboratory-confirmed cases were identified
107 in seven different units of BMH (see Figure 1). Details about the investigation and response to
108 the BMH outbreak using standard epidemiological methods have been described in Appendix
109 2 as well as elsewhere (13–15).

110

Figure 1 is about here

111

112 **Data collection**

113 Data was collected in March 2020 during the outbreak investigation and response activities.
114 For the SNA analysis, we compiled and extracted socio-demographic and occupational
115 information on cases and their exposure histories from records of the Rapid Response Team
116 (RRT) of the National Steering Committee for COVID-19 Prevention and Control in June
117 2020. During the BMH outbreak, the contact information of anyone testing positive for SARS-
118 CoV-2 was provided to the RRT who interviewed all cases via phone. Collected information
119 included demographic, occupational, and basic clinical information (age, sex, occupation, and
120 comorbidity), date of symptom onset, as well as a detailed movement and contact history
121 during the 14 days before the date of onset of symptoms or confirmation, whichever came first.
122 Video surveillance inside the hospital was reviewed alongside the case interview to verify and
123 complement the information provided by cases as part of outbreak response and to establish
124 the most likely place of infection and source(s) of infection for each case.
125 Variables available for this analysis were the cases' age, sex, occupation, comorbidities, date
126 of symptom onset, date of positive SARS-CoV-2 test result, place of presumed infection, and
127 sources of infection for each case.

128

129 **Data analysis**

130 We created a relational network dataset with confirmed COVID-19 cases as “nodes” and the
131 epidemiological contacts between them as “edges”. Each case was provided with a unique
132 identification number, and each case’s unique epidemiological contacts with other cases were
133 also identified and labelled. The relational data were analysed from a direct network
134 perspective, which contained directionality of infection emanated from a “source case” towards
135 the “target case” (16).

136 We calculated and compared the score rank of the social network centrality measures ‘degree
137 centrality’, ‘betweenness centrality’, ‘closeness centrality’, and ‘eigenvector centrality’ to
138 identify the key nodal cases that were particularly influential during this outbreak. We also
139 calculated network components and modularity to identify sub-network structures that
140 contributed disproportionately to the transmission of infection. Average path length and
141 network diameter measures were analyzed to assess the dispersion level of infection within
142 networks.

143 The relational data with nodes and edges were created in Microsoft Excel software and
144 transferred into Gephi software (version 0.9.2) for network illustration and into R (version
145 4.1.1, package “igraph”) for analyses (17,18). Network measures, components, and modularity
146 were generated, and the outputs were derived as tables and graphs. The network measure tables
147 from Gephi were exported to R for generating network summary measures. Network graphs
148 were created to visualize relationship patterns between source and target cases. Yifan Hu layout
149 and Fruchterman Reingold layout in Gephi software were used to visualize the networks (19).
150 We also calculated frequencies and percentages to describe the distribution of cases’ age, sex,
151 occupation, comorbidity, place of presumed infection, and departments of recorded cases in
152 the hospital using R (version 4.1.1).

153

154 **Ethics**

155 This manuscript was approved and exempted by the Internal Review Board, National Institute
156 of Hygiene and Epidemiology, Vietnam as a part of national COVID-19 outbreak investigation
157 and response activities.

158

159 **RESULTS**

160 **Case characteristics**

161 Overall, 46 cases were detected among ancillary support staff (27, 58.7%); caregivers (7,
162 15.2%); patients (6, 13%); nurses (2, 4.4%); and four secondary cases (8.7%) outside the

163 hospital. Most cases were female (85%), between 35 and 64 years old (69.6%), and with
164 comorbidities (71.7%). 40 (87%) cases acquired infection most likely inside the hospital, and
165 the remaining through family and community contacts. Nearly half of the cases (45.7%) had
166 COVID-19 compatible symptoms during their infection period, while the rest (25, 54.3%)
167 remained asymptomatic (Table 1).

168 **Table 1 is about here**

169
170 ***Relationship analysis***

171 There were a total of 68 epidemiological connections identified between the 46 laboratory-
172 confirmed cases, of which 27 were source cases and 17 were target cases.

173 Network measures showed that 29 cases (63%) had an in-degree centrality measure of zero and
174 thus lacked any epidemiological link with a source case. Of the remaining, seven cases (15.2%)
175 had an in-degree measure of two, implying that two source cases were identified for each of
176 them. A small number of cases had an in-degree measure of more than two (range 3 – 6). 19
177 (41.3%) of the total 46 cases had an out-degree centrality measure of zero and thus did not act
178 as a source of infection to other cases. The remaining 27 (58.7%) cases were found to have an
179 out-degree measure above one (range 1-6), thus presenting as sources of infection to a total of
180 17 target cases (Table 2).

181 **Table 2 is about here**

182
183 The average path length, indicating the average number of edges reflective of the length of the
184 generational transmission, between cases was 1.8. The network diameter, the largest path
185 length between cases reflective of the highest number of transmission generations, was 4.

186 Based on degree centrality metrics, case P27 was the node with the highest number of links to
187 other cases (10, 21.7% of the total cases in the network). Also, closeness, betweenness, and
188 eigenvector network centrality metrics indicated that P27 was the most important node in the
189 transmission network (closeness centrality = 0.0022, betweenness centrality = 335.9,
190 eigenvector centrality = 0.8). Case P28, P18, and P32 also ranked high on the four centrality
191 measures, and together these four cases contributed to 35 (51.5%) of all epidemiological
192 connections in the network (Figure 2a and Table 3).

193 The betweenness centrality measure was zero for 30 cases (65.2%), implying that they did not
194 play a role in the transmission of SARS-CoV-2 between any other pair of cases. The remaining
195 16 cases (34.8%) had a non-zero betweenness centrality value (range 1 to 30), indicating their

196 involvement in the transmission route between other cases in the network. The three cases with
197 the highest betweenness centrality were P27, P28, and P18 (Figure 2b).
198 Three cases (P20, P23, and P26) did not have many contacts with others (low degree centrality)
199 and were not a bridge in the transmission route (low betweenness centrality), however, P26
200 was a key nodal case who were influential in transmitting SARS-CoV-2 infection due to having
201 short distances to all other cases in the outbreak (closeness centrality: $P26 = 0.00216$), and P20
202 and P23 influenced the most important cases in the network (eigenvector centrality: $P20 = 0.8$,
203 $P23 = 0.8$) (Figure 2c and Figure 2d and Table 3).
204 Table 3 shows the measures of network centrality estimates for the 10 most important nodes
205 selected by the four-network metrics. A total of 17 cases were identified based on the score
206 rank of these network metrics. 12 out of 17 (70.6%) of them were ancillary support staff, two
207 (11.8%) were patients, and three (17.6%) were caregivers.

208 **Figure 2 is about here**

209 **Table 3 is about here**

210

211 Two connected components (sub-networks) and five cases without epidemiological contacts
212 were identified. The bigger of the two sub-networks ('giant components') accounted for 82.6%
213 (38) of the total cases and 94% (64) of all transmission contacts of the network. Ancillary
214 support staff contributed 71.1% (27 cases) in this component (Figure 3A).

215 We detected 10 communities (modules). The modularity score was 0.576, indicating the
216 possible presence of community structure. The largest module contained 14 cases and 20
217 contacts, which accounted for 30.4% of total cases and 29.4% of total transmission contacts in
218 the network. The two next second-largest communities contained nine cases each. The ancillary
219 support staff contributed to 68.8% (22 cases) of the total cases in the three largest communities
220 (Figure 3B).

221 **Figure 3 is about here.**

222

223 **DISCUSSION**

224 We used SNA for a detailed understanding of the individual-level transmission dynamics
225 during this first COVID-19 outbreak in the health care setting in Vietnam. Our findings
226 highlight the importance of ancillary support staff, a non-clinical cadre of hospital staff that is
227 often overlooked in the prevention of nosocomial infections, in driving the BMH outbreak. We
228 also demonstrate the value of SNA as an additional method to understand the heterogeneity in

transmission dynamics of COVID-19 outbreaks in closed settings in greater detail than standard outbreak investigation techniques allow.

We found high individual cases level variation in SARS-CoV-2 transmission. Several epidemiological studies have since shown the importance of heterogeneity in SARS-CoV-2 transmission and the need to measure transmissions and variations at individual levels (20–23). The out-degree centrality measures found in our study indicated that while nearly half (41.3%) of the cases in the network did not transmit infection, the rest (58.7%) were source cases that disproportionately transmitted to target cases. In-degree centrality measures in our analysis showed that no source of infection was found for 63% of cases and that 21.8% of cases had three or more sources of infection. In terms of the number of connected contacts (via both out-degree and in-degree centralities), case P18, P27, P28, and P32 were the top 4 cases, of which P27 was the most influential case. P27 was an ancillary support staff who distributed food in all wards of BMH. Case P27 was detected six days after showing COVID-19-compatible symptoms after exhaustive testing for all persons present inside the BMH at that time. This case was epidemiologically closely linked to seven other ancillary support staff who shared the same working and living space, and three patients treated in the BMH who had close contact during the infection period.

The importance of a case to others in a network is not only defined through its number of contacts but also by the interconnectivity of its secondary cases, which is measured through the betweenness metric. Betweenness centrality measures highlight that not all infections were directly transmitted from a few influential sources (with higher out-degree measures) to many target cases, but through influential bridging cases (with high betweenness measures) who acquired the infection from them. The high betweenness score of P27, P28, and P18 indicated that these three cases were not only connected to many other cases, but they also contributed as important pathways to further infection. On the other hand, the high degree of centrality but low betweenness score of P32, an ancillary support staff, indicated that while connecting many other cases, P32 was not a bridge of further transmission. In contrast, P39, another ancillary support staff, had a low degree centrality score but high betweenness score suggesting that although P39 did not have contact with many other cases, this case was critical in the spread of SARS-CoV-2 to others.

The path length metrics indicated that on average any source and target cases in the network could be reached by crossing 1.8 steps and at a maximum, it was four steps between the farthest placed source and target cases. This highlights that the transmission of infection was not widely

262 dispersed during the BMH outbreak through multiple generations; it is on average limited to
263 less than two generations.

264 Our in-depth analysis of the transmission network of the BMH outbreak using SNA has
265 relevant implications in two aspects. First, it could help the public health personnel comprehend
266 the key influential groups to prioritize early public health interventions to reduce the likelihood
267 of nosocomial spread (24). In this outbreak, the network metrics (degree centrality,
268 betweenness centrality, closeness centrality, eigenvector centrality) shed light on the potential
269 importance of non-clinical hospital staff in driving transmission dynamics during nosocomial
270 COVID-19 outbreaks. These were ancillary support staff who distributed food and cleaned
271 wards in the hospital. This type of work meant they moved at high frequency across BMH and
272 had contact with many people, including patients, caregivers, and health care workers.
273 However, they are often overlooked during the initial response to COVID-19 outbreaks in
274 hospitals due to not being directly involved in patient care. They were also neglected from the
275 infection prevention control training at the beginning of the pandemic. We recommended that
276 all types of hospital staff regardless of their involvement in patient care need to be considered
277 as potential drivers of transmission during a nosocomial outbreak response. Focussing only on
278 core clinical staff like doctors and nurses might delay successful outbreak containment.

279 Second, from a methodological perspective, integrating SNA alongside more established
280 epidemiological investigation techniques during an outbreak could help to target resources for
281 outbreak response more efficiently (5). The identification of highly influential cases (with high
282 out-degree and betweenness measures) and closely connected case sub-networks (components)
283 could allow for prioritizing contact tracing activities in a more targeted way. Cases that
284 disproportionately infect others and their networks could be identified quickly, and their
285 contacts could be monitored more intensely to interrupt transmission faster. Nonetheless, one
286 of the limitations of the practical use of SNA in field epidemiology is the time needed to collect
287 the necessary data during a real-time outbreak response. Given the time-sensitive and volatile
288 nature of infectious disease outbreaks, collecting data for network analyses alongside
289 traditional outbreak containment activities might be complicated, especially when resources
290 are stretched, and interfere with other response priority activities. Therefore, in a frontline
291 setting, the use of SNA to support an outbreak investigation may have to be limited to
292 unavoidable circumstances, e.g. contact tracing is not performed due to some reasons, e.g. rapid
293 spread of the virus in the community and lack of human resources.

294 SNA to inform SARS-CoV-2 contact tracing has shown to be useful for supporting control
295 transmission in South Korea; it was applied to support the efficiency of governmental responses

296 to COVID-19 (10). Another study from India used relational data to prioritize the most
297 susceptible regions for target testing and quarantining (11). A study in Hong Kong used contact
298 tracing data to identify the most important SARS-CoV-2 clusters in the community by
299 constructing a SARS-CoV-2 network of transmission (23). Awareness about the value of SNA
300 in COVID-19 outbreak response as well as technical skills to perform such analyses should be
301 increased among field epidemiologists, in particular in settings where timely genomic
302 sequencing is absent.

303 We acknowledge several limitations of our study. First, this analysis was based on data from
304 case interviews about movement and contact history over 14 days. The accuracy of some of
305 the provided information could not be verified during the early outbreak response phase. For
306 example, in our data, 63% of cases had no detected sources of infection, which was most likely
307 due to recall inaccuracy. To support the accuracy of SNA, we recommend designing a
308 standardized questionnaire to collect relational data and preparing trained interviewers for SNA
309 data collection. Second, because the data collection was not specifically designed for an SNA
310 analysis, we acknowledge the missing of some meaningful information for a deeper
311 understanding of SARS-CoV-2 transmission dynamics that could bias the network analysis,
312 for example, information on the cases' behaviors to reduce the risk of infection or onwards
313 transmission. Third, due to a lack of data for weighting directed edges, such as duration of
314 contact or location of contact (e.g. in small, enclosed rooms with poor ventilation or in larger,
315 well-ventilated areas), we had to treat all edges, representing contacts, as equal. Unweighted
316 edges might lessen the importance of ancillary support staff in the transmission network, given
317 their close working and living conditions. Fourth, we were not able to compare our results from
318 SNA to genomic sequencing data as this was not available for our analysis. Though the
319 outbreak was contained within three weeks (15), the initial source of infection for this outbreak
320 was uncovered.

321

322 **CONCLUSION**

323 This study shows the successful application of SNA for an in-depth investigation of Vietnam's
324 first COVID-19 outbreak in a hospital setting. We identified non-clinical ancillary support
325 staff, who are responsible for room service and food distribution in hospital wards in Vietnam,
326 as an important group with a disproportionally big impact on transmission dynamics during
327 this outbreak. Outbreak response measures in hospitals often focus on patients and core medical
328 staff such as doctors and nurses, while non-clinical hospital staff is overlooked during outbreak
329 response in health facilities. Our findings call for a comprehensive approach to hospital

330 infection prevention and control as well as nosocomial outbreak response that includes all
331 professions of the hospital workforce. Our findings also point to the potential of SNA as a
332 complementary method for field epidemiologists to better understand infection patterns in
333 hospitals and similar settings and prioritize appropriate interventions accordingly.
334

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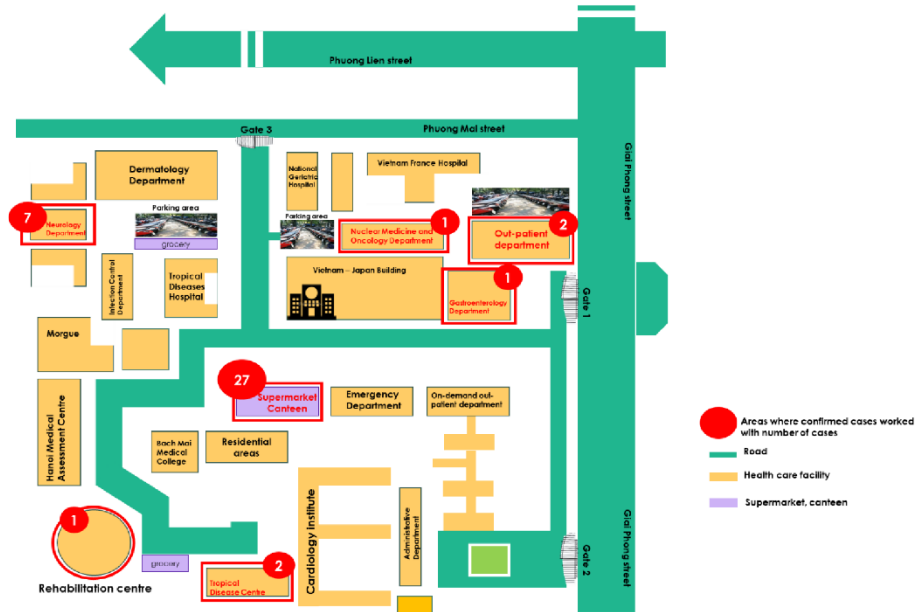
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430

431

Figure 1. Map of infected areas in the Bach Mai hospital outbreak

Note: The map is not indicated four secondary cases outside the Hospital

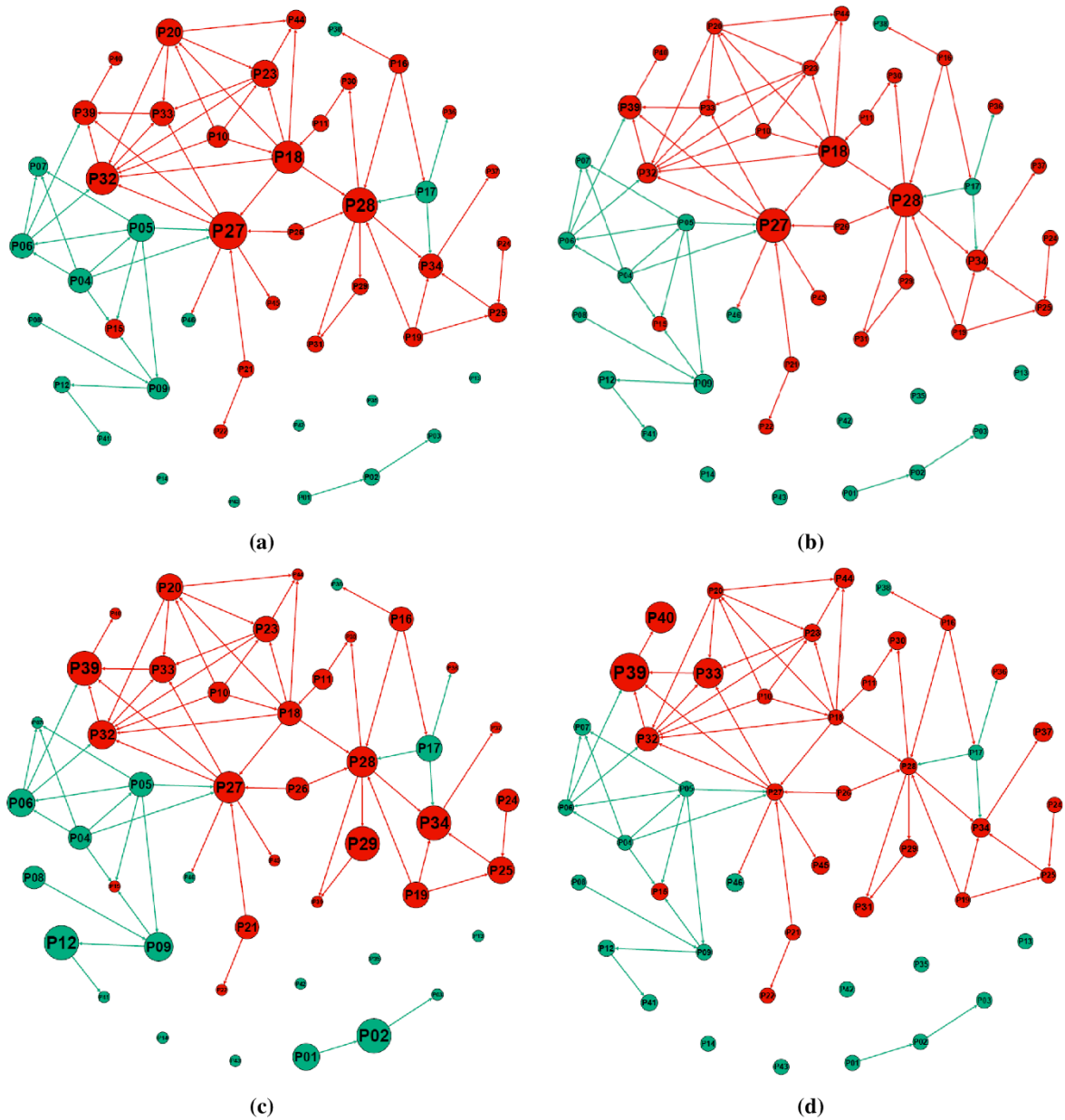
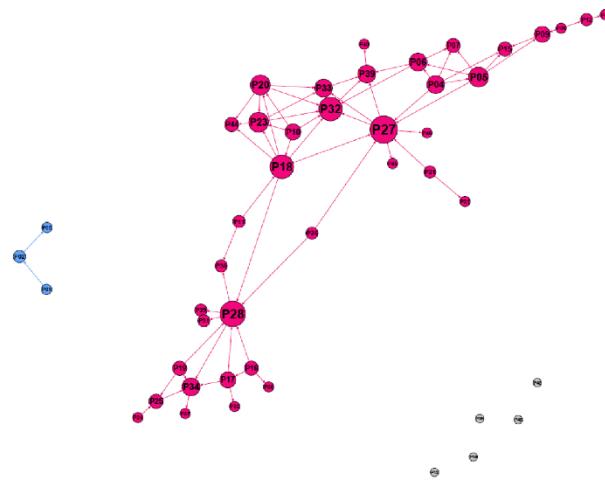


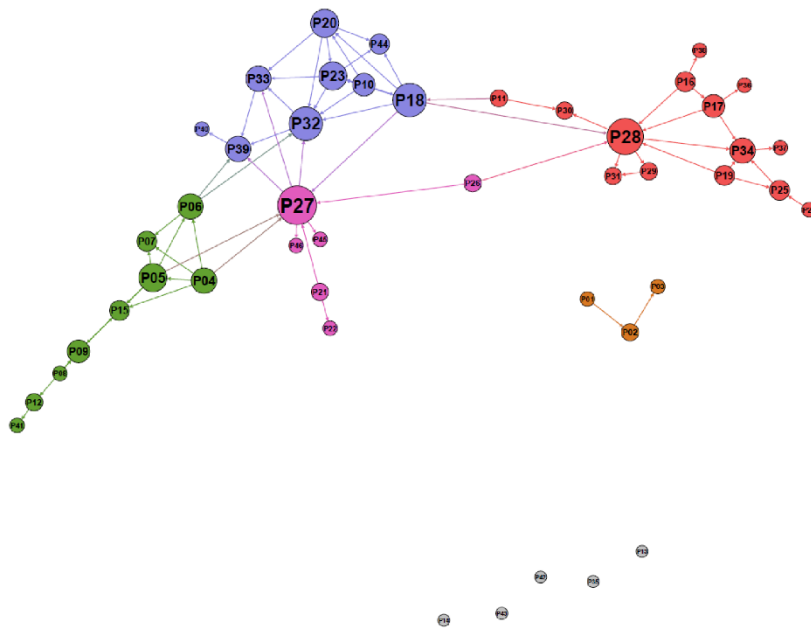
Figure 2. Network contact structure for the spread of SARS-CoV-2 infection in the Bach Mai Hospital.

435 *Larger sized nodes imply higher score of (a) degree centrality, (b) betweenness centrality, c)*
436 *closeness centrality, d) eigenvector centrality. Red circle indicated ancillary support staff and*
437 *blue circle for other cases.*
438 *The colour of the edges was based on the colour of source case.*

439
440



(a)



(b)

441
442

443 **Figure 3. Connected components (a) and modularity (b) in the Bach Mai outbreak.**
444 *Larger sized nodes imply higher score of degree centrality. Different colours indicated*
445 *different components (a) and modules (b). Cases in the same component (a) and module (b)*
446 *had the same colour.*

447

Table 1. Case characteristics during the Bach Mai outbreak

Characteristics	N=46	%
Age groups		
<35	11	23.9
35 – 64	32	69.6
65+	3	6.5
Sex		
Female	39	84.8
Male	7	15.2
Occupation		
Ancillary support staff	27	58.7
Caregiver	7	15.2
Nurse	2	4.3
In-patient	4	8.7
Out-patient	2	4.3
Others	4	8.7
Departments of recorded cases		
Supermarket/Canteen	27	58.7
Neurology	10	21.7
Gastroenterology	2	4.3
Rehabilitation	1	2.2
Tropical Disease Centre	3	6.5
Nuclear Medicine & Oncology	1	2.2
Out patient	2	4.3
Comorbidity		
Yes	33	71.7
No	13	28.3
Place of presumed infection		
Hospital	40	87
Family	3	6.5
Community	1	2.2
Index cases	2	4.3
Having COVID-19 compatible symptoms		
Yes	21	45.7
No	25	54.3

448

449

450 **Table 2. Case categorization based on degree centrality measures (n=46)**

Degree centrality	No of cases	Percent	Case categorization*
<i>In-Degree centrality measure</i>			
0	29	63	No identified source of infection
2	7	15.2	Target case
3	4	8.7	Target case
4	3	6.5	Target case
5	2	4.3	Target case
6	1	2.2	Target case
<i>Out-Degree centrality measure</i>			
0	19	41.3	Not transmitted infection to anyone identified
1	10	21.7	Source case
2	5	10.9	Source case
3	5	10.9	Source case
4	3	6.5	Source case
5	3	6.5	Source case
6	1	2.2	Source case

451 * Cases lacked source of infection if In-Degree centrality = 0; Target case had In-Degree
452 centrality ≥ 1 ; Cases did not transmit SARS-CoV-2 to anyone had Out-Degree centrality = 0;
453 Source case had Out-Degree centrality ≥ 1 .

454 **Table 3. Summary of contact network metrics for the top 10 scores of COVID-19 cases**
 455 **(node (score)).**

Score rank	Degree centrality	Betweenness centrality	Closeness centrality	Eigenvector centrality
1	P27* (10)	P27* (335.9)	P18* (0.00221)	P32* (1)
2	P28* (9)	P28* (329.0)	P27* (0.00220)	P18* (0.9)
3	P18* (8)	P18* (251.3)	P28* (0.00216)	P27* (0.8)
4	P32* (8)	P05 (152.3)	P32* (0.00216)	P20* (0.8)
5	P05 (6)	P09 (104.0)	P26* (0.00216)	P23* (0.8)
6	P20* (6)	P26* (92.0)	P05 (0.00211)	P33* (0.7)
7	P23* (6)	P34* (72.7)	P20* (0.00209)	P10* (0.6)
8	P04 (5)	P32* (65.8)	P23* (0.00209)	P39* (0.5)
9	P06 (5)	P17 (39.3)	P04 (0.00209)	P06 (0.4)
10	P33* (5)	P39* (38.3)	P06 (0.00208)	P44* (0.4)

456 **Asterisks were ancillary support staff*

Appendix 1. Measure definitions

Degree Centrality includes In-Degree and Out-Degree centralities. In-Degree centrality measures the number of epidemiological contacts incident upon a patient. If the measure is “zero”, the patients lack a source of infection because they have not been infected by any other patient in the network. “Non-zero” ones indicate “target patient” who had got the infection from at least one source patient. Out-Degree centrality measures the number of epidemiological contacts emanating from a patient that are directed to other patients. “Zero” measures imply that the patient had not transmitted infection to anyone and did not be a source patient. “Non-zero” values refer to the patient who is a source of infection for at least one patient in the network (24) (Figure).

Betweenness centrality was used to measure how frequently a given patient acted as a bridge in the transmission routes of other patients in the network. This measure is calculated by identifying the shortest contact paths between every possible pair of patients in the network and further measuring the number of times the given patient is found in those shortest paths. A non-zero value suggests that the patient contributes as a bridge to connect a source and target patient i.e., stands in the transmission route between a source and target patient. The higher the betweenness centrality is, the more potential a patient contributes to transmit the infection from the source patient (24) (Figure).

Closeness centrality was used to measure how "close" a patient is to all other patients in the network. This measure accounted for total shortest paths from a given patient to others. The higher value indicated the shorter distance from the given patient to others, thus the easier this patient influences the entire network (25) (Figure).

Eigenvector centrality measured the influence of a given patient on the whole network; higher values indicate more influential patients. Each patient in the network was assigned a relative score based on the assumption that high-scoring patients are connected to more other high-scoring patients than low-scoring ones (26) (Figure).

Network components are connected structures comprising of source and target patients who have epidemiological contacts between them but do not connect to other similar patient components. The component with the largest number of source and target cases was identified as a giant component (27) (Figure).

Modularity measures the strength of devising a network into subnetworks (modules). The network with high modularity has dense connections among patients within the subnetwork but sparse connections to patients in others. In our manuscript, modularity is

calculated using the heuristic method that is based on modularity optimization. The division of subnetwork was based on applying the eigenvector-based algorithm (28,29) (Figure).

Path length is the number of connections (edges) that presents between a given pair of patients. The average path length is the average of the shortest path length over every source and target patient in the network, thus denotes the average epidemiological contact distance between the source and target patient. Network diameter denotes the farthest epidemiological contact distance between the source and target patient in the network (30) (Figure).

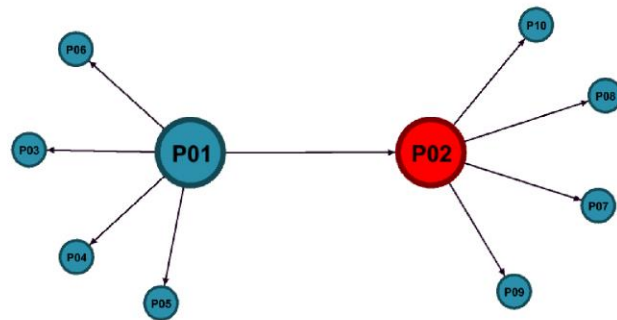


Figure. Graphical illustration of network measures.

A network of ten patients is denoted by round nodes and the epidemiological relations between them are denoted as directed lines with arrows. Patient P01 has an out-degree of 5 and has acted as a source of infection to five patients P02, P03, P04, P05, P06. Similarly, patient P02 has an out-degree of 4 and had acted as a source patient for P07, P08, P09, P10. Patient P02 has an in-degree of one and had acted as a target patient who received the infection from P01. Patient P02 depicted in red color is the node that has the highest betweenness centrality and closeness centrality in the network. It was interpreted as P02 was not only a bridge of the transmission from P01 to four other patients P07, P08, P09, P10, but also was a node that has the shortest way to all other nodes in the network. The path length between patient P01 and P02 is one while path length from P01 to P07, P08, P09, and P10 is two. The maximum path length in the network (i.e. network diameter) is two which lies between P01 and P07, P08, P09, P10. The number of network components for the depicted network is one as all patients are connected either directly or indirectly to each other; no one is left unconnected.

Appendix 2. Outbreak investigation and response

A SARS-CoV-2 outbreak in Bach Mai hospital - a major referral hospital in Vietnam subsequently led to a hard lockdown of the entire hospital, and about 52,200 persons were quarantined across Vietnam as part of the containment efforts.

The first index case

At 3:00 p.m. on 18 March 2020, the Rapid Response Team, the National Steering Committee of COVID-19 Prevention and Control received a laboratory-confirmed case of COVID-19, which was a nurse working at COVID-19 screening office in Tropical Disease Centre, Bach Mai hospital. The case displayed symptoms of fever and cough that morning and requested a SARS-CoV-2 test that afternoon.

The hospital's board of directors decided to lock down the Tropical Disease Centre for 14 days and immediately test 242 healthcare staff at this centre. 1,490 visitors who had come to the COVID-19 screening office since 04 March 2020 were also contacted and tested for SARS-CoV-2. Twenty-two close contacts of the nurse outside the hospital were also traced and tested, including family members and friends. None of them tested positive for SARS-CoV-2. There was no evidence for the initial hypothesis of transmission from the community to healthcare workers.

The case investigation was expanded to all healthcare workers who worked with the index case during the past 14 days from 18 March 2020 backward. At 8:00 p.m. on March 18 2020, found another nurse tested positive for SARS-CoV-2. This nurse had close contact with the index case on 15 March 2020. From 16 March 2020, this case was treated in Cardiovascular Department, Bach Mai hospital due to chest pain.

The second nurse had a complex travel history. The nurse travelled on vacation from 6th to 8th March with a group of 20 friends; they had taken four flights to and from Hanoi. Initial suspicion of infection was transmission in-flight, which was the most common source of infection for new COVID-19 cases in Vietnam at that time. However, all passengers on these flights were negative for SARS-CoV-2. We also found no evidence for the second suspicion of in-ward transmission as none of the people in the Cardiovascular Department tested positive for SARS-CoV-2.

The investigator team detected 85 close contacts of this nurse outside the hospital. A child who lived with the second nurse was the next infected case. This case showed no symptoms and all of her close contacts tested negative. At this point, there was insufficient evidence to support any of the hypotheses, and hospital-associated transmission was still an option; however, the source of infection remained undetermined.

The second index case

On 22 March 2020, a stroke patient tested positive for SARS-CoV-2 who was discharged from the Neurology Department, Bach Mai hospital on the same day. This patient developed a fever during the ambulance ride to another hospital.

Immediately, the hospital's board of directors decided to lock down the Neurology Department for 14 days. Testing SARS-CoV-2 for 319 patients, caregivers, and healthcare staff in this department revealed a further six confirmed cases. One patient was a roommate of the second index case, while four were caregivers for both the second index case and the roommate. Another case was a caregiver in another room that never had contact with other five cases. Two questions came up for the investigation team: 1) what was the source of infection for seven cases in the Neurology Department, and 2) what was the relationship between the two clusters of the first index case and second index case?

While investigating the travel history of these seven cases, on the morning of 25 March, a caregiver in the Gastroenterology Department was confirmed positive for SARS-CoV-2. The case displayed symptoms of fever at night, on 23 March.

Lockdown of Bach Mai Hospital

The spread of SARS-CoV-2 to other departments in Bach Mai Hospital continued. On 26 March, the board of hospital decided to test all people inside the hospital. The tests revealed two new cases among ancillary supported staff who prepared and distributed food to all wards in the hospital.

On 28 March 2020, the hospital was under a complete lockdown for 14 days, and everyone inside the hospital got tested for SARS-CoV-2. This extensive testing detected a total of 25 additional confirmed cases, all were ancillary support staff who prepared food in the canteen and grocery stores, and distributed it to all wards inside the hospital. No additional cases among healthcare staff were detected. Bach Mai hospital also compiled a list of about 52,200 persons who visited the hospital from 01 March 2020 onwards. The list was shared with 49 local Centers of Disease Control and Prevention to trace and test these visitors. No additional cases were found among these contacts.

Supermarket and canteen areas had the highest number of cases (ancillary support staff). These areas were always crowded with patients and their caregivers, but not often frequented by healthcare staff. All patients and caregivers that tested positive for COVID-19 had

frequented in the canteen for eating and other activities the past 14 days before their SARS-CoV-2 test confirmation.

Other prevention measures in the hospital

The COVID-19 infection pattern in Bach Mai Hospital was different from the common person-to-person transmission pattern. The Tropical Disease Centre, where the index case was first seen, had only three cases. This could be explained that the initial source of COVID-19 in Bach Mai might not be from that centre. There was no active SARS-CoV-2 outbreak in the community in Hanoi at that time as well, therefore, the hypothesis of the initial source originating from the community was also ruled out. Even though the outbreak was contained within three weeks with no new cases found in relation to the hospital, the initial source of SARS-CoV-2 infection remained inconclusive.

Appendix 2. Conference presentation

Conference presentation at the 9th Bi-Regional FETP COVID-19 Online Conference (virtual conference) on 10-12 November 2020

The slide features a dark blue background with a grid of light blue squares on the right side. At the top left, there are logos for Australian National University and the Field Epidemiology Training Institute of Applied Epidemiology. At the top right is the logo for the National Institute of Hygiene and Epidemiology (NIHE). The main title is in large, bold, orange and white text. Below the title, the conference details are in yellow text. The presenter's name is in white text, followed by their affiliation in smaller white text.

**Investigating COVID-19 transmission
in a tertiary hospital in Hanoi, Vietnam
using social network analysis**

the FETP COVID-19 Online Conference, 10 – 12 November 2020

Hoang Thi Ngoc-Anh

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Outline

- Section A: Background & Aim
- Section B: Methods
- Section C: Results
- Section D: Conclusions

Section A: Background

- 1st SARS-CoV-2 outbreak in a hospital in Hanoi, Vietnam on 16 March 2020
 - biggest tertiary hospital in Northern Vietnam
 - >1,400 beds and >4,000 staff
- Collaborative outbreak investigation of the National Steering Committee of COVID-19 Prevention & the Hospital

3

Section A: Aim of this study

Understand transmission patterns during a SARS-CoV-2 outbreak in a tertiary hospital in Vietnam using social network analysis

4

Section B: Methods

Data sources:

- Case interviews: Exposure, work place connections
- NIHE's testing management system: PCR test results
- Hospital's surveillance system: Movement monitoring
(mobile tracking and video surveillance)

5

Section B: Methods

Network analysis

Networks: A set of objects (nodes) with interconnections (edges)



Applied Social Network Analysis in Python,
<https://www.coursera.org/learn/python-social-network-analysis>

Source: WomenEd, <https://www.womened.org/blog/networking>

6

Section B: Methods

Network analysis

- Find important cases in a network
- **Network metrics:** Degree centrality, Betweenness centrality, Closeness centrality
- **Software, packages:** R, package (“igraph” and “CINNA”)

7

Section B: Methods

Degree Centrality

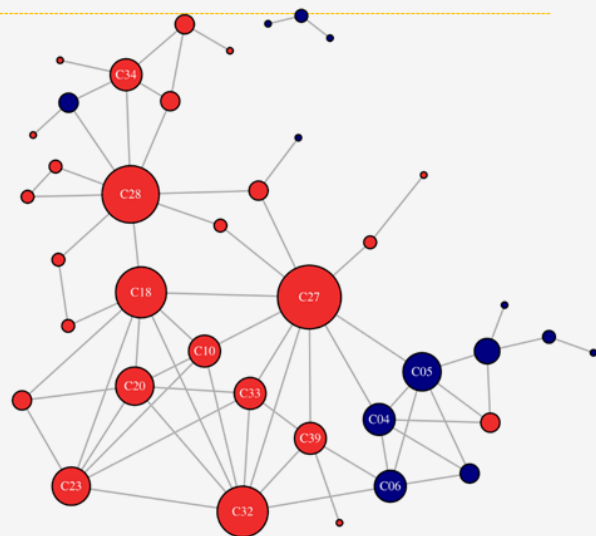
Assumption: important nodes have many connections

Closeness Centrality

Assumption: important nodes are close to other nodes

Betweenness Centrality

Assumption: important nodes connect other nodes



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Section C: Results

Testing (PCR from swabs):

- Inside the hospital: >7,200 tests among 1,982 persons at day 0, day 3-4, and day 14 after last exposure
- Outside the hospital: testing >26,000 people in 49 provinces who visited the hospital between 1st – 25th March

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Section C: Results

Characteristics	n (%)
Total case	45 (100)
Age	
20 - 39	16 (35.6)
40 - 59	24 (53.3)
≥ 60	5 (11.1)
Sex	
Male	8 (17.8)
Female	37 (82.2)
Profession	
Ancillary support staff	26 (57.8)
Caregivers	7 (15.6)
Out-patients	5 (11.1)
Nurses	2 (4.4)
Inpatients	2 (4.4)
Secondary cases	3 (6.7)

=23% of all
anc supp staff

16 Mar

- Index case confirmation
- Stop examination and receive patients in Tropical Disease Centre

19 Mar

- Stop examination and receive patients in Bach Mai Hospital

22 Mar

- Close groceries & canteen

28 Mar

- Test all patients, people in the Hospital
- Lock down the Hospital for 21st days



Living place
of ancillary
support staff



Pictures were used with the investigators' permission



Section D: Conclusions

- All staff matter!
- Social network analysis is valuable!
- The more you move the more you spread!

Acknowledgement

- Dr. Florian Vogt, my academic supervisor at Australian National University
- Dr. Thai Quang Pham, my field supervisor at NIHE
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- National Centre for Epidemiology and Population Health, Research School of Population Health, College of Health and Medicine, the Australian National University
- National Institute of Hygiene and Epidemiology
- Vietnam National Steering Committee for COVID-19 Prevention and Control
- Bach Mai Hospital
- Community healthcare workers from local 49 CDCs
- Ministry of Health, Ministry of Science and Technology

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Appendix 3. Booklet of conference presentation

Booklet of conference presentation at the Special Edition - Australasian COVID-19 Virtual Conference (virtual conference) on 09 December 2020 (page 41)



Concurrent Session 3C - International epidemiology

On Demand from 10:00am AEDT

Investigating COVID-19 transmission in Vietnam's tertiary hospital using social network analysis

Authors: Ms Ngoc-Anh Hoang^{1,2}, Ms Ha-Linh Quach^{1,2}, Dr Thai Pham², Dr Khanh Nguyen², Dr Florian Vogt¹

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Abstract:

Background: A cluster of 45 COVID-19 cases was identified in a large referral hospital in Hanoi, Vietnam on 18 March 2020, constituting the first SARS-CoV-2 outbreak in a healthcare setting nationwide. We assessed transmission patterns during this outbreak using social network analysis.

Methods: We investigated COVID-19 cases using contact tracing, PCR testing, and movement monitoring through mobile tracking and video surveillance. We conducted network analysis using degree centrality to identify cases with the highest number of connections; betweenness centrality to reveal cases that connect sub-clusters; and closeness centrality to indicate how close a case was to other cases in the network.

Results: A total of 7,200 tests were performed among 1,982 persons at day 0, day 3-4, and day 14 after last exposure to a known case. Overall, 26 (57.8%) ancillary support staff, seven (15.6%) caregivers, five (11.1%) out-patients, two (4.4%) nurses, two in-patients (4.4%), and three (6.7%) secondary cases outside the hospital tested positive. We identified a total of 67 connections between 45 cases. Three cases (a caregiver, an ancillary support staff, and a patient) had the highest score in each social network metric (degree, betweenness, and closeness centrality). The highest degree centrality was detected in one ancillary support staff who was linked to ten (22.2%) other cases. Among the ten most important cases selected by each network metric, transmission dynamics clustered in 15 cases. Among these, nine (60.0%) cases were ancillary support staff, while three (20.0%) were caregivers and three (20%) were patients.

Conclusions: Our analysis revealed the importance of ancillary support staff in transmission dynamics during this outbreak. This study shows the potential of social network analysis techniques to understand SARS-CoV-2 infection patterns in hospitals and similar contexts. All employees of health facilities with high-frequency movements should be monitored regularly for SARS-CoV-2 infection regardless of their profession.

Chapter 4. Evaluate a surveillance system

*Evaluating epidemic preparedness and response to COVID-19:
A nation-wide multi-sectorial Intra-Action Review of the Points of Entry surveillance system
in Vietnam, January to September 2020*

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List of Abbreviations – Chapter 4

COVID-19	Coronavirus 2019
FGDs	Focus Group Discussions
GDPM	the General Department of Preventive Medicine
IAR	Intra-Action Review
MoH	Ministry of Health
NSSC	the national surveillance system for COVID-19
PoEs	Points of Entry
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
WHO	The World Health Organization

Prologue

Background

Intra-Action Review (IAR) is a qualitative tool to conduct an assessment of national responses to the ongoing COVID-19 pandemic (1). It has been approved as a potential tool to assess the performance of systems' preparedness, collect lessons learned, and operational and functional improvement after a period of counteracting this pandemic (2). The World Health Organization (WHO) and European Centre for Disease and Control suggested applying IAR during the COVID-19 pandemic (3,4).

Until 30 August 2020, Vietnam has experienced three months of no community COVID-19 cases. However, the likelihood of COVID-19 reintroducing in the community increased as the country temporally paused some public health measures and gradually resumed international flights for repatriates and technical experts. Many instances of illegal trespassing into the country without sufficient testing or quarantine were another challenge to prevent local transmission. Given the importance of COVID-19 surveillance at Points of Entry (PoEs), it is critical to review and assess the COVID-19 surveillance system at PoEs, in order to capitalize on best practices and identify areas and actions to improve this system for the prolonged pandemic.

My role

The World Health Organization (WHO) issued guidance on After Action Reviews to assist countries with the evaluation of public health responses to disease threats and the generation of lessons learnt for operational improvements of public health response measures after the occurrence of a public health event. Faced with the rapidly evolving COVID-19 pandemic, the WHO published additional IAR guidance in July 2020 based on the existing AAR approach. In contrast to AAR, which focuses on evaluating completed responses to learn lessons for future events, the IAR is designed to inform and guide ongoing response operations and capture lived experiences during the emergency phase. It is therefore considered as a tool to learn lessons and improve public health emergency in real time. This COVID-19-specific IAR method is designated to provide a structure to evaluate the performance of public health systems to COVID-19.

At the time of planning to conduct IAR, Vietnam has experienced three months of being free from COVID-19 cases. However, given the surging and re-surfing of COVID-19 cases in other countries as well as the protracted and unpredicted nature of this pandemic, the Ministry of Health and WHO decided to execute the IAR to evaluate COVID-19 preparedness and response to the PoEs surveillance systems nationwide. The General Department of Preventive

Medicine (GDPM), Ministry of Health was a primary unit to conduct the IAR in Vietnam. My field supervisor involved me in this project, but only from the near end of it. I, unfortunately, did not have a chance to involve in the IAR workshop. My contribution was in compiling and managing qualitative data from the scripts, notes, and presentations in the IAR workshop. I also supported GDPM's officials in preparing presentations for the debriefing after IAR.

Achievement

This chapter consists of one published article (Appendix 2). The article entitled identical name to the Chapter "Evaluating epidemic preparedness and response to COVID-19: A nation-wide multi-sectorial Intra-Action Review of the Points of Entry surveillance system in Vietnam, January to September 2020". It was published in the Asia Pacific Journal of Public Health as short communication in April 2022. The aims of this study are to identify the successes and challenges of the PoE system to provide concrete recommendations to improve COVID-19 surveillance at PoE, both in Vietnam as well as in other countries in the region.

Abstract

Background:

International travel has been contributing significantly to the spread of COVID-19. Points of Entry (PoE) surveillance at national border crossings constitutes a major pillar of many countries' pandemic response but has rarely been evaluated.

Methods:

We conducted an Intra-Action Review (IAR) of Vietnam's PoE surveillance system for COVID-19 for the period January to September 2020, using a nation-wide multi-stakeholder consultation process and focus group discussions during a workshop with 60 participants held in Quang Ninh province, Vietnam in October 2020.

Results:

The National Surveillance System for COVID-19 (NSSC) was operated as an event-based surveillance system covering on four administrative levels. Identified strengths of the NSSC were the effective management of incoming travelers using health declaration forms; the early detection of cases through screening by rapid antigen tests; and effective control of cross-contamination through strict on-site quarantine procedures. However, its effectiveness was considered limited to low and medium case numbers and not be ready to deal with prolonged and intense transmission contexts. Three cross-cutting lessons learnt were identified include the need to improve procurement processes, strengthen emergency planning, and establish clear leadership from early.

Conclusion:

The PoE surveillance system was useful to reduce the introduction of COVID-19 into Vietnam during small and medium incidence contexts despite many challenges in human and financial resources, planning, and management. Our captured lessons learned should be addressed in the internal and external meetings at local and national levels to revise prolonged strategies to respond to the pandemic.

Lesson learned

The IAR brought me a great lesson on writing reports. I had to prepare and balance the reports for the Vietnam WHO, the GDPM, and the Vietnam Ministry of Health. Each report has different purposes for different audiences. For the Ministry of Health, the report's readers are mostly policymakers and multijurisdictional healthcare staff who require short coherent findings and lessons learned from the review. On the other hand, WHO's technical report requires detailed methodology, workshop process, and timeline, leaning more towards project management.

This project also gave me a great opportunity to work with qualitative data. Before, I had very little experience with qualitative data and analyses, and for this project, most if not all data are from focus groups discussion and conferences. In the beginning, I doubted using non-quantitative data can bring out action-packed messages, and the report might be a long essay rather than a subjective assessment. However, this project taught me to work closely with stakeholders, organizing and arranging their stories and reflections in a systematic way to build a complete story of trails and errors in the uncertain time of the epidemic. I finally realized, a good story should come from rigorous methods and coherent explanations, it not only relies on numbers.

Public health impact

The Vietnam COVID-19 IAR followed WHO's guidance (2,3) that aims to identify crucial challenges and make operational improvements to the COVID-19 surveillance system. We targeted for sustained enhancement of the response and preparedness to this prolonged and unpredicted pandemic (1). Our evidence, with more than 30 IAR in other countries, provided a snapshot of the battle of this pandemic (5). At the time of conducting this review, Vietnam experienced three months of clearance of community transmission while other countries suffered the resurgence of COVID-19 cases with new variants. Our sharing might help other

countries to plan a better COVID-19 strategy that mitigates the impact of these interventions on human life and well-being.

Vietnam had applied the whole-of-society approach by mobilizing active involvement of the political system, including multi-ministerial sectors at all levels, communists, and communities in response to this pandemic. Although it was considered an effective strategy, our findings questioned the quality of this cooperation. We shed evidence on the uncoordinated leadership in the border agency cooperation at PoEs. The roles of relevant units in shared activities were unclear, thus leading to conflicts in responsibilities. We also demonstrated the lessons on resource constraints for equipment and health declaration and weak planning for quarantine procedures for people and goods. They should be addressed in the next tactics to prevent the COVID-19 pandemic.

Recommendation

Although the national surveillance system for COVID-19 was useful to reduce the introduction of COVID-19 into Vietnam at PoEs, however, its capacity was limited within small and medium scopes of outbreaks. Prolonged and large outbreaks might challenge this system to respond timely and effectively due to its overburdened and understaffed status. For the next stage, we recommend that policymakers and relevant stakeholders should consider three primary challenges in human and financial resources, planning, and management. Vietnam should prioritize preparing contingency plans and exercising simulation for emergent events, establishing emergency procurement procedures, and building participation guides for shared activities among relevant stakeholders.

Acknowledgement

I would like to thank my academic supervisor, Dr. Florian Vogt for patiently supporting me throughout this project, as well as my field supervisor, Dr. Pham Quang Thai to introduce me to this project. Specially thank Dr. Emma Field from the Research School of Population Health, the Australian National University to help me with qualitative data analyses. I much appreciated officers from the GDPM to guide me with qualitative study and get me involved in several steps of this project. Also my warmest thanks for my husband – Dr. Hoang Van Ngoc from the DGPM to help facilitating the projects and provide the permission for including this in my thesis.

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Appendix 1. Advanced Manuscript

Title: Evaluating epidemic preparedness and response to COVID-19: A nation-wide multi-sectorial Intra-Action Review of the Points of Entry surveillance system in Vietnam, January to September 2020

INTRODUCTION

Vietnam had been vulnerable to the importation of COVID-19 since the start of the pandemic due to the high volume of cross-border trading and travel activities with neighboring countries, in particular with China (1). Points of Entry (PoE) surveillance at border crossings quickly became a cornerstone of the National Surveillance System for COVID-19 (NSSC) in the effort to prevent introduction of COVID-19 into Vietnam. The PoE surveillance comprises a large range of activities such as collection of international traveler information via health declaration forms; detection and quarantine of suspected cases; screening passengers and their property (luggage, goods, vehicles); and management of biosafety of imported and exported biological material. (2).

Evaluating the response of public health systems against COVID-19, such as PoE surveillance systems, is essential (3). The World Health Organization (WHO) issued guidance on After Action Reviews (AAR) in 2018 to assist countries with the evaluation of public health responses to disease threats and the generation of lessons learnt for operational improvements of public health response measures after the occurrence of a public health event (4). Faced with the rapidly evolving COVID-19 pandemic, the WHO published additional Intra Action Review (IAR) guidance in July 2020 based on the existing AAR approach (5). This COVID-19-specific IAR method comprises two core components: (i) reflection on countries' actions undertaken to prepare for and respond to COVID-19; and (ii) propose corrective actions to improve and strengthen continued COVID-19 response (5,6). In contrast to AAR, which focuses on evaluating completed responses to learn lessons for future events, the IAR is designed to inform and guide ongoing response operations and capture lived experiences during the emergency phase. It is therefore considered as a tool to learn lessons and improve public health emergency in real time (7). The IAR methodology is designated to provide a structure to evaluate the performance of public health systems to COVID-19. The WHO guidance for conducting IAR includes four recommended methods: a desk review of existing documents; a structured review of undertaken activities; a conference to share stakeholders' experiences and plans for the medium- and long-term COVID-19 response; and in-depth analysis of selected issues using

root cause analysis methods. WHO guidance also includes a list of adaptable discussion questions to review the public health measures implemented specifically at PoE (5).

Although some countries have used IAR to review their COVID-19 responses (8–10), it has not been used often to evaluate surveillance systems (11,12). PoE surveillance in particular has not been evaluated to date using IAR tool. More generally, evaluations of surveillance systems during the COVID-19 pandemic are scarce, in particular from low-and-middle-income countries, though the importance of these evaluations to improve public health response is widely recognized (13,14).

The General Department of Preventive Medicine (GDPM) of Vietnam's Ministry of Health conducted a multi-stakeholder evaluation of the nation-wide PoE surveillance system during the COVID-19 epidemic that culminated in a workshop in Quang Ninh province on 13-14 October 2020. Using the IAR format of WHO for this evaluation, we aimed to identify successes and challenges of the PoE system to provide concrete recommendations to improve COVID-19 surveillance at PoE, both in Vietnam as well as other countries in the region.

METHODS

The IAR methodology and study design

For this IAR we conducted (i) a desk review of relevant COVID-19 response plans and policy documents at national levels between 31 December 2019 and 30 September 2020; (ii) a structured review of COVID-19 related surveillance activities at PoE between 31 December 2019 and 30 September 2020; and (iii) a stakeholder consultation workshop with 60 participants from 29 different entities/institutions.

Data collection during the workshop

We invited a large range of stakeholders from all levels and agencies in PoE surveillance to a two-day IAR workshop in Quang Ninh province on 13-14 October 2020. The majority were chief-level officers who managed NSSC activities and were experienced in responding to large-scale public health incidents. The IAR workshop was led by an experienced facilitator with qualitative research skills and five moderators for group discussions. Figure 1 shows the different activities related to the workshop implementation.

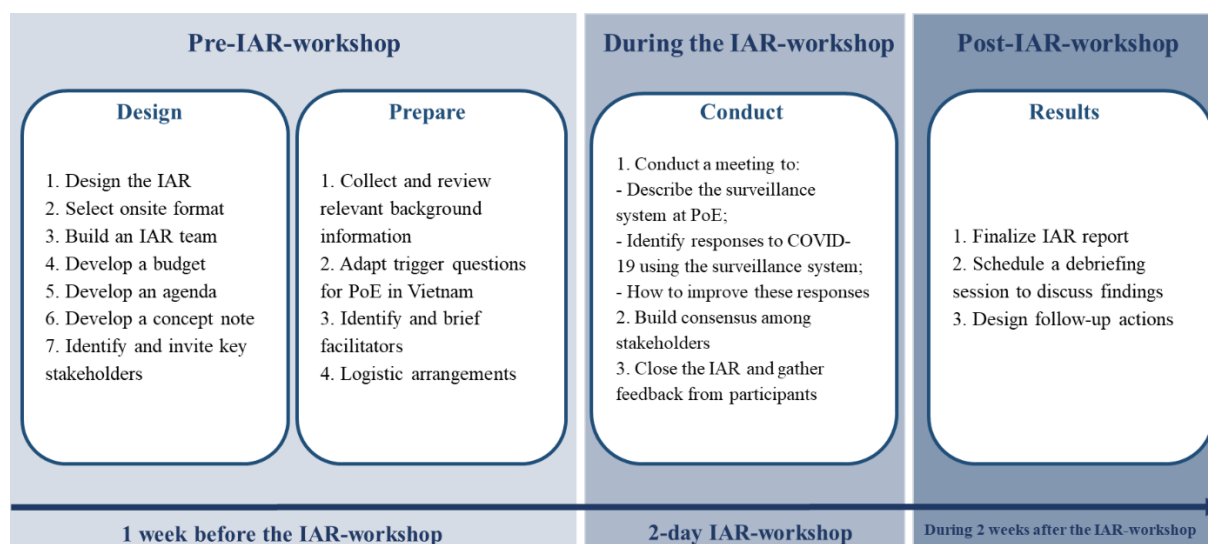


Figure 1. Activities for the Intra-Action Review workshop of the Points of Entry surveillance evaluation

We adapted the WHO question guide for the conduct of learning-oriented focus group discussions (FGD) during the workshop. Participants were divided into five thematic groups for FGDs to elicit their perspectives on strengths, weaknesses, and recommendations of the NSSC at PoE: 1) health declaration; 2) equipment; 3) quarantine procedures for people and goods; 4) border agency cooperation; and 5) laboratory system. It was ensured that each group included representatives from all hierarchical levels of the surveillance system: national levels (Ministry of Health, Ministry of Defense, and Ministry of Security), regional levels (Regional Institutes), provincial levels (Provincial Health Services and provincial CDCs), and field levels (Departments of Check Points, Department of Immigration and Exit, and officials in charge of different types of PoE: seaport, airport, ground crossing, and railway).

Participants in all five groups were first asked to describe the functioning of the NSSC for PoE surveillance from their respective perspectives and then to reflect what happened with the NSSC during the pandemic response at PoE level. Third, participants jointly reflected on improvements to the response strategy (see Table 1). The FGD lasted for about one hour on the first day and about five hours on the second day, after which each group presented their results to the plenary so that participants from other groups could contribute their views and experience under the direction of the facilitator. One note-taker per group independently documented the discussion for each group and shared a draft report with each group's participants to ensure that all views were adequately captured prior to producing a final report per thematic group.

Table 1. Trigger questions for the Vietnam's Intra-Action Review

Trigger questions		
Document existing systems in place	1	What were the existing country's COVID-19 response plans for preventing COVID-19 at PoE?
	2	What were activities undertaken at the national level for preventing COVID-19 at PoE?
	3	When was the surveillance system activated and when it marked as completed?
	4	How the surveillance system screened suspected cases and how to treat these cases?
	5	Describe the systems for transportation of suspected COVID-19 cases to designated medical facilities at PoE?
	6	What kind of bilateral or multilateral agreements with neighbouring countries was in place to prevent the international spread of COVID-19?
Identify and analyse what happened so far during the COVID-19 outbreak response	1	What existing systems were adapted for detecting, testing, isolating and transporting COVID-19 cases at PoE and what new systems were instituted ad-hoc? How well did these work?
	2	Were available plans and guidance materials for the COVID-19 response at PoE previously available or developed ad-hoc? Were they available at all PoE? How effectively were they used?
	3	How are infection prevention and control measures being implemented at PoE during the COVID-19 outbreak?
	4	What types of screening measures were put in place at PoE?
	5	How was the coordination of information exchange between conveyance operators, PoE authorities, and public health authorities during the COVID-19 response?
	6	What types of training and personal protective equipment did the rapid response team have at PoE? How were these training done?
	7	How was COVID-19 information provided to travellers (e.g., information broadcasting on board, information leaflet, posters in PoE)?
	8	What policies or measures have been put in place during the COVID-19 response for disadvantaged subpopulations? (e.g., people with disabilities, persons with low socioeconomic status, ethnic minorities, rural poor, migrants and others experiencing exclusion and discrimination)?
	9	Given the protracted nature of the COVID-19 outbreak, how were PoE able to consider the (potential of) concurrent emergencies during the pandemic in their policies, plans and measures put in place?
Improve existing COVID-19 outbreak	1	What actions taken enabled an efficient and timely detection of suspected COVID-19 cases at PoE?
	2	What new technologies or innovations were implemented to efficiently detect suspected COVID-19 cases at PoE and follow up on passengers in

response strategy		case a fellow passenger later tested positive for COVID-19 on their conveyance?
	3	What challenges were encountered in implementing public health measures and detecting COVID-19 at PoE?
	4	What actions were taken at PoE during the COVID-19 outbreak that allowed for a better than expected performance of the overall COVID-19 response?
	5	What were the overall strengths and weaknesses of public health activities conducted at PoE for COVID-19 response?

Data management and analysis

All transcripts were translated from Vietnamese to English, and proofread by a professional translator. Transcripts were anonymized by removing any names or other individually identifying references. We then conducted a conceptual content analysis of the final report from each thematic group (15). We developed three main themes (strengths, weakness, and recommendation) and five components for each (health declaration, equipment, quarantine procedures for people and goods, border agency cooperation, and laboratory). Two authors (NVH and NAH) independently coded two transcripts with the level of analyses being sentence for cross-validation. After discrepancies were discussed and adjustments made, author NAH completed the coding for all remaining transcripts. All the coding was done by hand.

Ethics statements

Ethics review of this research was waived by the General Department of Preventive Medicine of the Vietnam Ministry of Health as a part of routinely collected data to improve public health response. This study was also waived for ethics review by the Australian National University Human Research Ethics Committee under the waiver number HREC/17/ANU/909.

RESULTS

The public health importance of controlling COVID-19 at PoE, and the public health control strategy

Vietnam was among the first countries to be affected by the SARS-CoV-2 virus. This pandemic had months long changes to people's life and well-being. The public health measures are undertaken at PoE were significant components of Vietnam's strategy to prevent COVID-19. These places were where arriving passengers first approach COVID-19 information, i.e., how to manage the disease and what measures should be expected on arrival. Such measures at PoE included temperature screening, quarantine (if passengers have been exposed to

infectious sources or unwell), and sterilizing infected areas. Effective measurements at PoE might contribute to slow community spread, thus give health systems additional time to plan and prepare for increased demand for health care services.

Vietnam administered contextualized critical public health measures to prevent COVID-19 transmission at PoE including strengthening the surveillance system, establishing rapid response teams, monitoring all arriving passengers, strengthening infection prevention and control strategies, and applying mandatory health declaration. Three key authorities were involved in the COVID-19 prevention at PoE including health officers, immigration officers (airports), soldiers (land crossing points or borders). All were trained on infection prevention and control.

The COVID-19 prevention at PoE involved a range of government agencies and other stakeholders with functional responsibilities. From the very early of the pandemic, Vietnam Government indicated strong leadership in COVID-19 response by establishing the National Steering Committee for COVID-19 Prevention and Control - a multi-ministerial and multisectoral committee with the involvement of representatives from 63 provinces and 707 districts. The committee directed pandemic control and assessment on behalf of the government. The presence of key stakeholders and parties in the committee enabled it to make crucial decisions and systemically coordinated the implementation of containment measures. The arrangement of interagency coordination was placed to understand each other's roles.

The Government also applied the whole-of-society approach that engaging and mobilizing many stakeholders including civil society, academia, communities, etc. to prevent COVID-19 at PoE. Effective risk communication was crucial to help people understand the current situation and contribute to disease prevention. This required the provision of accurate information early and through channels and languages that people trust and understand.

The COVID-19 surveillance system at Points of Entry

Case definitions

The COVID-19 surveillance system used case definitions from the Vietnam's Ministry of Health guidelines. A confirmed case of COVID-19 is defined as any person with laboratory-confirmed SARS-CoV-2 by reverse transcription polymerase chain reaction (rt-PCR).

Primary case of COVID-19 is defined as the person who first identifies positive with SARS-CoV-2, and later successfully infected other people among their contacts. Secondary case of COVID-19 is a confirmed case who are initially close contacts with the primary case.

A close contact was defined as a person having had direct contact (≤ 2 -meter distance and ≥ 15 minutes) with a COVID-19 confirmed case. In Vietnam, if the confirmed case had a

travel history within 14 days from date of symptom onset or date of confirmation, whichever came first, all passengers on the same vehicles were categorized as close contacts. All close contacts were tested for SARS-CoV-2 infection.

The objectives of the system

The national surveillance system for COVID-19 at PoE was based on the international border surveillance system which is developed by the GDPM in 2015. The former system activated when passengers registered to arrive in Vietnam and completed by marking “Safe to Entry” or “Require testing before Entry” in the health declaration forms.

The NSSC used event-based surveillance for the detection of suspected COVID-19 cases that are implemented at four administrative levels: national, regional, provincial, and field levels. Its goal is to early detect COVID-19 suspected cases from a wide variety of sources, such as reports, stories, or rumors.

The system’s components and operation

Vietnam has 131 PoE, of which are: 10 international airports, 70 seaports, 48 ground crossings, and three railways. The NSSC at PoE is based on the international border surveillance system, which was developed by the GDPM in 2015.¹⁶ The NSSC uses event-based surveillance for the detection suspected COVID-19 cases that is implemented at four administrative levels: national, regional, provincial, and field levels. The system is under the leadership of the GDPM. PoE are managed by 13 quarantine stations and 34 provincial Centers for Disease Control and Prevention (CDCs), who report to four regional institutes and 47 provincial health services (Figure 2).

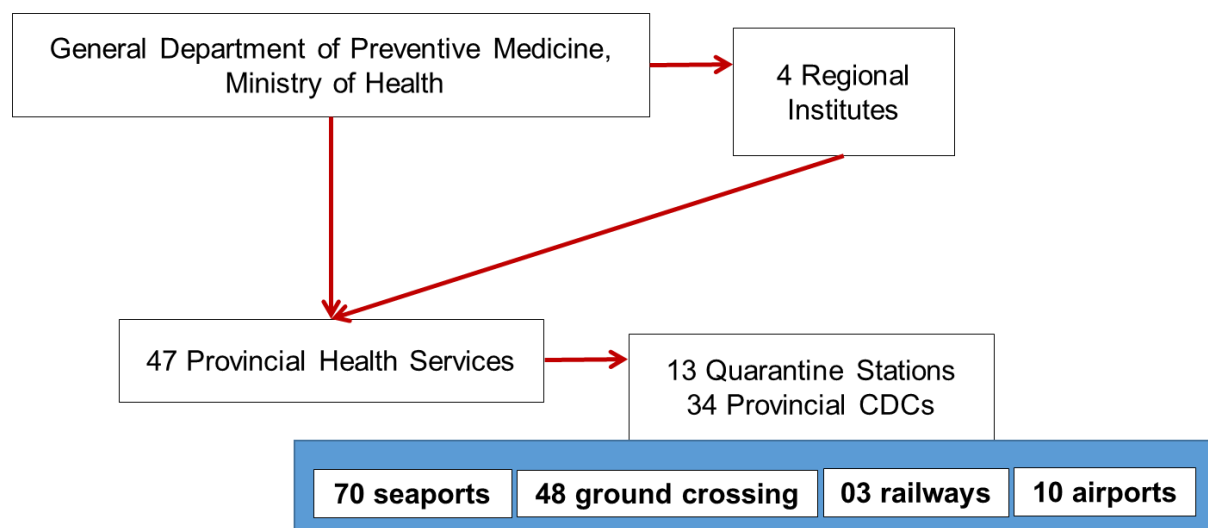


Figure 2. The hierarchy of multiple administrative levels systems for the National Surveillance System for COVID-19 at Points of Entry in Vietnam

The system was activated each time a passenger registered to travel into Vietnam and was completed once that person was transported to quarantine places or designated hospitals. Prior to arrival to Vietnam, all passengers were required to complete an online health declaration form. Managers of vehicles had to complete information on the overall health status of all passengers and the description of vehicles and goods. The health declaration form was designed specifically for COVID-19 and translated into 11 languages. Other forms to capture information of passengers, vehicles and goods were based on documents developed by the MoH in June 2018.² If a passenger could not access the online form, they were provided with a paper version from cabin crew or quarantine officers at PoE. While the online data were directly linked to the COVID-19 surveillance system, paper-based forms had to be entered manually by quarantine officers.

At arrival, the passengers' temperature was screened using forehead thermometers or thermal cameras. Quarantine officers also visually screened passengers for obvious signs and symptoms of respiratory infection. Passengers who self-reported COVID-19 compatible symptoms were transported immediately to individual quarantine rooms for a rapid antigen test (RAT). All asymptomatic travelers were separated by place of departure at PoE for RAT. A negative RAT results were followed up with a nasopharyngeal swab sample for rt-PCR testing for all passengers, and all passengers were immediately transported to a designated quarantine place for a 14-day irrespective of their results. If RAT was positive, they were sent to isolation rooms, where a 14-day travel history, health examination, and a specimen for rt-PCR testing was taken before being transported to designated hospitals. The travel history and contact information from the health declaration form of these passengers were sent to the Rapid Response Team, the National Steering Committee of COVID-19 Prevention and Control, and the provincial CDCs for contact tracing and case finding. Their belongings and vehicles were sterilized (Figure 3).

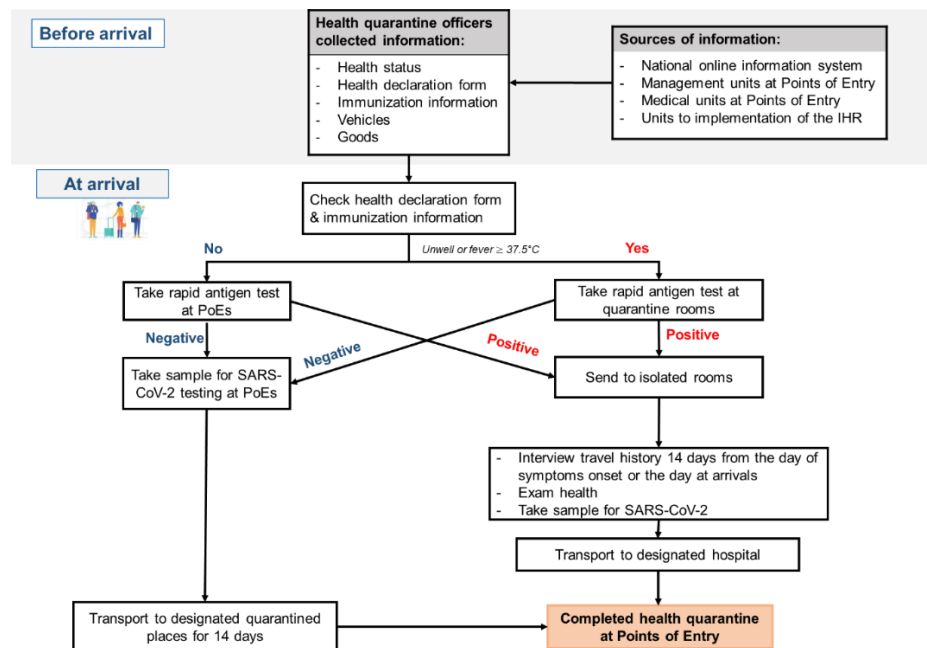


Figure 3. Flow chart of the procedures for arriving passengers at Points of Entry
Travel restrictions between December 2019 and September 2020

On the same day as the first COVID-19 cases were reported from Wuhan, China on 31 December 2019, Vietnam limited travel to and from Wuhan. These travel restrictions were applied to South Korea on 09 February, and expanded to the United Kingdom and 26 Schengen countries, the United States, Southeast Asian countries, and Russia in March. These restrictions were extended to all countries globally on 21 March; all borders (seaports, ground crossing, railways, and airports) were closed. All international flights as well as domestic flights were halted on 28 March. These measures remained in place during April and May 2020 until gradually being lifted towards end of May, when domestic flights resumed under strict hygiene measures like mask wearing, social distancing, and hand hygiene at airports and onboard. After three months without local cases, on 30 June 2020 the Vietnamese Government resumed providing visas for diplomats and technical experts, and repatriated Vietnamese nationals back into the country. Limited international flights for these people were resumed if they provided a negative polymerase chain reaction (PCR) test within the past three working days of the scheduled departure, and with a mandatory 14-day quarantine at designated facilities upon arrival.

Due to a resurgence of cases, all international flights were again halted in August 2020 before a controlled resumption of international flights was initiated on 23 September 2020 (see Figure 4).

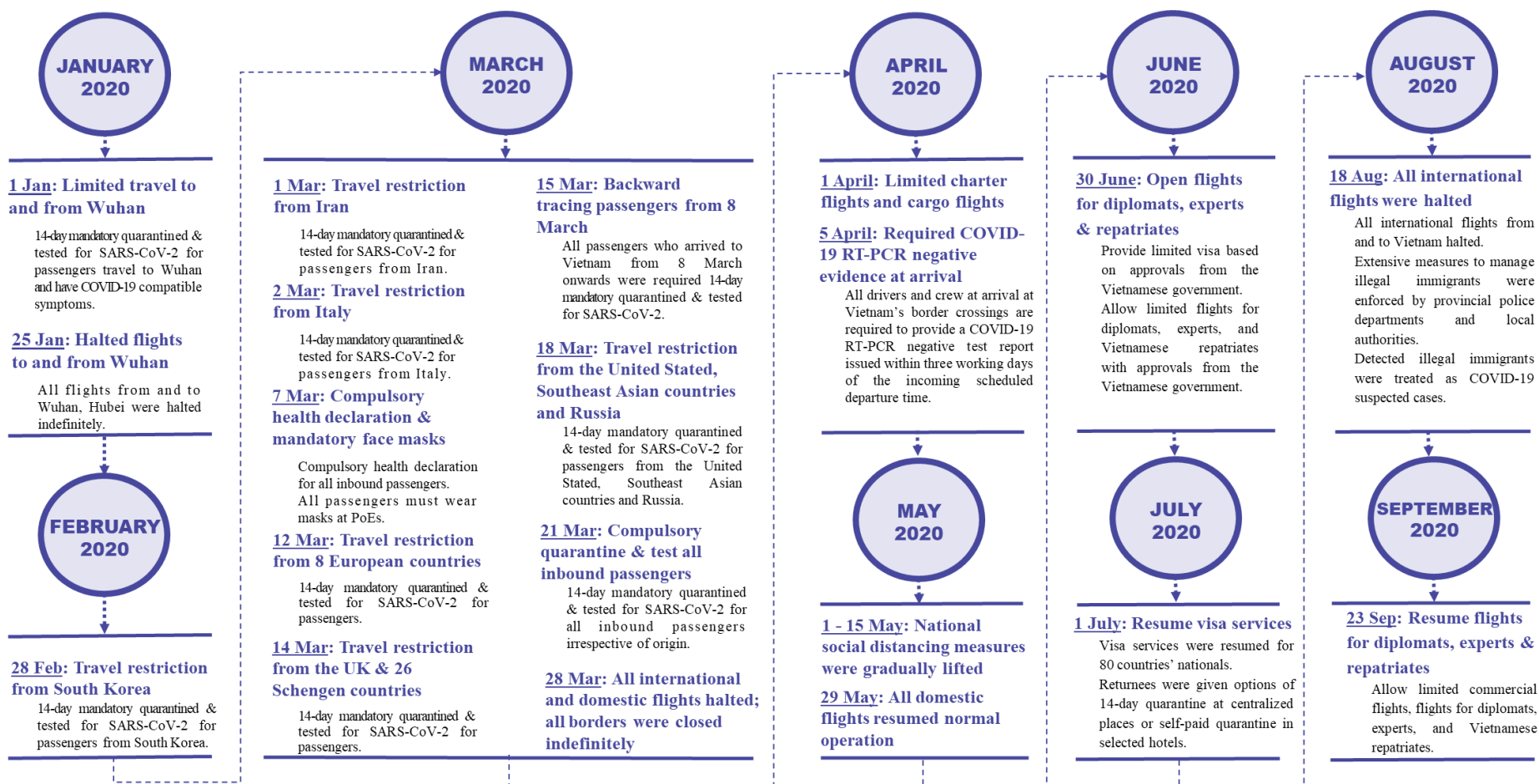


Figure 4. Timeline of public health measures implemented at Points of Entry from 31 December 2019 to 30 September 2020

Identified strengths of the NSSC at PoE

The overall consensus among workshop participants was that the implementation of the NSSC worked well and was effective at PoE. The system was considered well-adapted and flexible to the unpredictable nature of the COVID-19 situation.

Identified strengths of the NSSC at PoE level were the effective management of incoming passengers using health declaration forms, the early detection of cases through screening by RAT, and effective reduction of cross-contamination through strict on-site quarantine procedure. According to most participants, the health declaration form was issued to PoE quickly after the start of the COVID-19, regularly updated, and available in sufficient languages. The online version was considered convenient by quarantine officers, though feedback from passengers was not gathered. For tracing of passengers arriving on flights with confirmed COVID-19 cases, contact information could be extracted quickly from the NSSC thanks to the information collected via the health declaration form. Most workshop attendants considered a valuable strength of the NSSC that it was equipped with MoH's instructions for quarantine procedures. Effective triaging saved time for both officers and passengers, thereby reducing the likelihood of cross-contamination at PoE. Also, PoE had sufficient forehead thermometers and RAT, which helped to detect cases early. Although lacking on-site laboratory systems at PoE, the testing capacity was considered sufficiently high thanks to a strong cooperation with established laboratories in the same region. The turnaround time of the laboratories involved was considered sufficiently quick to ensure smooth on-site operations. The NSSC was also connected to the national COVID-19 responding focal points, thus any alert triggered by PoE notified all relevant agencies.

Identified weaknesses of the NSSC at PoE

While workshop participants were confident that the system was adequate to detect and manage small and medium-size COVID-19 case numbers and local outbreaks, its potential capacity to cope with prolonged time periods with high numbers of confirmed cases was questioned as it might have left the whole system overburdened and under-staffed.

Health declaration

After the MoH issued mandatory health declarations for all inbound passengers, several PoE with high passenger volume encountered a shortage of paper forms. Also, human resources were lacking at times to guide passengers in completing the form. Although the online version, which was launched on 07 March 2020, circumvented printing limitations in theory, PoE lacked internet-connected devices to assist passengers who had difficulties completing the online form themselves, especially the elderly, illiterate, disabled, and people without

smartphones. Accessing the online form sometimes failed or was slow due to overburdened servers, especially at the end of the day after a large number of records had been entered. Also, no automated mechanism existed to flag logical errors or incompleteness of data in submitted online forms.

Equipment

Another limitation of the NSSC at PoE was resource constraints for equipment. Only five PoE (38.5%) were equipped with thermal-imaging cameras while most used forehead thermometers, which required more human resources to operate. A few PoE lacked kits for taking and preserving SARS-CoV-2 samples, while others had enough kits but lacked staff for sample taking. Many PoE had insufficient materials to disinfect surfaces, and some quarantine rooms for suspected cases were poorly set up i.e., were not equipped with first aid kits.

Quarantine procedures for people and goods

Although the instructions were available, workshop participants reported weaknesses for almost all PoE in planning quarantine procedures for people and goods due to a shortage of human resources and insufficient preparation time. For example, due to insufficient space and shortages in equipment, most PoE could not arrange rooms that ensured the minimum distance (2 meters) between asymptomatic passengers while taking test samples. This weakness also highlighted limited and inconsistent communication between the crew and ground officers in case of delays or short-term changes of circumstances, leading to knock-on effects on queuing times of goods and people awaiting clearance.

Border agency cooperation

Inter-sectoral and multilateral meetings were not conducted regularly. No centralized system for sharing information was available, and individual responsibilities in shared activities were not always clearly defined, which sometimes lead to conflicting actions. Health officials and public security overlapped in triaging procedures in sometimes uncooperative ways and within isolated command structures. Furthermore, messages in health communication were sometimes misleading and conflicting between health officials and health communication specialists.

Laboratory

No standard laboratory was established at PoE because it requires an expensive investment in machinery, processes, and human resources for biosafety while other standard laboratories (CDCs and the local Institute of Hygiene and Epidemiology) were sufficiently close to PoE. Although the laboratories were mostly located within a short distance of PoEs,

this might have delayed diagnosis of a large volume of samples due transportation time and exchange of information among sites.

Recommendations

Recommendations derived from this analysis by thematic group are summarized in Table 2.

Table 2. Summary of recommendations

Contents	Recommendations
Health declaration	• PoE actively mobilize internet-connected devices and human resources to assist passengers. • MoH should issue guidance for supporting people who cannot complete the form themselves, including the elderly, disabled people, people without internet devices, illiterate people without guardians.
Equipment	• The PoE prepare contingency plans and assess their resources monthly (or even weekly). • The PoE conduct simulation exercises with a situation of lacking equipment for COVID-19 prevention. • MoH should issue national adaptable emergency procurement procedures that contain a list of stable equipment distributors as well as regulations on stockpiling equipment and stabilizing prices for materials.
Quarantine procedures for people and goods	• PoE develop contingency plans and simulation exercises in case of large COVID-19 outbreaks occurred. • The SARS-CoV-2 samples should be taken at quarantine places or at PoE with qualified rooms which endured safe distance among passengers. • PoE build a mechanism for communication between the crew and ground officers. • MoH should issue instructions on sterilized areas to avoid wasting human resources and chemicals.
Border agency cooperation	The Government should issue regulations to define the responsibilities of relevant agencies for COVID-19 shared activities at PoE.
The laboratory system	PoE should invest in taking, preserving, and transporting SARS-CoV-2 samples; and cooperating with local standard

laboratories to save human and financial resources while ensuring the timely SARS-CoV-2 testing process.

DISCUSSION

This Intra-Action Review was a collaboration between the GDPM, MoH and WHO to identify key strengths and weaknesses of the COVID-19 surveillance system at PoE. Our assessment highlighted important factors for success and challenges alike across the five assessed themes of the NSSC system at PoE in Vietnam: health declaration, equipment, quarantine procedures for people and goods, border agency cooperation, and the laboratory system.

The COVID-19 IAR was considered as a potential for a sustained response plan (2,3). This review was designated as a country-led process that looks back past response actions to identify crucial gaps and optimize strategy going forward that targeted for sustained improvement of the COVID-19 response (1). Focusing on specific elements of the COVID-19 response, the IAR methodology was designated to provide an ad hoc structure to evaluate the performance of the COVID-19 surveillance system at Points of Entry. WHO guidance for conducting IAR with four recommended methods, including a desk review of existing documents; a structured review of undertaken activities; a conference to share stakeholders' experiences and plan to COVID-19 response in the mid- or long-term; and in-depth analysis using root cause analysis methodology. WHO also published 23 adaptable discussion questions to review the functioning public health measures implemented at PoE (1).

In Vietnam's IAR, we adapted the WHO guidance for our context by using three of the first abovementioned recommended methods (a desk review, a structured review, a conference) and 20 triggered questions for learning-focused discussions during the conference. Our findings highlight the blockage in the system that would be overlooked during operation and provide practical steps to overcome current challenges. The GDPM and WHO scheduled a debriefing session to discuss findings from this review and design follow-up action (14). The findings were disseminated to all PoE in Vietnam, to provide a reflection of the system after nine months of operation. We expect that these findings will provide strategic and operational planning to enhance the surveillance system at PoE, thus contribute to strengthening the country's emergency preparedness and response capacity. Also, with more than 30 IAR in other countries that have already completed so far, ours is a puzzle of the IAR's global picture (5). At the time of conducting IAR, Vietnam was experienced three months of non-infection while others were starting to see a resurgence of cases again. Sharing our experiences and actions

might help other countries in similar settings to build a better COVID-19 preventive and control strategy. Given the protracted and unpredictable nature of the COVID-19 pandemic, we recommend that all countries should consider assessing the surveillance system at PoE periodically during the event.

The usefulness of the system by indicating actions

Overall, the system was found to be helpful to prevent the introduction of SARS-CoV-2 at PoE. It is estimated that it contributed to the detection of more than half of all COVID-19 cases recorded in Vietnam until September 2020 (17) and thus greatly helped to achieve three months without community transmission in Vietnam between April and July 2020 (18).

The IAR highlights factors that have allowed Vietnam to successfully control COVID-19 at PoE: the effective management of incoming passengers using health declaration forms, the early detection of cases through screening by RAT, and effective reduction of cross-contamination through strict on-site quarantine procedure.

Despite lacking laboratory for SARS-CoV-2 testing, the PoE still ensured testing capacity through the strong cooperation with the standard laboratory system in the province. Instead of investing large resources for standard laboratories, they focused on quick and safe sample transportation to these labs. The COVID-19 surveillance system is interconnected to the national COVID-19 responding focal points managed by the National Steering of COVID-19 Prevention and Control. Any alert would trigger quick responses from the healthcare system, local authorities, multiple jurisdictions, and the community.

However, its effectiveness was considered limited to low and medium case numbers and not to be ready to deal with prolonged and intense transmission contexts. In the case of Vietnam, the identification of weaknesses within the five reviewed thematic areas resulted in three cross-cutting lessons learnt:

Procurement processes need to be improved

Our review found the large-scale, rapidly changing nature and long duration of the COVID-19 pandemic to be the fundamental challenge for resources and consumables. While some materials for health declarations were pre-deployed, their quantity turned out to be inadequate to meet the actual needs at PoE as the pandemic continued and grew in size. The same shortages occurred for equipment for quarantine procedures such as thermal imaging cameras, kits for taking and preserving SARS-CoV-2 samples, automatic disinfection systems, and isolation rooms. The current acquisition systems in Vietnam are not designed to obtain large amounts of supplies rapidly. These constraints were caused by an uneven capacity and flexibility of emergency requisition and purchasing procedures. Bid laws and ordering

processes were cumbersome and required lengthy multi-level approval processes. The COVID-19 pandemic provides an invaluable lesson for Vietnam to make resource acquisition and management a major function of infectious disease management.

Emergency planning needs to be strengthened

Gaps in emergency planning at PoE level caused serious problems when the COVID-19 pandemic grew in scale, which led to gaps in certain areas such as shortage of human resources to triage passengers timely, poor preparations to take samples, and inconsistent communication between incoming vehicles and ground officers. All respondents agreed that the most fundamental reason was poor implementation of agreed emergency plans across agencies and jurisdictions. While agencies may be involved during the planning process, no requirement is placed to fully enact these plans for them. Better planning as well as better implementation of emergent plans were considered as a key preparation for the ongoing and future pandemics.

Clear leadership needs to be established early

The absence of an overarching command structure across all stakeholders can lead to duplicative and conflicting efforts (3). In Vietnam, coherent joint commands failed to emerge because of unstable cooperation and poor understanding of a unified command structure across agencies involved in the surveillance implementation. Two main reasons were identified: first, agreed plans and incentive to coordinate with each other were not always followed through. Different agencies were often unaware of what others were doing which resulted in gaps and overlap. Second, there was no mechanisms to solve conflicts over resource allocation between agencies. Our respondents recommended that regulations should be issued to define the roles and responsibilities of relevant agencies for shared COVID-19-related activities at PoE.

Limitations

We acknowledge several limitations of this study. First, we did not examine prospective elements to sustain response measures at PoE, which might have provided useful insights into the country's response capacity for future pandemics. Second, we did not conduct a root-cause analysis as part of this review, which might have allowed us to identify more systemic causes of flaws in the PoE surveillance system. Third, we could not audio-record group discussions at the workshop. Though one dedicated note taker per group was responsible for taking notes and participants reviewed the draft report for content, some information might have been missed due to the lively nature of the FGDs. Fourth, some critical attributes of the surveillance system (such as timeliness, acceptability of data quality, sensitivity, representativeness, and stability) were not assessed in this study. The evaluation also did not assess the data quality of the input

and output of the system due to data inaccessibility. Although many stakeholders voted the system was highly effective in small and medium scopes of the outbreak, actual reports and data extraction were not double-checked to evaluate its quality in representativeness and timeliness to adapt to the pandemic. We highlight the need for additional comprehensive evaluations, such as an evaluation that follows the US CDC Guidelines, to assess all critical attributes of a surveillance system as well as assess the quality of data, and the speediness of commands/dispatches across administrative levels.

CONCLUSIONS

The COVID-19 surveillance system was found to be effective to detect COVID-19 suspected cases at PoE, though only for small and medium case numbers. A prolonged and large outbreak may easily overburden the system. Three cross-cutting lessons learnt were identified include the need to improve procurement processes, strengthen emergency planning, and establish clear leadership early. The Government and jurisdictions should consider our findings to address these gaps in the response to the prolonged pandemic. Given the protracted and unpredictable nature of the COVID-19 pandemic, we recommend that all countries should consider assessing their surveillance system at PoE periodically during the event.

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Appendix 2. Journal Article

Hoang, N. V.^{*}, **Hoang, N. A.^{*}**, Pham Quang, T., Quach, H. L., Nguyen, K. C., Vu, L. N.,
Hoang, D. M., Field, E., & Vogt, F. (2022). **Evaluating Epidemic Preparedness and
Response to COVID-19: A Nation-Wide Multisectorial Intra-Action Review of the
Points of Entry Surveillance System in Vietnam, January to September 2020.** *Asia-
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^{*} Shared first authorship

Short Communication

Evaluating Epidemic Preparedness and Response to COVID-19: A Nation-Wide Multisectorial Intra-Action Review of the Points of Entry Surveillance System in Vietnam, January to September 2020

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and Florian Vogt, PhD^{2,4}

Introduction

Points of Entry (PoE) surveillance at internal borders is a cornerstone of the National Surveillance System for COVID-19 (NSSC) in Vietnam.¹ Recognizing the importance of evaluating surveillance systems during the COVID-19 pandemic, the World Health Organization (WHO) published Intra-Action Review (IAR) guidance in July 2020 to inform the real-time evaluations of public health response operations. This COVID-19-specific IAR method aimed to (1) take stock of countries' measures to prepare for and respond to COVID-19, and (2) propose corrective actions to improve and strengthen ongoing COVID-19 response.²

Only few countries have undertaken real-time evaluations of their COVID-19 responses³ and PoE surveillance in particular has not been evaluated during the COVID-19 pandemic. None has ever used the new COVID-specific IAR method from WHO to evaluate their surveillance systems. More generally, methodologically robust evaluations of surveillance systems are scarce, especially from low- and middle-income countries, despite their importance to improve public health response being widely recognized.⁴

In October 2020, the General Department of Preventive Medicine (GDPM) of Vietnam's Ministry of Health conducted a multistakeholder IAR evaluation of its nationwide PoE surveillance system during the beginning of the COVID-19 pandemic. Following the WHO IAR format for this evaluation, we aimed to identify successes and challenges of the PoE system to provide concrete recommendations to improve COVID-19 surveillance at PoE level, both in Vietnam and in other countries in the region.

Methods

We used the WHO IAR approach to conduct focus group discussions (FGDs) during a 2-day workshop in Quang

Ninh province, Vietnam, in October 13–14, 2020, with 60 stakeholders from 29 agencies involved in PoE surveillance nationwide. Participants were divided into five thematic FGDs to elicit their perspectives on strengths, weaknesses, and recommendations of the NSSC at PoE on the following topics: (1) health declaration procedures; (2) equipment; (3) quarantine procedures for people and goods; (4) inter-agency cooperation; and (5) laboratory systems. Participants were first asked to describe the functioning of the NSSC and then to reflect about its performance regarding the PoE surveillance component. Third, participants discussed about improvements of the response strategy; see Online Annex 1 for the detailed question guide. Figure 1 shows the different IAR-related activities by the research team during the workshop.

Results

Vietnam has 131 PoEs, of which are 10 international airports, 70 seaports, 48 road crossings, and three railway crossings (see Online Annex 2). The NSSC was activated

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Evaluating epidemic preparedness and response to COVID-19: A nation-wide multi-sectorial Intra-Action Review of the Points of Entry surveillance system in Vietnam, January to September 2020

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Manuscript Type:	R4L-Short Communication
Keywords:	COVID-19, Intra-Action Review, Points of Entry, Surveillance, Evaluation < EDUCATION (Public Health), Vietnam
Abstract:	Border surveillance for COVID-19 is important but has rarely been evaluated. We conducted an assessment of Vietnam's 'Points of Entry' surveillance system for COVID-19 from January to September 2020, using the Intra-Action Review (IAR) methodology developed by the World Health Organization. The National Surveillance System for COVID-19 (NSSC) operated as an event-based surveillance system across four administrative levels. Identified strengths were the effective management of incoming travelers using health declaration forms; the early detection of cases through screening by rapid antigen tests; and effective reduction of cross-contamination through strict on-site quarantine procedures. However, its effectiveness was limited to settings with low and medium case numbers, and it was not considered ready for prolonged and high-incidence transmission contexts. Lessons learnt include the need to improve procurement processes; to strengthen emergency planning; and establish clear leadership early on. Reviewing public health measures during ongoing incidences is important to ensure quality and adaptability.

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ABSTRACT

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Keywords: COVID-19, Intra-Action Review, Points of Entry, Surveillance, Evaluation, Vietnam

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METHODS

We used the WHO IAR approach to conduct focus group discussions (FGD) during a two-day workshop in Quang Ninh province, Vietnam in 13-14 October 2020, with 60 stakeholders from 29 agencies involved in PoE surveillance nationwide. Participants were divided into five thematic FGDs to elicit their perspectives on strengths, weaknesses, and recommendations of the NSSC at PoE on the following topics: i) health declaration procedures; ii) equipment; iii) quarantine procedures for people and goods; iv) inter-agency cooperation; and v) laboratory systems. Participants were first asked to describe the functioning of the NSSC and then to reflect about its performance regarding the PoE surveillance component. Third, participants discussed about improvements of the response strategy; see Annex 1 for the detailed question guide. Figure 1 shows the different IAR-related activities by the research team during the workshop.

Figure 1 here

RESULTS

Vietnam has 131 PoEs, of which are: 10 international airports, 70 seaports, 48 road crossings, and three railway crossings (see Annex 2). The NSSC was activated each time a passenger registered to travel into Vietnam and was completed once that person was transported to a designated quarantine location or hospital (see Annex 3 for detailed arrival procedures and flowchart). The consensus overall among workshop participants was that the NSSC worked well and was effective at PoE level. The system was considered fit for purpose and able to adapt quickly to the rapidly evolving COVID-19 situation. While most participants were confident that the system was adequate to detect and manage low and medium-level case numbers and associated local outbreaks, its capacity to cope with high incidence over

prolonged time periods was questioned since this might have left the whole system overburdened and under-staffed (see Annex 4 for detailed results from FGDs).

DISCUSSION

This was the first IAR using the COVID-specific approach of WHO to evaluate a national surveillance system during the COVID-19 pandemic. Identified weaknesses of the PoE surveillance system in Vietnam across five reviewed thematic areas resulted in three lessons learnt:

Procurement processes need to be improved

The rapidly changing nature and long duration of the COVID-19 pandemic was the fundamental challenge for resources and consumables. While some materials for health declarations were pre-deployed, their quantities turned out to be inadequate to meet the actual needs at PoE levels as the pandemic continued. The same shortages occurred for equipment for quarantine procedures such as thermal imaging cameras, kits for taking and preserving swab samples, automatic disinfection systems, and isolation rooms. The current acquisition systems in Vietnam are not designed to obtain large amounts of supplies rapidly. These constraints were caused by insufficient capacity and flexibility of emergency requisition and purchasing procedures. Bidding laws and ordering processes were cumbersome and required lengthy multi-level approval processes.

Emergency planning needs to be strengthened

Shortfalls in emergency planning at PoE level caused serious problems once the COVID-19 pandemic grew in scale, which led to gaps in human resources to triage passengers timely, poor preparations to take samples, and inconsistent communication between incoming vehicles and ground officers. All respondents agreed that the most fundamental reason was poor implementation of existing emergency plans across agencies and jurisdictions. While most agencies were involved in the planning, no requirement existed to fully enact these plans for them. Better planning as well as better implementation of emergency plans are key for ongoing and future pandemics.

Clear leadership needs to be established early

A coherent joint commands failed to emerge because of ad-hoc cooperation and limited communication across agencies involved in the surveillance implementation. The absence of an overarching command structure across all stakeholders sometimes led to duplicative and conflicting response efforts. Two main reasons were identified: first, agreed plans and incentives to coordinate with each other were not always followed through. Second, there was

no mechanisms to solve conflicts over resource allocation between agencies. Respondents recommended that regulations should be issued to specify the roles and responsibilities of relevant agencies for shared COVID-19-related activities at PoE level.

CONCLUSIONS

The COVID-19 surveillance system at PoE level in Vietnam was found to be effective overall to prevent large-scale case importation during 2020. However, prolonged high incidence may have easily overburdened the system. Lessons learnt were the need to improve procurement processes, to strengthen emergency planning, and to establish clear leadership early. Given the protracted and volatile nature of the COVID-19 pandemic, we recommend that all countries should consider assessing their surveillance system at PoE level periodically using adequate methods such as the WHO IAR tool.

FUNDING

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ETHICAL CONSIDERATION

Ethics review of this research was waived by the General Department of Preventive Medicine of the Vietnam Ministry of Health as a part of routinely collected data to improve public health response. This study was also waived for ethics review by the Australian National University Human Research Ethics Committee under the waiver number HREC/17/ANU/909.

DECLARATION OF CONFLICTING INTERESTS

The Authors declare that there is no conflict of interest

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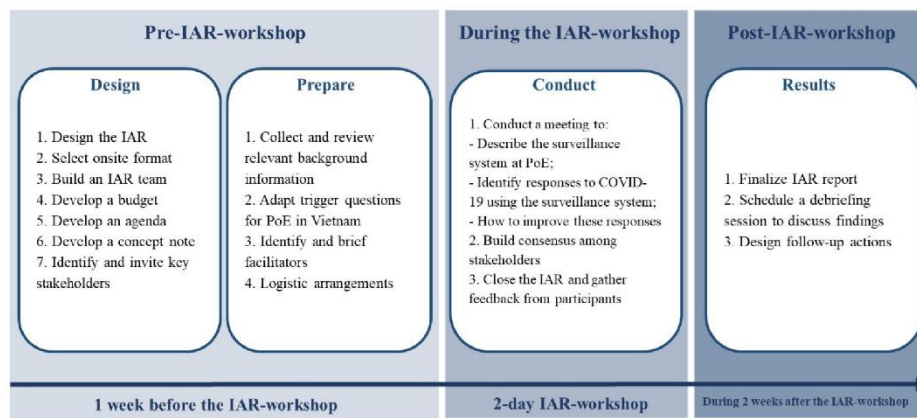


Figure 1. The implementation of the Intra-Action Review workshop in Quang Ninh province, 13-14 October 2020, for the Points of Entry surveillance evaluation in Vietnam

Evaluating epidemic preparedness and response to COVID-19: A nation-wide multi-sectorial Intra-Action Review of the Points of Entry surveillance system in Vietnam, January to September 2020

ABSTRACT

Border surveillance for COVID-19 is important but has rarely been evaluated. We conducted an assessment of Vietnam's 'Points of Entry' surveillance system for COVID-19 from January to September 2020, using the Intra-Action Review (IAR) methodology developed by the World Health Organization. The National Surveillance System for COVID-19 (NSSC) operated as an event-based surveillance system across four administrative levels. Identified strengths were the effective management of incoming travelers using health declaration forms; the early detection of cases through screening by rapid antigen tests; and effective reduction of cross-contamination through strict on-site quarantine procedures. However, its effectiveness was limited to settings with low and medium case numbers, and it was not considered ready for prolonged and high-incidence transmission contexts. Lessons learnt include the need to improve procurement processes; to strengthen emergency planning; and establish clear leadership early on. Reviewing public health measures during ongoing incidences is important to ensure quality and adaptability.

Keywords: COVID-19, Intra-Action Review, Points of Entry, Surveillance, Evaluation, Vietnam

INTRODUCTION

Points of Entry (PoE) surveillance at internal borders is a cornerstone of the National Surveillance System for COVID-19 (NSSC) in Vietnam.¹ Recognizing the importance of evaluating surveillance systems during the COVID-19 pandemic, the World Health Organization (WHO) published Intra Action Review (IAR) guidance in July 2020 to inform the real-time evaluations of public health response operations. This COVID-19-specific IAR method aims to (i) take stock of countries' measures to prepare for and respond to COVID-19; and (ii) propose corrective actions to improve and strengthen ongoing COVID-19 response.²

Only few countries have undertaken real-time evaluations of their COVID-19 responses,³ and PoE surveillance in particular has not been evaluated during the COVID-19 pandemic. None has ever used the new COVID-specific IAR method from WHO to evaluate their surveillance systems. More generally, methodologically robust evaluations of

surveillance systems are scarce, especially from low-and-middle-income countries, despite their importance to improve public health response being widely recognized.⁴

In October 2020, the General Department of Preventive Medicine (GDPM) of Vietnam's Ministry of Health conducted a multi-stakeholder IAR evaluation of its nationwide PoE surveillance system during the beginning of the COVID-19 pandemic. Following the WHO IAR format for this evaluation, we aimed to identify successes and challenges of the PoE system to provide concrete recommendations to improve COVID-19 surveillance at PoE level, both in Vietnam as well as other countries in the region.

METHODS

We used the WHO IAR approach to conduct focus group discussions (FGD) during a two-day workshop in Quang Ninh province, Vietnam in 13-14 October 2020, with 60 stakeholders from 29 agencies involved in PoE surveillance nationwide. Participants were divided into five thematic FGDs to elicit their perspectives on strengths, weaknesses, and recommendations of the NSSC at PoE on the following topics: i) health declaration procedures; ii) equipment; iii) quarantine procedures for people and goods; iv) inter-agency cooperation; and v) laboratory systems. Participants were first asked to describe the functioning of the NSSC and then to reflect about its performance regarding the PoE surveillance component. Third, participants discussed about improvements of the response strategy; see Annex 1 for the detailed question guide. Figure 1 shows the different IAR-related activities by the research team during the workshop.

Figure 1 here

RESULTS

Vietnam has 131 PoEs, of which are: 10 international airports, 70 seaports, 48 road crossings, and three railway crossings (see Annex 2). The NSSC was activated each time a passenger registered to travel into Vietnam and was completed once that person was transported to a designated quarantine location or hospital (see Annex 3 for detailed arrival procedures and flowchart). The consensus overall among workshop participants was that the NSSC worked well and was effective at PoE level. The system was considered fit for purpose and able to adapt quickly to the rapidly evolving COVID-19 situation. While most participants were confident that the system was adequate to detect and manage low and medium-level case numbers and associated local outbreaks, its capacity to cope with high incidence over

prolonged time periods was questioned since this might have left the whole system overburdened and under-staffed (see Annex 4 for detailed results from FGDs).

DISCUSSION

This was the first IAR using the COVID-specific approach of WHO to evaluate a national surveillance system during the COVID-19 pandemic. Identified weaknesses of the PoE surveillance system in Vietnam across five reviewed thematic areas resulted in three ~~cross-cutting~~ lessons learnt:

Procurement processes need to be improved

The rapidly changing nature and long duration of the COVID-19 pandemic was the fundamental challenge for resources and consumables. While some materials for health declarations were pre-deployed, their quantities turned out to be inadequate to meet the actual needs at PoE levels as the pandemic continued. The same shortages occurred for equipment for quarantine procedures such as thermal imaging cameras, kits for taking and preserving swab samples, automatic disinfection systems, and isolation rooms. The current acquisition systems in Vietnam are not designed to obtain large amounts of supplies rapidly. These constraints were caused by insufficient capacity and flexibility of emergency requisition and purchasing procedures. Bidding laws and ordering processes were cumbersome and required lengthy multi-level approval processes.

Emergency planning needs to be strengthened

Shortfalls in emergency planning at PoE level caused serious problems once the COVID-19 pandemic grew in scale, which led to gaps in human resources to triage passengers timely, poor preparations to take samples, and inconsistent communication between incoming vehicles and ground officers. All respondents agreed that the most fundamental reason was poor implementation of existing emergency plans across agencies and jurisdictions. While most agencies were involved in the planning, no requirement existed to fully enact these plans for them. Better planning as well as better implementation of emergency plans are key for ongoing and future pandemics.

Clear leadership needs to be established early

A coherent joint commands failed to emerge because of ad-hoc cooperation and limited communication across agencies involved in the surveillance implementation. The absence of an overarching command structure across all stakeholders sometimes led to duplicative and conflicting response efforts. Two main reasons were identified: first, agreed plans and incentives to coordinate with each other were not always followed through. Second, there was

no mechanisms to solve conflicts over resource allocation between agencies. Respondents recommended that regulations should be issued to specify the roles and responsibilities of relevant agencies for shared COVID-19-related activities at PoE level.

CONCLUSIONS

The COVID-19 surveillance system at PoE level in Vietnam was found to be effective overall to prevent large-scale case importation during 2020. However, prolonged high incidence may have easily overburdened the system. ~~Cross-cutting~~ Lessons learnt were the need to improve procurement processes, to strengthen emergency planning, and to establish clear leadership early. Given the protracted and volatile nature of the COVID-19 pandemic, we recommend that all countries should consider assessing their surveillance system at PoE level periodically using adequate methods such as the WHO IAR tool.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ETHICAL CONSIDERATION

Ethics review of this research was waived by the General Department of Preventive Medicine of the Vietnam Ministry of Health as a part of routinely collected data to improve public health response. This study was also waived for ethics review by the Australian National University Human Research Ethics Committee under the waiver number HREC/17/ANU/909.

DECLARATION OF CONFLICTING INTERESTS

The Authors declare that there is no conflict of interest

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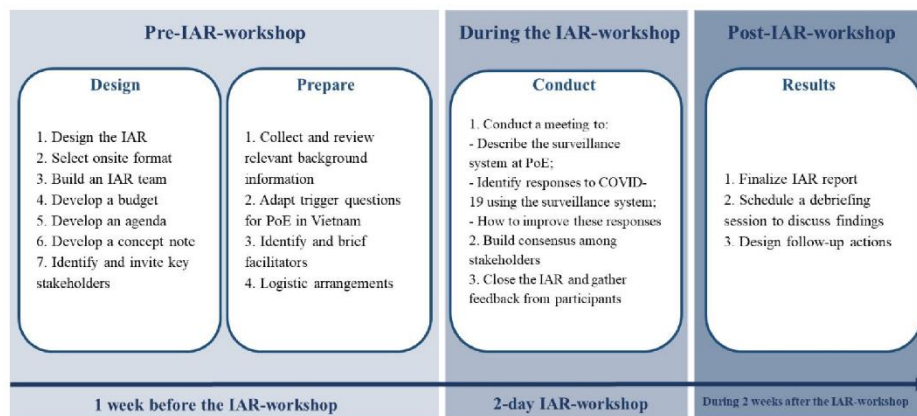


Figure 1. The implementation of the Intra-Action Review workshop in Quang Ninh province, 13-14 October 2020, for the Points of Entry surveillance evaluation in Vietnam

Annex 1. Question guide for the Vietnam's Intra-Action Review

Questions		
Document existing systems in place	1	What were the existing country's COVID-19 response plans for preventing COVID-19 at PoE?
	2	What were activities undertaken at the national level for preventing COVID-19 at PoE?
	3	When was the surveillance system activated and when it marked as completed?
	4	How the surveillance system screened suspected cases and how to treat these cases?
	5	Describe the systems for transportation of suspected COVID-19 cases to designated medical facilities at PoE?
	6	What kind of bilateral or multilateral agreements with neighbouring countries was in place to prevent the international spread of COVID-19?
Identify and analyse what happened so far during the COVID-19 outbreak response	1	What existing systems were adapted for detecting, testing, isolating and transporting COVID-19 cases at PoE and what new systems were instituted ad-hoc? How well did these work?
	2	Were available plans and guidance materials for the COVID-19 response at PoE previously available or developed ad-hoc? Were they available at all PoE? How effectively were they used?
	3	How are infection prevention and control measures being implemented at PoE during the COVID-19 outbreak?
	4	What types of screening measures were put in place at PoE?
	5	How was the coordination of information exchange between conveyance operators, PoE authorities, and public health authorities during the COVID-19 response?
	6	What types of training and personal protective equipment did the rapid response team have at PoE? How were these training done?
	7	How was COVID-19 information provided to travellers (e.g., information broadcasting on board, information leaflet, posters in PoE)?
	8	What policies or measures have been put in place during the COVID-19 response for disadvantaged subpopulations? (e.g., people with disabilities, persons with low socioeconomic status, ethnic minorities, rural poor, migrants and others experiencing exclusion and discrimination)?
	9	Given the protracted nature of the COVID-19 outbreak, how were PoEs able to consider the (potential of) concurrent emergencies during the pandemic in their policies, plans and measures put in place?
Improve existing COVID-	1	What actions taken enabled an efficient and timely detection of suspected COVID-19 cases at PoE?

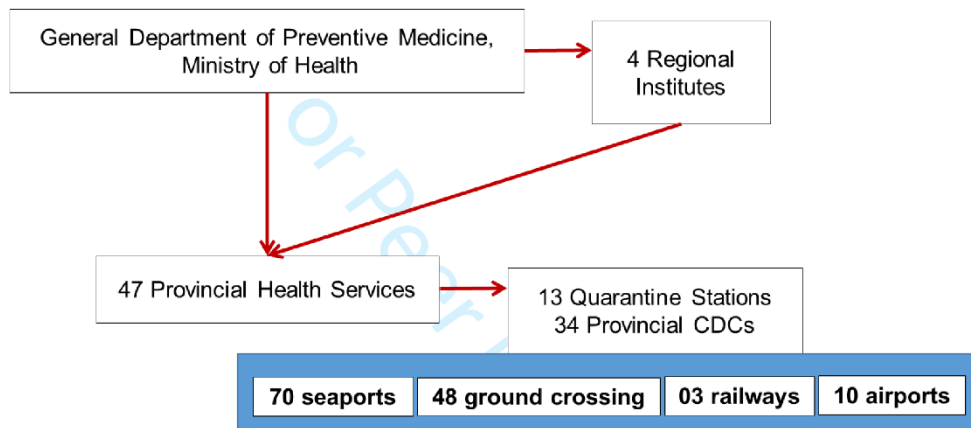
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19 outbreak response strategy	2	What new technologies or innovations were implemented to efficiently detect suspected COVID-19 cases at PoE and follow up on passengers in case a fellow passenger later tested positive for COVID-19 on their conveyance?
	3	What challenges were encountered in implementing public health measures and detecting COVID-19 at PoE?
	4	What actions were taken at PoE during the COVID-19 outbreak that allowed for a better than expected performance of the overall COVID-19 response?
	5	What were the overall strengths and weaknesses of public health activities conducted at PoE for COVID-19 response?

For Peer Review

Annex 2. The hierarchy of multiple administrative levels systems for the National Surveillance System for COVID-19 at Points of Entry in Vietnam

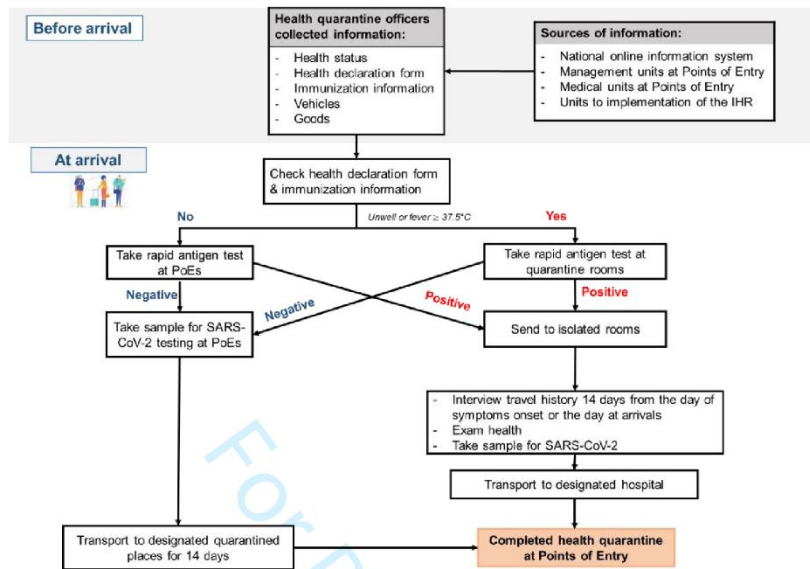
Vietnam has 131 PoE, of which are: 10 international airports, 70 seaports, 48 ground crossings, and three railways. The NSSC at PoE is based on the international border surveillance system, which was developed by the GDPM in 2015. The NSSC uses event-based surveillance for the detection suspected COVID-19 cases that is implemented at four administrative levels: national, regional, provincial, and field levels. The system is under the leadership of the GDPM. PoE are managed by 13 quarantine stations and 34 provincial Centers for Disease Control and Prevention (CDCs), who report to four regional institutes and 47 provincial health services.



Annex 3. The procedures for arriving passengers at Points of Entry

The NSSC was activated each time a passenger registered to travel into Vietnam and was completed once that person was transported to quarantine places or designated hospitals. Prior to arrival to Vietnam, all passengers were required to complete an online health declaration form. Managers of vehicles had to complete information on the overall health status of all passengers and the description of vehicles and goods. The health declaration form was designed specifically for COVID-19 and translated into 11 languages. Other forms to capture information of passengers, vehicles and goods were based on documents developed by the MoH in June 2018.¹ If a passenger could not access the online form, they were provided with a paper version from cabin crew or quarantine officers at PoE. While the online data were directly linked to the COVID-19 surveillance system, paper-based forms had to be entered manually by quarantine officers.

At arrival, the passengers' temperature was screened using forehead thermometers or thermal cameras. Quarantine officers also visually screened passengers for obvious signs and symptoms of respiratory infection. Passengers who self-reported COVID-19 compatible symptoms were transported immediately to individual quarantine rooms for a rapid antigen test (RAT). All asymptomatic travelers were separated by place of departure at PoE for RAT. A negative RAT results were followed up with a nasopharyngeal swab sample for rt-PCR testing for all passengers, and all passengers were immediately transported to a designated quarantine place for a 14-day irrespective of their results. If RAT was positive, they were sent to isolation rooms, where a 14-day travel history, health examination, and a specimen for rt-PCR testing was taken before being transported to designated hospitals. The travel history and contact information from the health declaration form of these passengers were sent to the Rapid Response Team, the National Steering Committee of COVID-19 Prevention and Control, and the provincial CDCs for contact tracing and case finding. Their belongings and vehicles were sterilized.



Annex 4. Strengths, weakness, and recommendation of the NSSC

Identified strengths of the NSSC at PoE

The overall consensus among workshop participants was that the NSSC's implementation worked well and was effective at PoE. The system was considered well-adapted and flexible to the unpredictable nature of COVID-19.

Identified strengths of the NSSC were the effective management of incoming passengers using health declaration forms, the early detection of cases through screening by RAT, and effective reduction of cross-contamination through strict on-site quarantine procedure. The health declaration form was issued quickly after the start of the COVID-19, regularly updated, and available in sufficient languages. The online version was considered convenient by quarantine officers, though feedback from passengers was not gathered. For tracing of passengers arriving on flights with confirmed COVID-19 cases, contact information could be extracted quickly from the NSSC thanks to the information collected via the health declaration form. Most attendants considered a valuable strength of the NSSC that it was equipped with MoH's instructions for quarantine procedures. Effective triaging saved time for both officers and passengers, thereby reducing the likelihood of cross-contamination at PoE. Also, PoE had sufficient forehead thermometers and RAT, which helped to detect cases early. Although lacking on-site laboratory systems at PoE, the testing capacity was considered sufficiently high thanks to a strong cooperation with established laboratories in the same region. The turnaround time of the laboratories involved was considered sufficiently quick to ensure smooth on-site operations. The NSSC was also connected to the national COVID-19 responding focal points, thus any alert triggered by PoE notified all relevant agencies.

Identified weaknesses of the NSSC at PoE

While workshop participants were confident that the system was adequate to detect and manage small and medium-size COVID-19 case numbers and local outbreaks, its potential capacity to cope with prolonged time periods with high numbers of confirmed cases was questioned as it might have left the whole system overburdened and under-staffed.

Health declaration

After the MoH issued mandatory health declarations for all inbound passengers, several PoE with high passenger volume encountered a shortage of paper forms. Also, human resources were lacking at times to guide passengers in completing the form. Although the online version, which was launched on 07 March 2020, circumvented printing limitations in theory, PoE lacked internet-connected devices to assist passengers who had difficulties completing the

1
2
3 online form themselves, especially the elderly, illiterate, disabled, and people without
4 smartphones. Accessing the online form sometimes failed or was slow due to overburdened
5 servers, especially at the end of the day after a large number of records had been entered. Also,
6
7 no automated mechanism existed to flag logical errors or incompleteness of data in submitted
8
9 online forms.
10

11 *Equipment*

12
13 Another limitation was resource constraints for equipment. Only five PoE (38.5%) were
14 equipped with thermal-imaging cameras while most used forehead thermometers, which
15 required more human resources to operate. A few PoE lacked kits for taking and preserving
16 SARS-CoV-2 samples, while others had enough kits but lacked staff for sample taking. Many
17 PoE had insufficient materials to disinfect surfaces, and some quarantine rooms for suspected
18 cases were poorly set up i.e., were not equipped with first aid kits.
19
20

21 *Quarantine procedures for people and goods*

22
23 Although the instructions were available, workshop participants reported weaknesses
24 for almost all PoE in planning quarantine procedures for people and goods due to a shortage of
25 human resources and insufficient preparation time. For example, due to insufficient space and
26 shortages in equipment, most PoE could not arrange rooms that ensured the minimum distance
27 (2 meters) between asymptomatic passengers while taking test samples. This weakness also
28 highlighted limited and inconsistent communication between the crew and ground officers in
29 case of delays or short-term changes of circumstances, leading to knock-on effects on queuing
30 times of goods and people awaiting clearance.
31
32

33 *Border agency cooperation*

34
35 Inter-sectoral and multilateral meetings were not conducted regularly. No centralized
36 system for sharing information was available, and individual responsibilities in shared
37 activities were not always clearly defined, which sometimes lead to conflicting actions. Health
38 officials and public security overlapped in triaging procedures in sometimes uncooperative
39 ways and within isolated command structures. Furthermore, messages in health communication
40 were sometimes misleading and conflicting between health officials and health communication
41 specialists.
42

43 *Laboratory*

44
45 No standard laboratory was established at PoE because it requires an expensive
46 investment in machinery, processes, and human resources for biosafety while other standard
47 laboratories (CDCs and the local Institute of Hygiene and Epidemiology) were sufficiently
48 close to PoE. Although the laboratories were mostly located within a short distance, this might
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have delayed diagnosis of a large volume of samples due transportation time and exchange of information among sites.

Recommendations

Contents	Recommendations
Health declaration	- PoE actively mobilize internet-connected devices and human resources to assist passengers. - MoH should issue guidance for supporting people who cannot complete the form themselves, including the elderly, disabled people, people without internet devices, illiterate people without guardians.
Equipment	- The PoE prepare contingency plans and assess their resources monthly (or even weekly). - The PoE conduct simulation exercises with a situation of lacking equipment for COVID-19 prevention. - MoH should issue national adaptable emergency procurement procedures that contain a list of stable equipment distributors as well as regulations on stockpiling equipment and stabilizing prices for materials.
Quarantine procedures for people and goods	- PoE develop contingency plans and simulation exercises in case of large COVID-19 outbreaks occurred. - The SARS-CoV-2 samples should be taken at quarantine places or at PoE with qualified rooms which endured safe distance among passengers. - PoE build a mechanism for communication between the crew and ground officers. - MoH should issue instructions on sterilized areas to avoid wasting human resources and chemicals.
Border agency cooperation	The Government should issue regulations to define the responsibilities of relevant agencies for COVID-19 shared activities at PoE.
The laboratory system	PoE should invest in taking, preserving, and transporting SARS-CoV-2 samples; and cooperating with local standard

laboratories to save human and financial resources while
ensuring the timely SARS-CoV-2 testing process.

For Peer Review

Chapter 5. Design and conduct an epidemiological study

*Assessing the mental effects of COVID-19 related work
on depression among community health workers in Vietnam*

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List of Abbreviations – Chapter 5

AIC	Akaike's Information Criteria
BIC	Schwarz's Bayesian Information Criteria
COVID-19	Coronavirus 2019
CHWs	Community health workers
IRB	Institutional review board
NIHE	The National Institute of Hygiene and Epidemiology
OR	Odds ratio
PHQ-9	Patient Health Questionnaire
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

Prologue

Background

The COVID-19 outbreak identified in Wuhan City, China, in December 2019 now affects all countries and territories worldwide. A well-prepared health workforce is a key pillar to enhancing health systems' capacity in this ongoing pandemic (1,2). Community health workers (CHWs) constitute a significant proportion of the frontline health workforce and play important roles in the control and prevention of the COVID-19 pandemic (3).

In Vietnam, CHWs provide culturally appropriate health education and information, assist people at the community level to get the care they need, give counseling and guidance on health behaviors, and provide some direct health services, such as first aid and blood pressure screening (4). The COVID-19 pandemic has placed CHWs in an unprecedented situation; their tasks expanded substantially into areas outside their usual, pre-pandemic activities. The most common activities include pandemic fronts line work such as raise community awareness about COVID-19, conducting screening and testing in the community, organizing quarantine and isolation, and tracing close contacts of COVID-19 cases.

There is evidence suggesting that the clinical cadre of the health care workforce like nurses and doctors are at considerable risk of developing mental illness due to their work with COVID-19 patients (3,4), with depression being among the most frequent disorders. Working in high-risk areas, in close contact with SARS-CoV-2 patients, long working hours, high workload, shortage of sleep, and poor working conditions have been suggested as risk factors for developing COVID-19-related depression among clinical staff. However, all existing evidence about the link between COVID-19-related work and mental health is limited to staff performing patient-centred clinical duties in health facilities. Evidence from non-clinical health care workers outside health facilities such as CHWs remains limited.

My role

This project was my first experience leading entirely an epidemiological study. This project's idea came from a brief chat with my ex-colleague on the lack of evidence on CHWs in literature even though they were involved much in COVID-19 prevention and response. After the chat, I read up on the literature on mental health situations among CHWs. In Vietnam, CHWs are a main human resource during the pandemic preventing the spreading of SARS-CoV-2 in the community. Despite CHWs being intensively involved in COVID-19-related work and often exposed to many COVID-19 stressors, their mental well-being is often neglected. After many discussions and weeks-long of endeavors with my supervisors, we

finalized an epidemiological study on the mental health of CHWs during the COVID-19 pandemic in Vietnam.

After finalizing the aim and methodology, I conducted a tentative data analysis plan and submitted ethical applications to the ethics committees at the Australian National University and the National Institute of Hygiene and Epidemiology (NIHE). This was an interesting experience, as the internal review process required an utmost safe and careful process of data collection, analysis, and storage to protect confidentiality. After receiving ethical approval, I designed an online questionnaire on KoBoToolbox, piloted the questionnaire, then sent them out to CHWs across Vietnam thanks to my field supervisor's support. The questionnaire was opened from 17 March 2021 to 21 April 2021 and participated CHWs were asked to evaluate their mental well-being and related factors before the COVID-19 pandemic and after a major outbreak of SARS-CoV-2 in Tet holiday (on February 2021) in Vietnam.

Abstract

Background

Community health workers (CHWs) involved in the COVID-19 response might be at increased risk of developing depression, though evidence is scarce. We investigated effects of COVID-19 related work on changes in depression levels among CHWs in Vietnam, and to identify sub-groups among CHWs who are at particular risk of developing severe depression.

Methods

We conducted a cross-sectional online survey among 979 CHWs who were involved in the COVID-19 response in Vietnam, in particular during the 2021 Tet holiday outbreak between January and March 2021. Respondents were asked to report depression symptoms at two-time points, before the start of the COVID-19 pandemic (average June to December 2019) and during the 2021 Tet holiday outbreak using the PHQ-9 mental health questionnaire. We estimated depression levels at both time points and developed univariate and multivariable logistic regression models to estimate odds ratios and 95% confidence intervals (95%CI) to explore the association between deterioration to high depression levels and selected risk factors.

Results

Median depression levels among CHWs in Vietnam doubled from 3 (IQR = 2-7) before COVID-19 to 6 (IQR = 3-9) on the PHQ-9 scale during the Tet holiday outbreak. The

proportion with normal/minimal levels decreased from 77.1% (95%CI = 74.4 – 79.7) to 59.9% (95%CI = 47.7 - 54) (p-value <0.001), while the proportion of CHWs with moderate, moderately severe, and severe depression levels increased 4.3, 4.5, and 5-fold, respectively. Less sleep and poor sleep quality, working in unfavorable work environments, and being involved in contact tracing and the organization of quarantine for suspected cases were associated with an increased risk of deterioration to high depression levels.

Conclusions

We found a substantial increase in overall depression levels among CHWs in Vietnam due to their COVID-19 related work, and a particularly worrisome rise in CHWs suffering from severe depression. CHWs are an indispensable yet often overlooked cadre of work in many low and middle income countries and shoulder a heavy psychological burden during the COVID-19 pandemic. Targeted psychological support for CHWs is needed to improve their mental health, and to ensure the sustainability of community-based health interventions during COVID-19 and future epidemics.

Achievement

From the finding of the investigation, I published an article in the Human Resources for Health journal. The aim of this article was to determine associated factors in order to identify sub-groups among CHWs that might be at particularly high risk of suffering a deterioration to high depression levels. This was the first time evidence of the mental well-being of CHWs in Vietnam was assessed and addressed. Vietnamese CHWs suffered a substantial increase in depression across all severity levels during the 2021 Tet holiday outbreak compared to pre-pandemic baseline levels which were likely attributable to their COVID-19-related work. CHWs had poor sleep conditions and worked in unfavorable working environments might be at particular risk of deterioration to high depression levels. CHWs involved in contact tracing and the organization of quarantine for suspect cases were also at increased risk of deterioration. These findings will also be published in a Vietnamese newspaper to inform and alert the depression situation among CHWs. I will also present my findings at a domestic conference to require attention on mental care-being for CHWs in Vietnam.

Lessons learned

This project gave me a great opportunity to lead an epidemiological study on my own. Being a leader means you have to try on all the roles, project manager, project officer, data collector, data analytic, proofreading, etc. I can say I have grown so much through this project, and I am more confident in my research capacity to conduct a study on my own now.

I also understand the importance of careful preparation and organization in project management. Well-prepared is halfway done, the project cannot go on without a sufficient plan and a willing leader. The first challenge we have to take on for the study was not to come up with the idea but to go through the ethical application. We developed the project's idea when Vietnam was in the beginning of a third COVID-19 wave. Because we intended to assess the depression symptoms in CHWs before the COVID-19 pandemic vs. during the third wave, the survey should be completed within two weeks after the outbreak was under control. Due to time restraints, we have to rapidly prepare the application and thus cannot avoid many mistakes and questions from the institutional review boards. The questions, albeit long and quite tiring, were insightful to point out the existing gaps in the study plan. Thanks to the questions, we got to slow down, spending time to reflect and revise the study plan. Overall, I truly appreciate the ethics application process, this work gets me familiar with the peer-review process as well as provides an introspective opportunity for my own study.

Each project is an exciting journey to apply new knowledge. I got to practice likelihood ratio tests and criteria to compare between un-nested regression models (AIC and BIC) for this project.

Public health impact

The COVID-19 pandemic has been a near-ubiquitous exposure in Vietnam with unknown effects on depression symptoms. CHWs are responsible for front-line work and expose to many COVID-19 stressors such as frequently exposed to the SARS-CoV-2 sources, high workload, and lack of sleep, but are often neglected in psychological studies. Our findings suggest that the prevalence of depression symptoms in Vietnamese CHWs was 2.1-fold higher than before COVID-19, likely reflecting the far more pervasive influence of COVID-19 and its social and economic consequences than other mass traumatic events. These figures were 1.6-fold higher for mild depression symptoms, 4.3-fold higher for moderate depression symptoms, 4.5-fold higher for moderately severe depression symptoms, and 5-fold higher for severe depression symptoms categories during COVID-19 compared with before COVID-19.

This study was conducted two weeks after Vietnam declared to control the third COVID-19 wave. On the final day of the survey, 21 April 2021, the death toll was 36 individuals in Vietnam, with more than 1,700 cases confirmed. Before this wave, Vietnam only experienced 814 cases of infection. The findings suggested individuals with higher intensity of tracing close contacts to COVID-19 confirmed cases and organizing isolation places for COVID-19 suspected cases increased the likelihood of deterioration to high depression levels. Addressing mental health support for these individuals will be an interesting and important discussion for health professionals, particularly if a large number of depression cases are due to situational factors.

Recommendation

During- and post-COVID-19 plans should account for the probable increase in depression among CHWs. For the effective establishment and scale-up of evidence-based interventions, it is critical to understand the implementation strategies that are needed to train and support mental health services, especially for special groups like CHWs. Such evidence is needed to inform health policy to provide more targeted psychological care for CHWs in the COVID-19 pandemic in Vietnam and elsewhere, as well as to inform health workforce planning for an improved community-based response to other infectious disease outbreaks in the future.

Acknowledgement

I would like to acknowledge my academic supervisor (Dr. Florian Vogt) for his patience in guiding me through every steps of this project. I acknowledged my field supervisor (Dr. Pham Quang Thai) for helping me contact Vietnamese CHWs as well as ethical submission at NIHE. I thank all participated CHWs for their time completing the survey. I especially thank Dr. Pham Quang Thai and Dr. Hoang Van Ngoc for facilitating the survey's disseminations and for their help in the survey's pilot testing and technical issues. I also thank Ms. Quach Ha-Linh for her support during the MAE program.

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Appendix. Journal Article

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RESEARCH

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Assessing the mental effects of COVID-19-related work on depression among community health workers in Vietnam

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Abstract

Background: Community health workers (CHWs) involved in the COVID-19 response might be at increased risk of developing depression, though evidence is scarce. We investigated effects of COVID-19-related work on changes in depression levels among CHWs in Vietnam and identified sub-groups among CHWs who are at particular risk of developing severe depression.

Methods: We conducted a cross-sectional online survey among 979 CHWs who were involved in the COVID-19 response in Vietnam, in particular during the 2021 Tet holiday outbreak between January and March 2021. Respondents were asked to report depression symptoms at two-time points, before the start of the COVID-19 pandemic (average June to December 2019) and during the 2021 Tet holiday outbreak using the PHQ-9 mental health questionnaire. We estimated depression levels at both time points and developed univariate and multivariable logistic regression models to estimate odds ratios and 95% confidence intervals (95% CIs) to explore the association between deterioration to high depression levels and selected risk factors.

Results: Median depression levels among CHWs in Vietnam doubled from 3 (IQR = 2–7) before COVID-19 to 6 (IQR = 3–9) on the PHQ-9 scale during the Tet holiday outbreak. The proportion with normal/minimal levels decreased from 77.1% (95% CI = 74.4–79.7) to 50.9% (95% CI = 47.7–54) (p -value < 0.001), while the proportion of CHWs with moderate, moderately severe, and severe depression levels increased 4.3, 4.5, and five-fold, respectively. Less sleep and poor sleep quality, working in unfavorable work environments, and being involved in contact tracing and the organization of quarantine for suspected cases were associated with an increased risk of deterioration to high depression levels.

Conclusions: We found a substantial increase in overall depression levels among CHWs in Vietnam due to their COVID-19 related work and a particularly worrisome rise in CHWs suffering from severe depression. CHWs are an indispensable yet often overlooked cadre of work in many low- and middle-income countries and shoulder a heavy psychological burden during the COVID-19 pandemic. Targeted psychological support for CHWs is needed to improve

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their mental health and to ensure the sustainability of community-based health interventions during COVID-19 and future epidemics.

Keywords: COVID-19, Depression, Community health workers, Vietnam

Background

Community health workers (CHWs) constitute an important cadre of the health care workforce in the response to COVID-19 in low- and middle-income countries [1]. In Vietnam, CHWs provide culturally appropriate health education and information, assist people at community level to get the care they need, give counselling and guidance on health behaviors, and provide some direct health services, such as first aid and blood pressure screening [2]. The COVID-19 pandemic has placed CHWs in an unprecedented situation; their tasks expanded substantially into areas outside their usual, pre-pandemic activities. The most common activities include pandemic front line work such as raise community awareness about COVID-19, conduct screening and testing in the community, organize quarantine and isolation, and trace close contacts of COVID-19 cases.

There is evidence suggesting that clinical cadre of the health care workforce like nurses and doctors are at considerable risk of developing mental illness due to their work with COVID-19 patients [3, 4], with depression being among the most frequent disorders. For example, in studies from China by Lai et al. and by Chen et al., nearly half of health care workers who were exposed to COVID-19 patients reported symptoms of depression [5, 6]. Similarly, in a pooled study by Olaya et al., depression prevalence in front line health care workers during COVID-19 from 57 studies was 43% [7]. Another study by Kang et al. among medical and nursing staff in Wuhan, China, identified 37% of clinical staff as suffering from depression [8]. In Vietnam, reported rates of clinical staff who were involved in the COVID-19 response and suffered from some degree of depression range between 17 and 35% [9–11]. Working in high-risk areas, in close contact with SARS-CoV-2 patients, long working hours, high workload, shortage of sleep, and poor working conditions have been suggested as risk factors for developing COVID-19-related depression among clinical staff [12, 13]. However, all existing evidence about the link between COVID-19-related work and mental health is limited to staff performing patient-centered clinical duties in health facilities. Evidence from non-clinical health care workers outside health facilities such as CHWs remains limited [14]. To our knowledge, the mental health effects of COVID-19-related work among CHWs has not been quantified to date.

Aiming to address this gap, we assessed the effects of COVID-19-related work on depression among CHWs in Vietnam by comparing baseline depression levels before the COVID-19 pandemic and during the 2021 Tet holiday outbreak, a major nationwide COVID-19 outbreak during January and March 2021. We also aimed to determine associated factors in order to identify sub-groups among CHWs that might be at particular high risk of suffering a deterioration to high depression levels.

Methods

Study design

We conducted a cross-sectional online survey among CHWs in Vietnam who were involved in the COVID-19 response during the 2021 Tet holiday outbreak. The survey comprised questions about two time points: the pre-pandemic baseline period (6-month average June to December 2020) and the period of the 2021 Tet holiday outbreak (average January to March 2021).

Study setting

Until March 2021, Vietnam experienced three waves of COVID-19 (Fig. 1). The first wave, which was dominated by imported cases among returning travelers, lasted until mid-April 2020 with a total of 106 cases. The second wave was characterized by local transmission in the community and hospitals during mid-2020 and resulted in a total of 554 cases. On 28 January 2021, the third, and until, the largest wave (also referred to as the “2021 Tet holiday outbreak”) started with the detection of a COVID-19 cluster among employees at an industrial complex in Hai Duong Province, Northern Vietnam. The outbreak spread quickly across 12 other provinces. CHWs got activated in virtually all provinces across Vietnam as part of massive outbreak response activities, which was eventually achieved on 25 March 2021 after resulting in 934 cases nationwide (Fig. 2). We conducted our survey shortly after the peak of the Tet holiday outbreak (Fig. 1).

Our study population were CHWs in Vietnam aged 18 years or older who were involved in the 2021 Tet holiday outbreak through at least one of the following activities: tracing of close contacts of confirmed or suspected COVID-19 cases; organizing quarantine for suspected COVID-19 cases and their contacts; screening for people with COVID-19 symptoms in the community; participating in any other activities that involved direct exposure to potential SARS-CoV-2 cases.

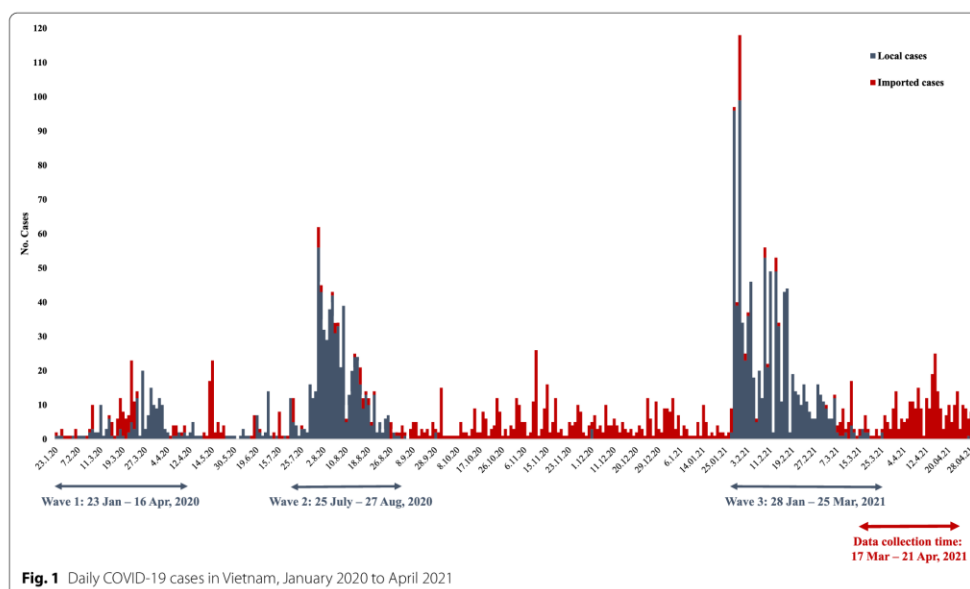


Fig. 1 Daily COVID-19 cases in Vietnam, January 2020 to April 2021

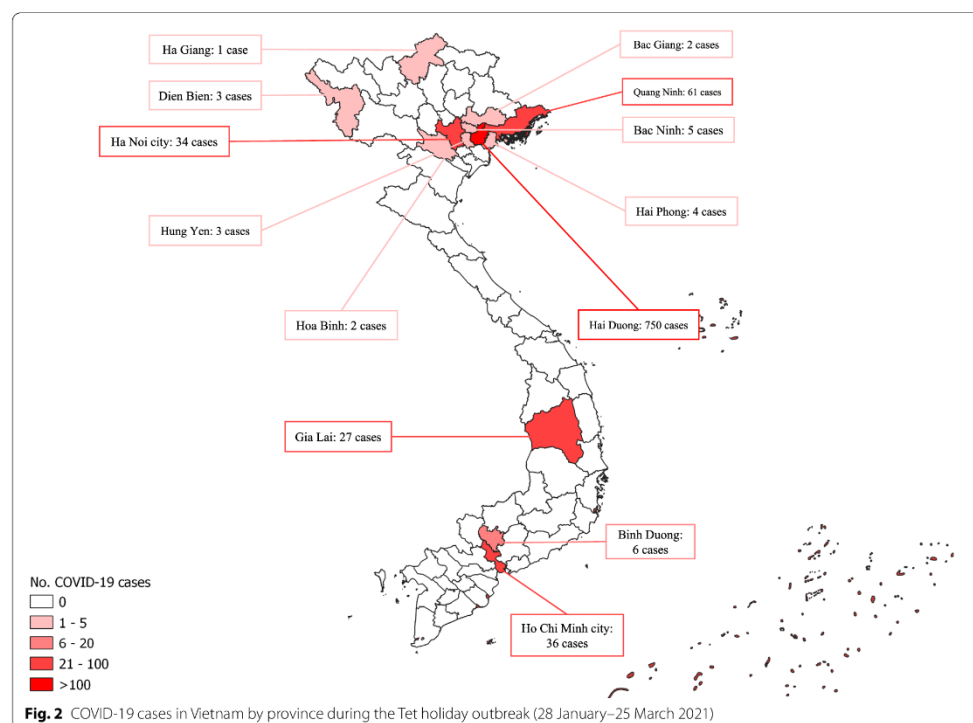
Data collection

Shortly after the beginning of the COVID-19 pandemic in Vietnam, the Ministry of Health created a group on Zalo, a popular social media application for smartphones in Vietnam [15], to link CHWs across all 64 provinces and cities together. The aim of this group is to enable quick and informal peer-to-peer communication about COVID-19-related work, e.g., be up to date about contact tracing across provinces, and sharing of individual stories, knowledge, and experiences. About 200 CHWs had joined this group at the time of our study. We obtained permission from the national-level administrators of this group to invite its members to complete a short online survey. Completing the survey was entirely voluntary, confidential, and anonymous. We created the survey using the KoBoToolbox [16] and piloted the questionnaire prior to dissemination to ensure appropriateness, clarity, user-friendliness, and a realistic completion time of approximately 15 min. The survey was opened on 17 March 2021 by posting an invitation on Zalo with a participant information sheet and a link to the online questionnaire (Additional file 1). CHWs were encouraged to disseminate the survey link to other CHWs outside the group. We posted two reminders 2 and 4 weeks after the first invitation. The link was deactivated on 21 April 2021.

Variables

Outcome of interest

We used the Vietnamese version of the Patient Health Questionnaire (PHQ-9) to quantify depression levels among respondents (Additional file 1). The PHQ-9 has been in widespread use around the world since its development in 1999 [17] and its Vietnamese version has been used in several previous studies [18–21]. The PHQ-9 contains nine items about depression-related symptoms. Each item has four response categories regarding their frequencies (> 4 days/week, 3–4 days/week, 1–2 days/week, not at all) resulting in a total range score from 0 to 27. The recommended cut-off points for depression thresholds are as follows: normal/minimal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) [22]. We asked about self-reported depression levels at two time points: 6 months before the pandemic and during the 2021 Tet holiday outbreak. For the regression models, the outcome variable “deterioration to high depression levels” was created. People who reported normal/minimal, mild, or moderate depression levels before the pandemic and an increase to moderately severe or severe levels during the 2021 Tet holiday outbreak; and those with moderately severe depression levels before the start of the pandemic and an increase to severe levels during the 2021 Tet holiday outbreak were



categorized as having deteriorated to high depression levels.

Co-variables

The variables collected on socio-demographic characteristics were age, sex, marital status, living with children under the age of five or with elderly persons, socio-economic status (SES), and years of work experience. We also asked about pre-existing physiological or mental health conditions, and other acute medical issue, as well as the number of hours of sleep per day and quality of sleep. Questions about work conditions referred to changes in feeling overloaded before the pandemic and during the 2021 Tet holiday outbreak; estimated working hours per day; working overtime, working on weekends; the number of paid workplaces for respondents; and five questions on their overall perceived working environment. Work-related intensity of exposure to SARS-CoV-2 was assessed through four questions on the estimated weekly frequencies of four activities: (1) the participation in contact tracing/case finding; (2) the organization of

quarantine for suspected cases and close contacts; (3) the screening for COVID-19 symptoms in the community by taking swab samples or measuring temperature; and (4) any other activities that required direct exposure to potential SARS-CoV-2 cases. Using the national COVID-19 incidence database, we also calculated the number of confirmed COVID-19 cases per province during the 2021 Tet holiday outbreak to categorize CHWs into three groups: CHWs working in provinces with zero confirmed case; with low case numbers (<27 cases); or high case numbers (≥ 27 cases). See Additional file 1: Supplement 1.1 for the full questionnaire and Additional file 2 for details on variable management.

Sample size

This was an exploratory study without hypothesis testing, hence no formal sample size was calculated. In total, 979 participants submitted sufficient data to be included in the analysis, which corresponds to 6% of the approximated total 15,600 CHWs in Vietnam [23].

Data analysis

Data were extracted from the KoBo Toolbox software into Excel for management and imported to STATA 16.0 for cleaning and analysis. First, we tabulated the socio-demographic characteristics, pre-existing health conditions, exposure intensity to SARS-CoV-2, sleep conditions, and work conditions by outcome status (deterioration to high depression levels), and used Wilcoxon rank-sum tests, Pearson's Chi-squared tests, and Fisher's exact tests to detect statistically significant differences. We used box plots to compare baseline depression levels before the start of the COVID-19 pandemic with levels during the 2021 Tet holiday outbreak and used Spearman's correlation coefficient to measure the association between depression levels at these two time points. We calculated the prevalence and 95% confidence intervals (95% CIs) of depression levels across the five severity categories pre-COVID-19 (baseline) and during the 2021 Tet holiday outbreak. We also created a heat map to illustrate distributions across the five depression levels at the two time points. We then used univariate and multivariable logistic regression to estimate odds ratios (ORs) and 95% CIs of the associations between co-variants (socio-demographic characteristics, health condition, intensity to exposure to SARS-CoV-2 sources, sleep condition, and work condition) and deterioration to high depression levels. We developed four multivariable logistic regression models to explore differences in the association of covariates and the outcome when adjusting for different sets of risk factors. The Base Model (Model 0) included socio-demographic characteristics and pre-existing health conditions as independent variables. In Model 1, we added work-related exposure intensity to SARS-CoV-2; the addition of sleep/work conditions with and without exposure intensity resulted in Models 2 and Model 3, respectively. The effect of each variable in the models was calculated using likelihood-ratio tests. We then used Akaike's Information Criteria (AIC) and Schwarz's Bayesian Information Criteria (BIC) to compare the fit among these four models [24].

Results

A total of 979 participants were included in the final analysis. Of these, 71 participants (7.3%) showed deterioration to high depression levels. The median PHQ-9 score increased from 3 (IQR 2–7) from before the pandemic to 6 (IQR 3–9) during the 2021 Tet holiday outbreak (Fig. 3A). We detected a moderate positive correlation between the depression scores at both time points, with a Spearman's rank correlation coefficient of 0.59 (Fig. 3B).

The prevalence of depression symptoms was higher in every depression severity category during the Tet holiday outbreak compared to before the COVID-19 pandemic.

While the majority (77.1%, 95% CI = 74.4–79.7) of CHWs showed no relevant depression levels pre-COVID, only about half (50.9%, 95% CI = 47.7–54) were free of depression during the Tet holiday outbreak (p -value < 0.001). Mild depression symptoms were present in 18.8% (95% CI = 16.5–21.4) of respondents before COVID-19 compared with 30.7% (95% CI = 27.9–33.7) during the Tet holiday outbreak (p -value < 0.001); moderate depression symptoms prevalence was 2.3% (95% CI = 1.5–3.4) compared with 10% (95% CI = 8.3–12.1) (p -value < 0.001); moderately severe depression symptom prevalence was 1.3% (95% CI = 0.8–2.3) compared with 5.9% (95% CI = 4.5–7.6%) (p -value < 0.001); and severe depression prevalence was 0.5% (95% CI = 0.2–1.2) compared with 2.5% (95% CI = 1.6–3.6) (p -value < 0.001) (Fig. 4A and Table 1). This corresponds to a 1.6-fold increase for mild depression levels, a 4.3-fold increase for moderate depression levels, a 4.5-fold increase for moderately severe depression levels, and a fivefold increase for severe depression levels during the Tet outbreak compared with before COVID-19 (Table 1). The prevalence of CHWs with normal/minimal depression levels before COVID-19 and changed to moderate, moderately severe, severe symptoms during the Tet holiday outbreak was 5.6%, 3.5%, and 0.7%, respectively. This figure among CHWs with mild depression levels pre-COVID was 3.2%, 1.5%, and 0.4% (Fig. 4B).

The comparison of covariates by the main outcome (deterioration to high depression levels) is shown in Tables 2, 3, 4. The median age of participants was 37 (interquartile ranges [IQR]: 32–45). More than half of CHWs were female (52%) and were living with children under the age of five or with elderly (65.9%). Most of the participating CHWs were married (89.4%), had no pre-existing long-term physiological health problems (84.9%), had no pre-existing mental health disorders (96.6%), and had no acute/sudden-onset medical problems (96.6%). CHWs who deteriorated to high depression levels were more likely to be younger [median (IQR): 35 (31–42) vs. 38 (32–45), p -value = 0.026], had fewer years of job experience (less than five years: 15.2% vs. 26.8%), had a lower SES level (32.5% vs. 49.3%, p -value = 0.009), and had more pre-existing diagnosed mental health disorders (3.1% vs. 7%, p -value = 0.08) compared to those who did not deteriorate to high depression levels.

About half of CHWs participated daily in tracing close contacts of confirmed COVID-19 cases (49.1%) and screening for COVID-19 symptoms in the community (53.7%) during the Tet holiday outbreak. More than one-third of CHWs daily organized isolation places for suspected cases (37.1%), while 32% worked on other activities with exposure to potential of SARS-CoV-2 sources. CHWs who did daily contact tracing or

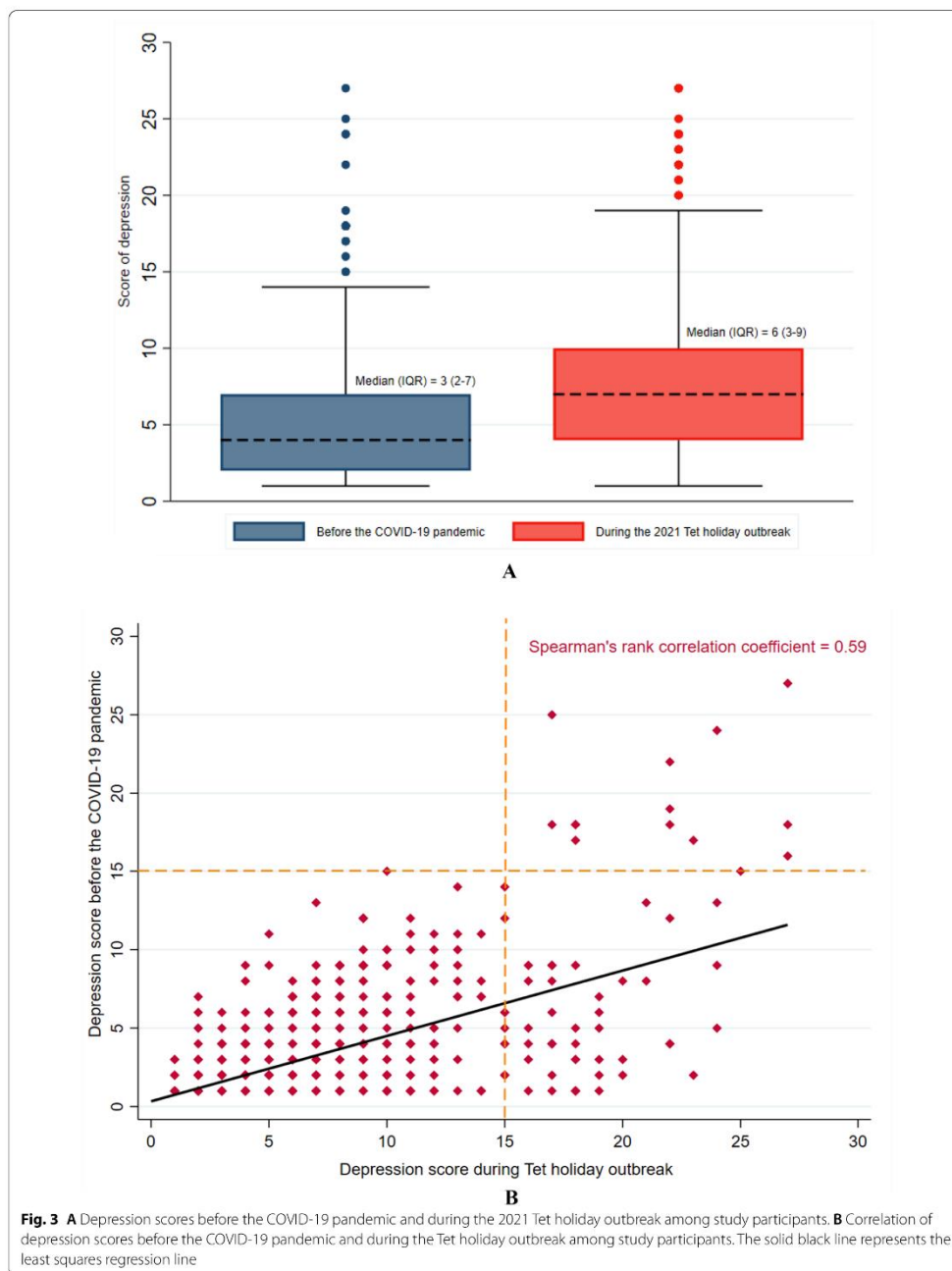
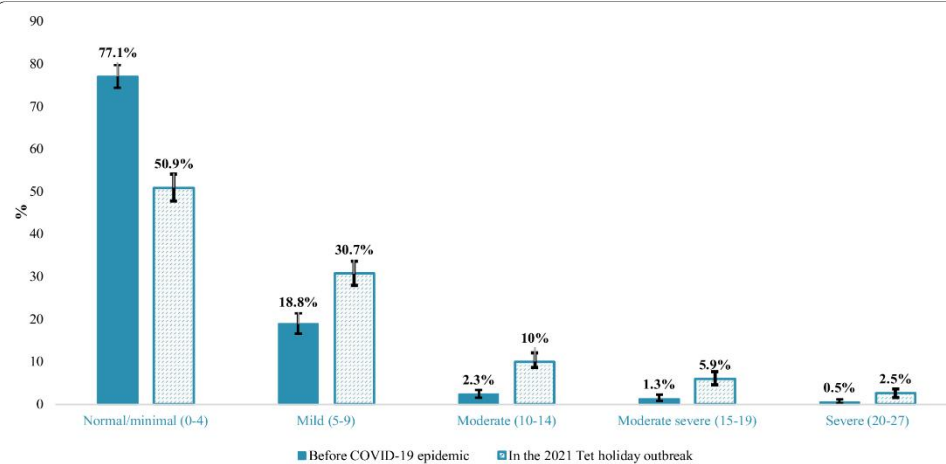


Fig. 3 **A** Depression scores before the COVID-19 pandemic and during the 2021 Tet holiday outbreak among study participants. **B** Correlation of depression scores before the COVID-19 pandemic and during the Tet holiday outbreak among study participants. The solid black line represents the least squares regression line



A.

Depression levels in Tet holiday outbreak

	normal/minimal (0-4)	mild (5-9)	moderate (10-14)	moderately severe (15-19)	severe (20-27)	total
severe (20-27)	0	0	0	1 (0.1%)	4 (0.4%)	5 (0.5%)
moderately severe (15-19)	0	0	1 (0.1%)	6 (0.6%)	6 (0.6%)	13 (1.3%)
moderate (10-14)	0	6 (0.6%)	11 (1.2%)	2 (0.2%)	3 (0.3%)	22 (2.2%)
mild (5-9)	18 (1.8%)	116 (11.9%)	31 (3.2%)	15 (1.5%)	4 (0.4%)	184 (18.8%)
normal/minimal (0-4)	480 (49%)	179 (18.3%)	55 (5.6%)	34 (3.5%)	7 (0.7%)	755 (77.1%)
total	498 (50.9%)	301 (30.7%)	98 (10%)	58 (5.9%)	24 (2.5%)	979 (100%)

B.

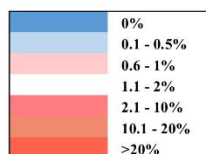


Fig. 4 A Categorized depression levels before the COVID-19 pandemic and during the 2021 Tet holiday outbreak among study participants. The vertical error bar indicates the 95% confidence intervals. B Heat map of categorized depression levels before the COVID-19 pandemic and during the 2021 Tet holiday outbreak among study participants

Table 1 Comparison of depression levels before the COVID-19 pandemic and during the 2021 Tet holiday outbreak among study participants

Depression levels	% (95% CI)		p-value*	% difference	
	Before COVID-19 pandemic	During the 2021 Tet holiday outbreak		Absolute	Relative
Normal/minimal (0–4)	77.1 (74.4–79.7)	50.9 (47.7–54)	< 0.001	– 26.2	0.7
Mild (5–9)	18.8 (16.5–21.4)	30.7 (27.9–33.7)	< 0.001	11.9	1.6
Moderate (10–14)	2.3 (1.5–3.4)	10 (8.3–12.1)	< 0.001	7.7	4.3
Moderately severe (15–19)	1.3 (0.8–2.3)	5.9 (4.5–7.6)	< 0.001	4.6	4.5
Severe (20–27)	0.5 (0.2–1.2)	2.5 (1.6–3.6)	< 0.001	2	5

*p-value from Fisher's exact test

organized isolation places had higher rates of deteriorating to high depression levels compared to those who did not (62% vs. 48.1% and 46.5% vs. 36.3%, respectively). CHWs who worked in provinces with more recorded COVID-19 cases during the Tet holiday outbreak had higher percentages of deteriorating to high depression levels compared to those worked in provinces with less cases, though not on a statistically significant level (Table 3).

During the 2021 Tet holiday outbreak, respondents who deteriorated to high depression levels had higher percentages of poor sleep in both quantity and quality than non-deteriorating participants (sleeping less than seven hours per day: 87.3% vs. 48.8%; report quality of sleep as normal: 47.9% vs. 28.3%; report quality of sleep as not good: 38% vs. 10.1%). In general, working overtime and work on weekends were common among CHWs (87.6% and 88.8%, respectively). The percentages who worked in two or more places and who worked at least nine hours per day was nearly double among CHWs deteriorating to high depression levels compared to non-deteriorating CHWs (25.4% vs. 13.7% and 71.8% vs. 38.9%). While 15.6% of participants who did not deteriorate to high depression levels considered their jobs intense during the 2021 Tet holiday outbreak, this figure was 62% among the ones who did deteriorate to high depression levels. CHWs deteriorating to high depression levels were more likely to work in less favorable environments, i.e., in more insecure jobs (33.8% vs. 16.7%), were more dissatisfied with the working environment (22.5% vs. 7%), had worse relationship with their co-workers (45.1% vs. 20.3%), and were more dissatisfied with the appreciation/reward system (45.1% vs. 24.8%). They also felt more overloaded during the COVID-19 outbreak than non-deteriorating CHWs (69% vs. 39.9%) (Table 4).

In the univariate regression analysis (see Table 5), younger participants with fewer years of job experience

and higher SES had higher odds of deterioration to high depression levels compared to older participants with more experience [age, OR (95% CI): 0.97 (0.94–0.99); years of job experience (ref: < 5 years), 5–14 years: 0.53 (0.29–0.96), 15 years and above: 0.44 (0.23–0.86)]; and lower SES [ref: upper and middle SES, lower SES: 2.02 (1.24–3.28)]. Both the Base Model and Model 1 confirmed the association between SES and deterioration to high depression levels, but showed weakened effects of age and years of job experience. Model 2 and Model 3 turned all above-mentioned associations statistically insignificant. CHWs with pre-existing long-term health problems and mental health disorders had increased odds to develop high depression levels in all of our models, though not at statistically significant levels. CHWs with higher exposure intensity during contact tracing had a 1.86-fold increase in the odds of deterioration to high depression levels (OR: 1.86, 95% CI: 1.02–3.41) and 1.81 times in the odds of deterioration when it came to organizing isolation (OR: 1.81, 95% CI: 1.03–3.2) in the unadjusted analysis compared with CHWs with a lower work-related SARS-CoV-2 exposure intensity. After adjusting for socio-demographic factors, pre-existing health conditions, and sleep/work conditions (Model 1 and Model 3), these associations were weakened to statistically insignificant levels. All other activities related to exposure intensity remained not associated on statistically significant levels in all our models.

All our models showed that individuals who slept less than seven hours or who reported poor quality of sleep were more likely to deteriorate to high depression levels [Model 2: sleep less than seven hours: (ref: sleep 7+ hours) 2.55, 95% CI: 1.14–5.69; quality of sleep (ref: good), normal: 2.36, 95% CI: 1.03–5.40, not good: 3.09, 95% CI: 1.21–7.92]. Compared with CHWs who worked less than eight hours per day, those who worked more than nine hours per day had a 5.6-fold increase in the

Table 2 Socio-demographic characteristics and health conditions of study participants by deterioration to high depression levels

Variables	Total	Deterioration to high depression levels		p-value*
		No	Yes	
	n (%)	n (%)	n (%)	
Total	979 (100)	908 (92.7)	71 (7.3)	
Sociodemographic				
Age [median (IQR)]	37 (32–45)	38 (32–45)	35 (31–42)	0.026
Age groups				
< 30 y	116 (11.8)	103 (11.3)	13 (18.3)	0.300
30–34 y	242 (24.7)	221 (24.3)	21 (29.6)	
35–39 y	228 (23.3)	212 (23.3)	16 (22.5)	
40–44 y	130 (13.3)	123 (13.5)	7 (9.9)	
45–49 y	124 (12.7)	116 (12.8)	8 (11.3)	
50+	139 (14.2)	133 (14.6)	6 (8.5)	
Sex				
Male	470 (48.0)	435 (47.9)	35 (49.3)	0.820
Female	509 (52.0)	473 (52.1)	36 (50.7)	
Marital status				
Single	84 (8.6)	76 (8.4)	8 (11.3)	0.470
Married	875 (89.4)	814 (89.6)	61 (85.9)	
Divorced/widow	20 (2.0)	18 (2.0)	2 (2.8)	
Living with children or elderly				
No	334 (34.1)	315 (34.7)	19 (26.8)	0.170
Yes	645 (65.9)	593 (65.3)	52 (73.2)	
Years of job experiences				
< 5 y	157 (16.0)	138 (15.2)	19 (26.8)	0.100
5–9 y	180 (18.4)	164 (18.1)	16 (22.5)	
10–14 y	294 (30.0)	278 (30.6)	16 (22.5)	
15–19 y	122 (12.5)	116 (12.8)	6 (8.5)	
20–24 y	99 (10.1)	92 (10.1)	7 (9.9)	
25+	127 (13.0)	120 (13.2)	7 (9.9)	
Social economic status				
Upper	55 (5.6)	50 (5.5)	5 (7.0)	0.009
Middle	594 (60.7)	563 (62.0)	31 (43.7)	
Lower	330 (33.7)	295 (32.5)	35 (49.3)	
Health condition				
Pre-existing long-term physiological health problems				
No	831 (84.9)	772 (85.0)	59 (83.1)	0.660
Yes	148 (15.1)	136 (15.0)	12 (16.9)	
Pre-existing diagnosed mental health disorders				
No	945 (96.6)	880 (96.9)	65 (92.9)	0.080
Yes	33 (3.3)	28 (3.1)	5 (7.0)	
Missing value	1 (0.1)	0 (0)	1 (0.1)	
Acute/sudden-onset medical problems				
No	946 (96.6)	879 (96.8)	67 (94.4)	0.270
Yes	33 (3.4)	29 (3.2)	4 (5.6)	

*p-value from Wilcoxon rank-sum, Pearson's Chi-squared and Fisher's exact test

Table 3 Intensity of exposure to SARS-CoV-2 by deterioration to high depression levels among study participants during the 2021 Tet holiday outbreak

Variables	Total	Deterioration to high depression levels		p-value*
		No	Yes	
	n (%)	n (%)	n (%)	
Total	979 (100)	908 (92.7)	71 (7.3)	
Frequency of contact tracing per week				
Did not perform	292 (29.8)	277 (30.5)	15 (21.1)	0.180
Less than one day	63 (6.4)	60 (6.6)	3 (4.2)	
1–2 days	75 (7.7)	72 (7.9)	3 (4.2)	
3 days +	68 (6.9)	62 (6.8)	6 (8.5)	
Daily	481 (49.1)	437 (48.1)	44 (62.0)	
Frequency of organizing isolation per week				
Did not perform	402 (41.1)	381 (42.0)	21 (29.6)	0.290
Less than one day	68 (6.9)	62 (6.8)	6 (8.5)	
1–2 days	66 (6.7)	61 (6.7)	5 (7.0)	
3 days +	80 (8.2)	74 (8.1)	6 (8.5)	
Daily	363 (37.1)	330 (36.3)	33 (46.5)	
Frequency of screening for COVID-19 per week				
Did not perform	255 (26.0)	240 (26.4)	15 (21.1)	0.160
Less than 1 day	53 (5.4)	51 (5.6)	2 (2.8)	
1–2 days	78 (8.0)	75 (8.3)	3 (4.2)	
3 days +	67 (6.8)	58 (6.4)	9 (12.7)	
Daily	526 (53.7)	484 (53.3)	42 (59.2)	
Frequency of doing other activities had to expose to SARS-CoV-2 sources per week				
Did not perform	475 (48.5)	446 (49.1)	29 (40.8)	0.480
Less than 1 day	52 (5.3)	46 (5.1)	6 (8.5)	
1–2 days	73 (7.5)	67 (7.4)	6 (8.5)	
3 days +	66 (6.7)	60 (6.6)	6 (8.5)	
Daily	313 (32.0)	289 (31.8)	24 (33.8)	
Number of confirmed cases per province [†]				
None	743 (75.9)	696 (76.7)	47 (66.2)	0.130
< 27 cases	139 (14.2)	124 (13.7)	15 (21.1)	
≥ 27 cases	97 (9.9)	88 (9.7)	9 (12.7)	

*p-value from Fisher's exact test

odds of deteriorating to high depression levels in univariate analysis, however these odds reduced to 1.2 after adjusting for socio-demographic factors, pre-existing health condition, and SARS-CoV-2 exposure intensity (Model 2 and Model 3).

In univariate analysis, experiencing poor working conditions such as work on weekends, work at more than one workplace, intense and insecure work, dissatisfaction with the work environment and the appreciation/reward system, poor relationship with co-workers, and feeling more overloaded than before COVID-19 were associated with higher odds of deterioration on statistically

Table 4 Sleep and work conditions of study participants during the 2021 Tet outbreak by deterioration to high depression levels

Variables	Total <i>n</i> (%)	Deterioration to high depression levels		<i>p</i> -value*
		No <i>n</i> (%)	Yes <i>n</i> (%)	
Total	979 (100)	908 (92.7)	71 (7.3)	
Sleep condition				
Hours of sleep per day				
7+ hours	474 (48.4)	465 (51.2)	9 (12.7)	< 0.001
Less than 7 h	505 (51.6)	443 (48.8)	62 (87.3)	
Quality of sleep				
Good	569 (58.1)	559 (61.6)	10 (14.1)	< 0.001
Normal	291 (29.7)	257 (28.3)	34 (47.9)	
Not good	119 (12.2)	92 (10.1)	27 (38.0)	
Work condition				
Working hours				
< 8 h	240 (24.5)	234 (25.8)	6 (8.5)	< 0.001
8–9 h	335 (34.2)	321 (35.4)	14 (19.7)	
9+ hours	404 (41.3)	353 (38.9)	51 (71.8)	
Work overtime in workdays				
No	121 (12.4)	117 (12.9)	4 (5.6)	0.090
Yes	858 (87.6)	791 (87.1)	67 (94.4)	
Work on weekends				
No	110 (11.2)	109 (12.0)	1 (1.4)	0.003
Yes	869 (88.8)	799 (88.0)	70 (98.6)	
Work overtime in workdays and work on weekends				
No	147 (15.0)	143 (15.7)	4 (5.6)	0.023
Yes	832 (85.0)	765 (84.3)	67 (94.4)	
Working in two places +				
No	837 (85.5)	784 (86.3)	53 (74.6)	0.007
Yes	142 (14.5)	124 (13.7)	18 (25.4)	
Job intensity				
Not intense	270 (27.6)	267 (29.4)	3 (4.2)	< 0.001
Normal	523 (53.4)	499 (55.0)	24 (33.8)	
Intense	186 (19.0)	142 (15.6)	44 (62.0)	
Job security				
Secure	363 (37.1)	347 (38.2)	16 (22.5)	< 0.001
Normal	440 (44.9)	409 (45.0)	31 (43.7)	
Insecure	176 (18.0)	152 (16.7)	24 (33.8)	
Working environment satisfaction				
Satisfied	386 (39.4)	376 (41.4)	10 (14.1)	< 0.001
Normal	513 (52.4)	468 (51.5)	45 (63.4)	
Dissatisfied	80 (8.2)	64 (7.0)	16 (22.5)	
Relationship with co-workers				
Good	238 (24.3)	225 (24.8)	13 (18.3)	< 0.001
Normal	525 (53.6)	499 (55.0)	26 (36.6)	
Not good	216 (22.1)	184 (20.3)	32 (45.1)	

Table 4 (continued)

Variables	Total <i>n</i> (%)	Deterioration to high depression levels		<i>p</i> -value*
		No <i>n</i> (%)	Yes <i>n</i> (%)	
Appreciation/reward system satisfaction				
Satisfied	246 (25.1)	241 (26.5)	5 (7.0)	< 0.001
Normal	476 (48.6)	442 (48.7)	34 (47.9)	
Dissatisfied	257 (26.3)	225 (24.8)	32 (45.1)	
Change in feeling overloaded before and during the COVID-19 outbreak				
Less overload	46 (4.7)	46 (5.1)	0 (0)	< 0.001
No change	522 (53.3)	500 (55.1)	22 (31.0)	
More overload	411 (42.0)	362 (39.9)	49 (69.0)	

**p*-value from Pearson's Chi-squared and Fisher's exact test

significant levels compared with those who did not. These above-mentioned relationships were confirmed in multivariable analysis, however only CHWs who worked at more than one workplace with high intensity, poor relationship with co-workers, and feeling more overloaded than before COVID-19 remained with increased odds of deterioration to high depression levels at a statistically significant level (Model 2 and Model 3).

Both AIC and BIC indicated that Model 2, which included socio-demographic factors, pre-existing health conditions, and sleep/work conditions, was the best model fit (AIC = 413.8, BIC = 555.5) (Table 6).

Discussion

To our knowledge, this was the first study worldwide to quantify the effects of COVID-19-related work on depression levels among CHWs. We found a substantial increase in depression across all severity levels among CHWs during the 2021 Tet holiday outbreak compare to pre-pandemic baseline levels that was likely attributable to their COVID-19-related work. Our findings also indicated that CHWs who reported poor sleep conditions and worked in unfavorable working environments might be at particular risk of deterioration to high depression levels. CHWs involved in contact tracing and the organization of quarantine for suspect cases were also at increased risk of deterioration, however, these associations weakened after adjusting for socio-demographic factors, pre-existing health conditions, and sleep/work conditions.

Our results of the effects of COVID-19-related work among CHWs, a cadre of the health workforce that is

Table 5 Factors related to deterioration to high depression levels among study participants

Intercepts	n (%) ^a	Univariate associations			Base model ^b			Model 1 ^{***}			Model 2 ^{***}			Model 3 ^{****}		
		Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value ^c	Odds ratio	95% CI	p-value ^c	Odds ratio	95% CI	p-value ^c	Odds ratio	95% CI	p-value ^c
Sociodemographic																
Age [median, IQR]	35 (31, 42)	0.97	0.94–0.99	0.038	0.98	0.93–1.03	0.465	0.97	0.92–1.03	0.324	0.99	0.93–1.05	0.638	0.98	0.93–1.05	0.612
Sex							0.940			0.986			0.726			0.682
Male	35 (49.3)	Ref.			Ref.			Ref.			Ref.			Ref.		
Female	36 (50.7)	0.95	0.58–1.53	0.822	1.02	0.62–1.69		1.00	0.59–1.71		1.11	0.62–1.98		1.13	0.62–2.07	
Marital status							0.902			0.923			0.795			0.710
Single and divorced	10 (14.1)	Ref.			Ref.			Ref.			Ref.			Ref.		
Married	61 (85.9)	0.70	0.35–1.42	0.328	0.95	0.43–2.11		0.96	0.42–2.19		1.13	0.45–2.80		1.19	0.47–3.02	0.633
Living with children or elderly							0.316			0.430			0.542			
No	19 (26.8)	Ref.			Ref.			Ref.			Ref.			Ref.		
Yes	52 (73.2)	1.45	0.84–2.50	0.177	1.35	0.74–2.45		1.27	0.69–2.34		1.23	0.63–2.42		1.18	0.59–2.35	0.270
Years of job experiences							0.273			0.231			0.314			
<5 y	19 (26.8)	Ref.			Ref.			Ref.			Ref.			Ref.		
5–14 y	32 (45.1)	0.53	0.29–0.96	0.035	0.57	0.29–1.12		0.54	0.27–1.08		0.56	0.25–1.23		0.51	0.23–1.16	
15 y+	20 (28.2)	0.44	0.23–0.86	0.015	0.63	0.22–1.82		0.60	0.20–1.77		0.42	0.12–1.49		0.41	0.11–1.54	0.770
Social economic status							0.021			0.023			0.732			
Upper and middle	36 (50.7)	Ref.			Ref.			Ref.			Ref.			Ref.		
Lower	35 (49.3)	2.02	1.24–3.28	0.005	1.82	1.10–3.02		1.82	1.09–3.05		1.11	0.6–2.05		1.10	0.59–2.04	
Health condition																
Long-term health problems							0.575			0.717			0.722			0.787
No	59 (83.1)	Ref.			Ref.			Ref.			Ref.			Ref.		
Yes	12 (16.9)	1.15	0.60–2.20	0.663	1.23	0.60–2.50		1.14	0.56–2.36		1.16	0.52–2.55		1.12	0.50–2.52	
Mental health disorders							–			–			–			–
No	65 (92.9)	Ref.			Ref.			Ref.			Ref.			Ref.		

Table 5 (continued)

Intercepts	n (%) ^a	Univariate associations			Base model ^b			Model 1 ^{***}			Model 2 ^{***}			Model 3 ^{****}		
		Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio ^c	95% CI	p-value ^d	Odds ratio ^e	95% CI	p-value ^d	Odds ratio ^f	95% CI	p-value ^g
Intensity of direct exposure to SARS-CoV-2																
Yes	5 (2.1)	2.42	0.90–6.47	0.079	2.11	0.77–5.78		2.26	0.8–6.39		1.65	0.52–5.26		1.85	0.56–6.13	
Contact tracing																
Lower	15 (21.1)	Ref.						Ref.						Ref.		0.826
Middle	12 (16.9)	1.14	0.52–2.49	0.739				0.91	0.37–2.22					0.75	0.26–2.11	
Higher	44 (62.0)	1.86	1.02–3.41	0.045				1.5	0.75–3.01					0.97	0.43–2.16	
Organizing isolation																0.805
Lower	21 (29.6)	Ref.						Ref.						Ref.		
Middle	17 (23.9)	1.57	0.81–3.04	0.185				1.45	0.69–3.07					0.83	0.35–1.97	
Higher	33 (46.5)	1.81	1.03–3.20	0.039				1.46	0.73–2.9					1.11	0.50–2.44	
Screening and testing																0.888
Lower	15 (21.1)	Ref.						Ref.						Ref.		
Middle	14 (19.7)	1.22	0.57–2.59	0.609				1.11	0.48–2.58					0.82	0.31–2.16	
Higher	42 (59.2)	1.39	0.75–2.55	0.291				1.08	0.52–2.25					0.83	0.36–1.92	
Other exposure activities																0.362
Lower	29 (40.8)	Ref.						Ref.						Ref.		
Middle	18 (25.4)	1.60	0.87–2.96	0.133				1.60	0.81–3.15					1.62	0.72–3.65	
Higher	24 (33.8)	1.28	0.73–2.24	0.392				1.16	0.63–2.14					0.89	0.43–1.84	
Distribution of confirmed cases in provinces																0.838
No case	47 (66.2)	Ref.						Ref.						Ref.		
Low number of cases	15 (21.1)	1.79	0.97–3.30	0.062				1.83	0.95–3.52					1.13	0.54–2.37	
High number of cases	9 (12.7)	1.51	0.72–3.20	0.276				1.68	0.75–3.76					0.82	0.33–2.04	
Sleep condition																
Hours of sleep per day																0.021
																0.016

Table 5 (continued)

Intercepts	n (%) ^a	Univariate associations			Base model ^b			Model 1 ^{***}			Model 2 ^{***}			Model 3 ^{****}		
		Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio ^c	95% CI	p-value ^d	Odds ratio ^e	95% CI	p-value ^d	Odds ratio ^e	95% CI	p-value ^d
7+ hours	9 (12.7)	Ref.														
Less than 7 h	62 (87.3)	7.23	3.55–14.72	<0.001							Ref.	2.55	1.14–5.69	2.51	1.11–5.69	
Quality of sleep													0.044			0.042
Good	10 (14.1)	Ref.														
Normal	34 (47.9)	7.40	3.60–15.20	<0.001							Ref.	2.36	1.03–5.40	2.45	1.05–5.69	
Not good	27 (38.0)	16.41	7.69–35.02	<0.001							3.09	1.21–7.92	3.17	1.21–8.29		
Work condition																
Working hours													0.879			0.890
<8 h	6 (8.5)	Ref.														
8–9 h	14 (19.7)	1.70	0.64–4.49	0.284							Ref.	1.02	0.33–3.12	1.06	0.34–3.32	
9+ hours	51 (71.8)	5.63	2.38–13.34	<0.001							1.21	0.41–3.52	1.23	0.41–3.68		0.476
Work over-time in weekdays													0.426			
No	4 (5.6)	Ref.														
Yes	67 (94.4)	2.48	0.89–6.92	0.083							Ref.	0.53	0.12–2.40	0.57	0.12–2.60	0.288
Work on weekends													0.293			
No	1 (1.4)	Ref.														
Yes	70 (98.6)	9.55	1.31–69.44	0.026							Ref.	3.50	0.28–42.88	3.53	0.29–43.18	0.044
Working in two places+													0.050			
No	53 (74.6)	Ref.														
Yes	18 (25.4)	2.15	1.22–3.79	0.008							Ref.	1.92	1.01–3.74	2.05	1.04–4.03	<0.001
Work intensity													<0.001			
Not intense	3 (4.2)	Ref.														
Normal	24 (33.8)	4.28	1.28–14.35	0.018							Ref.	1.36	0.36–5.19	1.36	0.35–5.29	
Intense	44 (62.0)	27.58	8.41–90.39	<0.001							5.40	1.37–21.29	5.24	1.28–21.52		0.704
Work security													0.707			
Secure	16 (22.5)	Ref.														
Normal	31 (43.7)	1.64	0.88–3.06	0.116							Ref.	0.73	0.35–1.53	0.73	0.34–1.54	

Table 5 (continued)

Intercepts	n (%) ^a	Univariate associations			Base model [*]			Model 1 ^{**}			Model 2 ^{***}			Model 3 ^{****}		
		Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value [†]	Odds ratio	95% CI	p-value [†]	Odds ratio	95% CI	p-value [†]	Odds ratio	95% CI	p-value [†]
Insecure working environment satisfaction	24 (33.8)	3.42	1.77–6.63	<0.001							0.78	0.33–1.86	0.635	0.78	0.32–1.87	0.637
Satisfied	10 (14.1)	Ref.									Ref.			Ref.		
Normal	45 (63.4)	3.62	1.80–7.27	<0.001							1.43	0.62–3.32		1.45	0.62–3.38	
Disatisfied	16 (22.5)	9.40	4.09–21.63	<0.001							1.65	0.54–5.04		1.65	0.53–5.12	
Relationship with co-workers													0.014			0.014
Good	13 (18.3)	Ref.									Ref.			Ref.		
Normal	26 (36.6)	0.90	0.45–1.79	0.767							1.23	0.56–2.72		1.15	0.51–2.58	
Not good	32 (45.1)	3.01	1.54–5.90	0.001							2.82	1.23–6.45	0.146	2.77	1.19–6.42	0.151
Appreciation/reward system satisfaction																
Satisfied	5 (7.0)	Ref.									Ref.			Ref.		
Normal	34 (47.9)	3.71	1.43–9.60	0.007							2.59	0.86–7.74		2.61	0.85–8.01	
Disatisfied	32 (45.1)	6.86	2.63–17.90	<0.001							2.87	0.91–9.04		2.91	0.91–9.37	
Feeling more overloaded during COVID-19													0.029			0.044
No	22 (31.0)	Ref.									Ref.			Ref.		
Yes	49 (69.0)	3.36	2.00–5.65	<0.001							1.95	1.06–3.58		1.88	1.01–3.51	

^{*}Base model: socio-demographic + pre-existing health condition^{**}Model 1: base model + direct exposure ^{***}Model 2: base model + sleep/work condition ^{****}Model 3: base model + direct exposure + sleep/work condition[†]p-value from likelihood-ratio test^aFrequency and percentage of CHWs' groups of deterioration to high depression levels

Table 6 Comparison of logistic regression models

Model	Matrix		Degrees of freedom (df)	AIC [†]	BIC [†]
	Log likelihood of null model	Log likelihood of full model			
Base model*	− 252.02	− 243.39	10	506.78	555.64
Model 1**	− 252.02	− 236.27	20	512.55	610.26
Model 2***	− 252.02	− 177.91	29	413.83	555.51
Model 3****	− 252.02	− 176.30	39	430.61	621.14

[†] AIC: Akaike's Information Criteria; BIC: Schwarz's Bayesian Information Criteria

*Base model: socio-demographic + pre-existing health condition

Model 1: base model + direct exposure *Model 2: base model + sleep/work condition ****Model 3: base model + direct exposure + sleep/work condition

involved in non-clinical public health activities at community level in many low- and middle-income countries, are comparable with findings from studies among frontline clinical staff caring for COVID-19 patients. A large study among health care workers in China using the Hospital Anxiety and Depression Scale reported 36.1% of medical staff as suffering from depression [22]. Another study from China that used the same PHQ-9 questionnaire as in our study estimated the depression levels among clinical staff treating COVID-19 patients at 57.6% [26]. A pooled analysis of 57 cross-sectional studies using self-reported standardized questionnaires to assess depressive symptoms estimated a prevalence of depression of 43% (range 14.3–99.5%) among health care workers with direct contact to COVID-19 patients [7]. The fact that the prevalence of depression among CHWs in our study was even higher than this summary estimate points to the unrecognized burden of CHWs and other non-clinical public health staff during the COVID-19 pandemic.

The psychological response of health care workers to the pandemic is complex [27]. We found CHWs in Vietnam to be at substantial risk of infection because of their close, frequent contact with potential SARS-CoV-2 sources as well as working longer hours than usual and even working on the weekends. Most CHWs in our study who deteriorated to high depression levels were relatively young, had few years of work experience, low SES, and poor sleep conditions that also contributed to the deterioration. Health workers in Vietnam do usually not receive mental health training, which might have contributed to this development. Particular attention is warranted regarding the mental health well-being of CHWs, especially those working in areas with substantial community transmission. In our study, CHWs with high frequencies of exposure to potential SARS-CoV-2 cases were more likely to

deteriorate to high depression levels. This is congruent with evidence from Ethiopia and China among clinical health care workers [5, 28].

The importance of a healthy workplace to support mental health is evident from the scientific literature [29, 30] as well as our results. Our findings highlight that certain factors that might increase the risk for deterioration to high depression levels during the COVID-19 pandemic include work intensity, insecure work conditions, dissatisfied working environments and reward systems, and poor relationships with co-workers. These risks are unlikely to act in an isolated manner, but, instead, typically interact to exponentially elevate the risks of depression [31]. Such evidence is needed to inform health policy to provide more targeted psychological care for CHWs in the COVID-19 pandemic in Vietnam and elsewhere, as well as to inform health workforce planning for improved community-based response to other infectious disease outbreaks in the future.

Noteworthy strengths of our study include the use of a validated questionnaire, a relatively large sample size, and that we were able to compare depression at two time points in the same population, before the start of the COVID-19 pandemic and during the height of a nationwide outbreak about one year into the pandemic, while most other studies only asked about depression symptoms at one single time point without comparisons. Furthermore, our target population was novel—CHWs, an important cadre of frontline workers in most low- and middle-income countries who perform crucial tasks during the response to COVID-19, but who are often overlooked in occupational mental health interventions. Indeed, all current evidence investigating work-related depression was done among clinical health care workers working in health facilities.

We acknowledge certain limitations of our study. First, reducing our originally 1–30 scaled continuous outcome variable into five and two categories resulted inevitably in a loss of variability. We did so in order to identify those CHWs who might qualify for priority mental health interventions. Second, information on depression symptoms and all covariates were self-reported. Third, recall bias for the pre-COVID period might have affected our results. Since recall is known to improve when following an ordered sequence of events [32], we structured our outcome assessment by starting with questions about the pre-pandemic period first before asking about the Tet holiday period, thereby attempting to reduce recall bias (see Additional file 1). However, given the considerable length of the recall period, we acknowledge the potentially high likelihood of recall bias for the questions relating to the

pre-pandemic period. Unfortunately, no evidence exists on pre-pandemic depression levels using the PHQ-9 questionnaire among CHWs working in public health in Vietnam and in other settings worldwide that could serve as reference. Fourth, sleep and work condition were only captured for the period of the 2021 Tet holiday outbreak, hence we could not rule out reverse causality effects between certain covariates like unhealthy working conditions and poor sleep conditions with deterioration to high depression levels. Fifth, as participation was voluntary and the sample was self-selected, there might have been differences among CHWs who decided to participate compared to those who either did not. We were not able to assess the extent of this potential selection bias. Sixth, because we designed the questionnaire to be completed within 15 min, we might have missed to collect other potentially relevant factors such as feelings of vulnerability or loss of control, concerns about health, the spread of the virus, or the health of family. Further qualitative research might be needed to provide complementary evidence.

Conclusions

We found a substantial increase in depression levels among CHWs in Vietnam due to their COVID-19 related work. In particular, the 4- to 5-fold increase in CHW suffering from severe depression levels is worrisome. CHWs are an indispensable yet often overlooked cadre of work in many low- and middle-income countries and shoulder a heavy psychological burden during the COVID-19 pandemic due to the nature of their work. Targeted psychological support for CHWs is crucial to improve mental health and ensure sustainability of community-based health interventions during COVID-19 and future epidemics.

Abbreviations

CHWs: Community health workers; PHQ-9: Patient Health Questionnaire; SES: Socio-economic status; 95% CIs: 95% Confidence intervals; ORs: Odds ratios; AIC: Akaike's information criteria; BIC: Schwarz's Bayesian information criteria; NIHE: National Institute of Hygiene and Epidemiology; IQR: Interquartile range.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12960-022-00760-x>.

Additional file 1. Supplement 1. Questionnaire in english version.

Additional file 2. Supplement 2. Details of variable management in this project.

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Author contributions

NAH and FV are responsible for conceptualization and methodology. NAH and NVH collected and cleaned data. NAH validated and did formal analyses. NVH, HLQ, KCN, DHL, TQP did data curation and data visualization. NAH and FV wrote original draft preparation. NAH, TQP, FV review and editing manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author (NAH) on reasonable request.

Declarations

Ethics approval and consent to participate

This research was approved by the Human Research Ethics Committee of the Australian National University (Decision No. 2020/655) and the Institutional Review Board in Bio-Medical Research of the National Institute of Hygiene and Epidemiology in Vietnam (NIHE IRB-28/2020).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Supplement 1:

1.1. QUESTIONNAIRE IN ENGLISH VERSION

A. INCLUSION/EXCLUSION CRITERIA

A1. Did you participate in contact tracing/case finding for COVID-19 confirmed cases or suspected cases in the 2021 Tet holiday outbreak?	1. Yes 2. No
A1.1. If yes, In general, how often did you perform these activities?	1. Daily 2. > 3 days per week 3. 1-2 days per week 4. Less than once per week
A2. Did you participate in organizing isolation for COVID-19 confirmed cases and/or organizing quarantine for COVID-19 suspected cases in the 2021 Tet holiday outbreak?	1. Yes 2. No
A2.1. If yes, In general, how often you did perform these activities?	1. Daily 2. > 3 days per week 3. 1-2 days per week 4. Less than once per week
A3. Did you participate in screening for COVID-19 symptoms in the community in the 2021 Tet holiday outbreak? (for example: taking SARS-CoV-2 swab samples, interviewing people for clinical symptoms, or measuring temperature)	1. Yes 2. No
A3.1. If yes, In general, how often you did these activities?	1. Daily 2. > 3 days per week 3. 1-2 days per week 4. Less than once per week
A4. If the answer is No for all three above questions, did you participate in any other activity which involved direct exposure to potential SARS-CoV-2 sources in the 2021 Tet holiday outbreak? (If yes, specify)	1. Yes 2. No
A4.1. If yes, In general, how often you did these activities?	1. daily 2. > 3 days per week 3. 1-2 days per week 4. less than once per week

B. GENERAL INFORMATION

B1. DEMOGRAPHICS	
B1.1. During the 2021 Tet holiday outbreak, what was the level in the health system you were working in?	1. National level (move B1.3) 2. Provincial level 3. District level 4. Commune and lower levels
B1.2. During 2021 Tet holiday outbreak, what was the province/city you were working in? (Skip this question for CHWs at national level)	Dropdown a list of 64 provinces and cities in Vietnam
B1.3. Age	

B1.4. Sex	1. Male 2. Female
B1.5. Marital status	1. Single 2. Married 3. Others
B1.6. Living with children under 5 or elders (65+) in the household	1. Yes 2. No
B1.7. Years of job experience in preventive medicines and public health	(years)
B1.8. Subjective social economic status	1. High 2. Middle 3. Low-middle 4. Low
B2. HEALTH CONDITION	
B2.1. Do you have any long-term health problems, like heart disease, diabetes etc	1. Yes 2. No (Move to B.2.2)
B2.1.1. Which long-term health problem do you have? (Multiple choices)	1. COPD 2. Asthma 3. Rheumatoid arthritis 4. High blood pressure 5. Mental health disorders (Depression/Stress/Anxiety) (skip question B2.2) 6. Hepatitis 7. Obesity 8. Diabetes 9. Chronic kidney disease 10. Any types of cancers 11. Others (specify)
B2.2. Do you have any mental health disorders which has been diagnosed by certified doctors before? (If yes, specify)	1. Yes 2. No (Move to B2.3)
B2.2.1. Which pre-existing mental health disorders do you have? (Multiple choices)	1. Depression 2. Bipolar disorders 3. Schizophrenia 4. Amnesia 5. Personality disorders 6. Others (specify)
B2.3. Have you had any acute/sudden-onset medical problems since the beginning of the 2021 Tet outbreak? (If yes, specify)	1. Yes 2. No
B2.3.1. Which acute/sudden-onset medical problems do you have? (Multiple choices)	1. Stroke 2. Heart attack 3. Brain injury 4. Bone fractures 5. Any types of burns 6. Others (specify)

B3. SLEEP CONDITION

B3.1. Do you have enough time to sleep (at least 7 hours) in the 2021 Tet holiday outbreak?	1. Yes 2. No
B3.2. Please describe the rest you obtain during your night sleep	1. Good 2. Normal 3. Not good 4. Bad

C. WORKING CONDITIONS

C1. In general, how many hours did you usually work per day in the 2021 Tet holiday outbreak (from February 2021)?	1. <7 hours 2. 7-8 hours 3. 9-10 hours 4. >10 hours
C2. Did you work overtime in the 2021 Tet holiday outbreak (from February 2021)? <i>(bonus at least 2 hours in either shift work or night work in at least two days in a week)</i>	1. Yes 2. No
C3. Did you work at weekends in the 2021 Tet holiday outbreak (from February 2021)? <i>(bonus at least 4 days in a month)</i>	1. Yes 2. No
C4. In general, how intense was your job in the 2021 Tet holiday outbreak?	1. Very intense, I cannot complete 50% of tasks during normal work time 2. Intense, I cannot complete 75% of tasks during normal work time 3. OK, I can control all tasks during work time 4. Not intense, I feel I could do many more tasks
C5. Do you have to work in more than one workplace in the 2021 Tet holiday outbreak? <i>Note: Only consider where pay wages for you</i>	1. Yes 2. No
C6. How secure do you feel in your job in the 2021 Tet holiday outbreak?	1. Highly secure 2. Secure 3. OK 4. Insecure
C7. In general, how do you feel about your working environment in the 2021 Tet holiday outbreak?	1. Highly satisfied 2. Satisfied 3. OK 4. Dissatisfied
C8. In general, what is the quality of the work relationship with your employers and co-workers in the 2021 Tet holiday outbreak?	1. Very good 2. Good 3. OK 4. Bad
C9. Did you receive any COVID-19 related monetary welfare?	1. Yes 2. No

C10. Are you satisfied with the appreciation or reward system in the 2021 Tet holiday outbreak?	1. Highly satisfied 2. Satisfied 3. OK 4. Dissatisfied
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D. WORKLOAD

D1. On average, how often did you feel overloaded in the 2021 Tet holiday outbreak?	1. Often
	2. Sometimes
	3. Almost never
	4. Never
D2. On average, how often did you feel overloaded in six months before COVID-19 pandemic (from June 2019 to December 2019)?	1. Often
	2. Sometimes
	3. Almost never
	4. Never

F. DEPRESSION SYMPTOMS AS PER PATIENT HEALTH QUESTIONNAIRE 9

How often have you experienced any of the following problems?

	On average during the six months before COVID-19 pandemic				2021 Tet holiday outbreak			
	>4 days/week	3-4 days/week	1-2 days/week	Not at all	>4 days/week	3-4 days/week	1-2 days/week	Not at all
F1. Little interest or pleasure in doing things	0	1	2	3	0	1	2	3
F2. Feeling down, depressed, or hopeless	0	1	2	3	0	1	2	3
F3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3	0	1	2	3
F4. Feeling tired or having little energy	0	1	2	3	0	1	2	3
F5. Poor appetite or overeating	0	1	2	3	0	1	2	3
F6. Feeling bad about yourself or that you are a failure or have let yourself or your family down	0	1	2	3	0	1	2	3
F7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3	0	1	2	3
F8. Moving or speaking so slowly that other people could have noticed. Or the opposite being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3	0	1	2	3
F9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3	0	1	2	3

1.2. QUESTIONNAIRE IN VIETNAMESE VERSION

A. Thông tin chung:

A1. Anh/Chị có tham gia điều tra truy vết các trường hợp tiếp xúc với ca dương tính COVID-19 tại cộng đồng trong đợt dịch COVID-19 Tết Tân Sửu không?	1. Có 2. Không
A1.1. Anh/Chị có thường xuyên thực hiện công việc đó không?	1. Hàng ngày 2. >3 ngày/tuần 3. 1-2 ngày/tuần 4. Ít hơn 1 ngày/tuần
A2. Anh/Chị có thực hiện tổ chức cách ly ca nghi ngờ hoặc ca khẳng định mắc COVID-19 trong đợt dịch COVID-19 Tết Tân Sửu không? (Bao gồm cả hoạt động cách ly những người nước ngoài nhập cảnh vào Việt Nam)	1. Có 2. Không
A2.1. Anh/Chị có thường xuyên thực hiện công việc đó không?	1. Hàng ngày 2. >3 ngày/tuần 3. 1-2 ngày/tuần 4. Ít hơn 1 lần/tuần
A3. Anh/Chị có tham gia sàng lọc COVID-19 tại cộng đồng trong đợt dịch COVID-19 Tết Tân Sửu không? (ví dụ: lấy mẫu các đối tượng nghi ngờ và đo nhiệt độ tại các điểm công cộng)	1. Có 2. Không
A3.1. Anh/Chị có thường xuyên thực hiện công việc đó không?	1. Hàng ngày 2. >3 ngày/tuần 3. 1-2 ngày/tuần 4. Ít hơn 1 lần/tuần
A4. Anh/Chị có tham gia vào bất kỳ hoạt động nào khác có nguy cơ tiếp xúc với nguồn lây nhiễm COVID-19 trong đợt dịch COVID-19 Tết Tân Sửu không?	1. Có 2. Không
A4.1. Vui lòng liệt kê tên các hoạt động đó	
A4.2. Anh/Chị có thường xuyên thực hiện công việc đó không?	1. Hàng ngày 2. >3 ngày/tuần 3. 1-2 ngày/tuần 4. Ít hơn 1 lần/tuần

B. THÔNG TIN CỦA NGƯỜI THAM GIA

B1. THÔNG TIN NHÂN KHẨU HỌC	
B1.1. Hiện nay, Anh/Chị đang công tác tại tuyến nào? (Vui lòng chọn tuyến cao nhất)	1. Tuyến trung ương (Chuyển B1.3) 2. Tuyến tỉnh 3. Tuyến huyện 4. Tuyến xã/dưới xã (thôn, bản, ấp...)
B1.2. Anh/chị đang công tác tại tỉnh/thành phố nào?	Danh sách 64 tỉnh thành
B1.3. Năm sinh dương lịch của Anh/Chị	
B1.4. Giới tính của Anh/Chị	1. Nam 2. Nữ
B1.5. Tình trạng hôn nhân của Anh/Chị	1. Độc thân 2. Đã kết hôn 3. Khác (ly thân/ly hôn...)

B1.6. Anh/Chị có đang sống cùng nhà với người già (trên 65 tuổi) hoặc trẻ em dưới 5 tuổi không?	1. Có 2. Không
B1.7. Số năm Anh/Chị công tác trong lĩnh vực Y tế công cộng	(năm) 1. Khá 2. Trung bình 3. Trung bình - thấp 4. Thấp
B2. TÌNH TRẠNG SỨC KHỎE	
B2.1. Hiện Anh/Chị có đang mắc bệnh lý mạn tính nào không?	1. Có 2. Không
B2.1.1. Anh/Chị đang mắc bệnh lý mạn tính nào? (Câu hỏi nhiều lựa chọn)	1. Viêm phổi tắc nghẽn mạn tính (COPD) 2. Hen suyễn 3. Viêm khớp mạn 4. Cao huyết áp 5. Trầm cảm 6. Viêm gan mạn 7. Béo phì 8. Tiểu đường 9. Bệnh thận mạn 10. Ung thư 11. Khác (ghi rõ)
B2.1.1.1. Vui lòng liệt kê tên các bệnh lý mạn tính khác	
B2.2. Anh/Chị đã từng mắc bất kì bệnh/triệu chứng sức khỏe tâm thần nào được chẩn đoán bởi nhân viên y tế chưa?	1. Đã từng 2. Chưa bao giờ
B2.2.1. Anh/Chị đã từng mắc bệnh/triệu chứng sức khỏe tâm thần nào? (Câu hỏi nhiều lựa chọn)	1. Trầm cảm 2. Rối loạn cảm xúc lưỡng cực 3. Tâm thần phân liệt 4. Giảm/mất trí nhớ 5. Rối loạn phát triển 6. Khác (ghi rõ)
B2.2.1.1. Vui lòng liệt kê tên các bệnh/triệu chứng sức khỏe tâm thần khác	
B2.3. Anh/Chị có bị bất kỳ tổn thương/chấn thương trên cơ thể nào tính từ khi bắt đầu đợt dịch COVID-19 Tết Tân Sửu (27/01/2021) không? <i>ví dụ, gãy tay, chân</i>	1. Có 2. Không
B2.3.1. Anh/Chị đã bị tổn thương/chấn thương nào? (Câu hỏi nhiều lựa chọn)	1. Đột quỵ 2. Nhồi máu cơ tim 3. Chấn thương sọ não 4. Chấn thương xương, mô mềm (ví dụ, gãy tay, chân) 5. Bỏng 6. Khác (ghi rõ)
B2.3.1.1. Vui lòng liệt kê các tổn thương/chấn thương khác	
B3. TÌNH TRẠNG GIÁC NGỦ	

B3.1. Trong đợt dịch COVID-19 Tết Tân Sửu, Anh/Chị có được ngủ có được ngủ tối thiểu 7 giờ/ngày không? <i>hoặc ngủ ít hơn 7 giờ/ngày nhưng luôn ở trạng thái tỉnh táo mà không cần sự hỗ trợ của chất kích thích như cafe, trà...</i>	1. Có 2. Không
B3.2. Chất lượng giấc ngủ của Anh/Chị trong đợt dịch COVID-19 Tết Tân Sửu?	1. Tốt 2. Bình thường 3. Kém 4. Rất kém

C. ĐIỀU KIỆN LÀM VIỆC

C1. Thời gian làm việc trung bình 1 ngày trong đợt dịch COVID-19 Tết Tân Sửu? <i>Tổng thời gian làm việc không chỉ riêng cho hoạt động phòng chống dịch COVID-19</i>	1. <7 giờ 2. 7 - 8 giờ 3. 9 - 10 giờ 4. > 10 giờ
C2. Anh/Chị có phải làm việc ngoài giờ hành chính trong đợt dịch COVID-19 Tết Tân Sửu không? <i>chọn Có nếu Anh/Chị làm thêm ít nhất 2 giờ/ngày và ít nhất 2 ngày/tuần)</i>	1. Có 2. Không
C3. Anh/Chị có phải làm việc vào Thứ 7 và/hoặc Chủ nhật trong đợt dịch COVID-19 Tết Tân Sửu không? <i>chọn Có nếu Anh/Chị làm ít nhất 4 ngày Thứ 7/Chủ nhật trong tháng</i>	1. Có 2. Không
C4. Cường độ công việc của Anh/Chị trong đợt dịch COVID-19 Tết Tân Sửu như thế nào? <i>Chọn "Rất căng thẳng" nếu không thể hoàn thành được 1 nửa khối lượng công việc cần làm trong 8 tiếng; "Không căng thẳng" nếu kiểm soát công việc tốt</i>	1. Rất căng thẳng 2. Căng thẳng 3. Bình thường 4. Không căng thẳng
C5. Anh/Chị có làm việc kiêm nhiệm ở cơ quan nào khác trong đợt dịch COVID-19 tết Tân Sửu không? <i>(chỉ tính các đơn vị mà Anh/Chị được trả lương khi làm việc)</i>	1. Có 2. Không
C6. Anh/Chị có cảm thấy an toàn khi làm việc trong đợt dịch COVID-19 tết Tân Sửu không?	1. Rất an toàn 2. An toàn 3. Bình thường 4. Không an toàn
C7. Anh/Chị có hài lòng với môi trường làm việc trong đợt dịch COVID-19 tết Tân Sửu không?	1. Rất hài lòng 2. Hài lòng 3. Bình thường 4. Không hài lòng
C8. Anh/Chị cảm thấy mối quan hệ với các đồng nghiệp trong đợt dịch COVID-19 tết Tân Sửu như thế nào?	1. Rất tốt 2. Tốt 3. Bình thường 4. Không tốt
C9. Anh/Chị có được hỗ trợ thêm kinh phí liên quan tới các hoạt động phòng chống dịch COVID-19 không?	1. Có 2. Không
C10. Anh/Chị có hài lòng với chế độ đãi ngộ (cơ chế thưởng/phạt) trong hoạt động phòng chống dịch COVID-19 không?	1. Rất hài lòng 2. Hài lòng 3. Bình thường 4. Không hài lòng

D. KHỐI LƯỢNG CÔNG VIỆC

D1. Anh/Chị có thường xuyên cảm thấy quá tải bởi khối lượng công việc trong đợt dịch COVID-19 tết Tân Sửu (bắt đầu từ 27/01/2021) không?	1. Thường xuyên 2. Thỉnh thoảng 3. Hiếm khi 4. Không bao giờ
D2. Trong vòng 6 tháng trước dịch COVID-19 (6/2019 – 12/2019), Anh/Chị có thường xuyên cảm thấy quá tải bởi khối lượng công việc không?	1. Thường xuyên 2. Thỉnh thoảng 3. Hiếm khi 4. Không bao giờ

E. TÌNH TRẠNG TRẦM CẢM

Vui lòng chọn tần suất Anh/Chị cảm thấy:

	Trước dịch COVID-19				Trong dịch COVID-19			
	>4 ngày/tuần	3-4 ngày/tuần	1-2 ngày/tuần	Hoàn toàn không	>4 ngày/tuần	3-4 ngày/tuần	1-2 ngày/tuần	Hoàn toàn không
F1. Không hứng thú với các công việc thường ngày	0	1	2	3	0	1	2	3
F2. Buồn chán, dễ cáu gắt	0	1	2	3	0	1	2	3
F3. Khó ngủ hoặc ngủ quá nhiều	0	1	2	3	0	1	2	3
F4. Cơ thể mệt mỏi/uể oải	0	1	2	3	0	1	2	3
F5. Chán ăn hoặc ăn quá nhiều	0	1	2	3	0	1	2	3
F6. Bản thân không làm được gì có ích	0	1	2	3	0	1	2	3
F7. Khó tập trung vào các hoạt động thông thường như đọc báo, xem tivi	0	1	2	3	0	1	2	3
F8. Cơ thể chậm chạp, ì ạch hoặc kích thích, vận động quá mức	0	1	2	3	0	1	2	3
F9. Có ý nghĩ đến tử tử hoặc tự làm tổn thương bản thân mà trước đây chưa từng có	0	1	2	3	0	1	2	3

Supplement 2: Details of variable management in this project

Depression levels

We used the Vietnamese version of PHQ-9 to quantify depression levels among respondents. The PHQ-9 has been in widespread use around the world since its development in 1999 (12), and its Vietnamese version has been used in several previous studies(13–16). The PHQ-9 contains nine items about the frequency of depression-related symptoms. Each item has four response categories: “Not at all” (=0), “Several days” (=1), “More than half of the days” (=2), and “Nearly every day” (=3), resulting in a total range score from 0 to 27. The recommended cut-off points for depression thresholds are as follows: normal/minimal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) (17).

We asked self-reported depression levels at two time points: six months before the pandemic and during the 2021 Tet holiday outbreak. For regression models, the outcome variable "deterioration to high depression levels" was created. People who reported normal/minimal, mild, or moderate depression levels before the pandemic and an increase to moderately severe or severe levels during the 2021 Tet holiday outbreak; and those with moderately severe depression levels before the start of the pandemic and an increase to severe levels during the 2021 Tet holiday outbreak were categorized as having deteriorated to high depression levels.

Socio-demographic characteristics

Age was collected as a discrete variable and subsequently categorized into six groups: 18 to 29 years, 30 to 34 years, 35 to 39 years, 40 to 44 years, 45 to 49 years, or 50 years or older. Sex was defined as a binary variable for males and females. Marital status was comprised of three groups: single, married, or divorced/widowed. Living with children under the age of five or with elderly persons was defined as a binary variable (yes/no). Self-reported SES was captured in three levels: upper, middle, or lower. Years of experience in public health and

preventive medicine was collected as a discrete variable and then categorized into six levels: less than 5 years, 5 to 9 years, 10 to 14 years, 15 to 19 years, 20 to 24 years, or 25 years or higher.

Pre-existing health conditions

We asked if respondents had been diagnosed with any pre-existing physiological or mental health conditions, or an acute medical issue (yes/no).

Intensity of exposure to SARS-CoV-2 sources

Work-related intensity of exposure to SARS-CoV2 was assessed through four questions on the estimated weekly frequencies of four activities: 1) the participation in contact tracing/case finding; 2) the organization of quarantine for suspected cases and close contacts; 3) the screening for COVID-19 symptoms in the community by taking swab samples or measuring temperature; and 4) any other activities that required direct exposure to potential SARS-CoV-2 cases. Answers were categorized into five levels for each question: not performed, performed less than one day per week, 1 to 2 days, 3 to 6 days, or daily. For regression models, exposure intensity was re-categorized into three groups: low (those who did not perform a particular activity), middle (performed less than one day, 1 to 2 days, or 3 to 6 days per week), and high (performed daily).

Sleep condition

We asked two questions about sleep conditions, including the estimated number of hours to sleep daily and the self-reported quality of sleep (good/normal/not good).

Work condition

Work condition referred to changes in feeling overloaded before the pandemic and during the 2021 Tet holiday outbreak (less, no change, more); estimated working hours per day; working overtime (defined as working at least two hours more than normal or work during night time unless stipulated), working at weekends (yes/no); and the number of paid

workplaces for respondents. We also asked participants five questions on their overall perceived working environment: job intensity (not intense/normal/intense); job security (secure/normal/insecure); relationship with employers and co-workers (good/normal/not good); satisfaction with the working environment; and the appreciation or reward system (satisfied/normal/dissatisfied).

Case load during the 2021 Tet holiday outbreak

Using the national COVID-19 incidence database, we used the number of confirmed COVID-19 cases per province during the 2021 Tet holiday outbreak to categorize CHWs into three groups: CHWs working in provinces with zero confirmed case; with low case numbers (<27 cases); or high case numbers (≥ 27 cases).

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Chapter 6. Literature review

*Assessing the robustness of SARS-CoV-2 vaccine efficacy trials:
systematic review and meta-analysis*

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List of Abbreviations – Chapter 6

COVID-19	Coronavirus 2019
RCTs	Randomized controlled trials
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
FI	Fragility index
PRISMA	the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement
MeSH	Search medical subject headings
IQR	Interquartile ranges

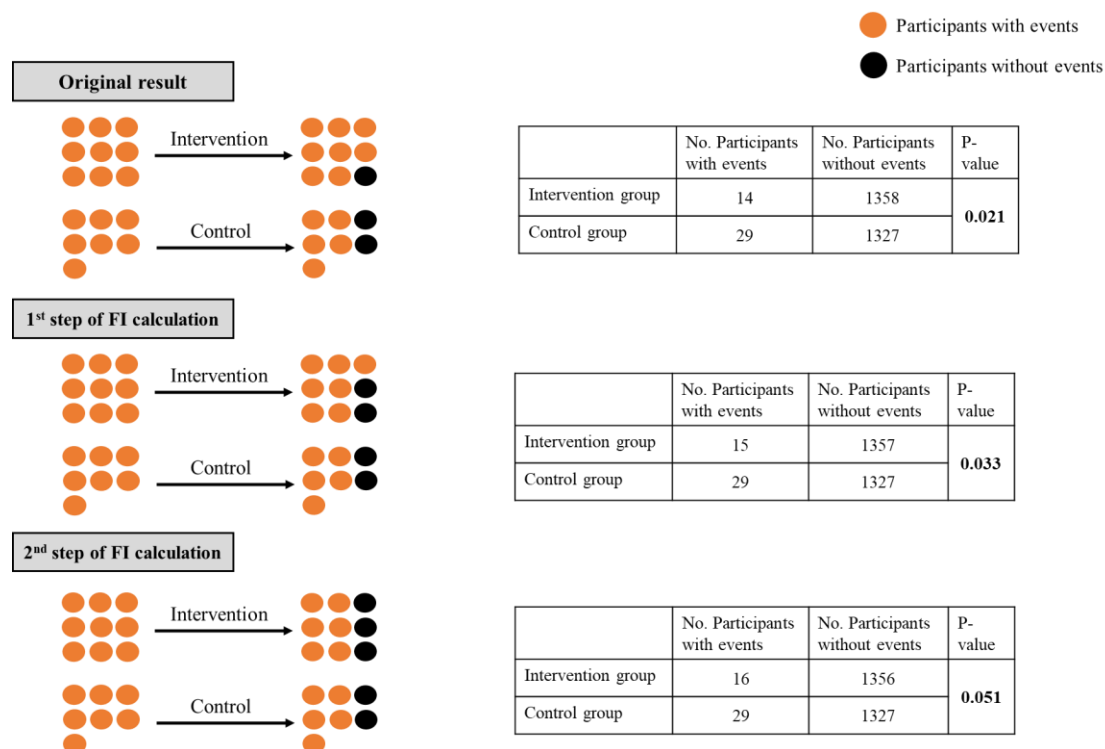
Prologue

Background

Several SARS-CoV-2 vaccines have been developed, and many indicated good profiles with high vaccine efficacy reported. However, the robustness of these vaccine trial results has not been investigated to date. Given how crucial SARS-CoV-2 vaccines have become in the global fight against COVID-19, this constitutes a major evidence gap.

Fragility index (FI) and fragility quotient (FQ) were developed to address the robustness of SARS-CoV-2 vaccines. The FI constitutes the minimum number of trial participants whose outcome event would need to change for the statistical significance of the entire trial to switch from ‘statistically significant’ to ‘statistically not significant’, with smaller FI indicating more fragile results. The FI does not aim to replace or invalidate the use of p-values, but rather to provide a complementary, easily interpretable metric to gauge how robust a trial result is. Since the FI is an absolute measure and does not account for sample size, comparisons across different studies or establishing a set of reference values to categorize fragility levels proved difficult. To overcome this, the fragility quotient (FQ) was proposed by Ahmed et al. in 2016 as a relative measure of trial robustness. The FQ is simply the FI divided by the trial sample size, and thus expresses the proportion of trial participants whose outcome events would need to change to non-events in order to turn a trial result from ‘statistically significant’ to ‘statistically not significant’.

Below is an example of FI calculation. There are 1,372 participants in the intervention group and 1,356 participants in the control group in the original result, in which, 14 and 29 participants experience events at the end of the trial, respectively. The original p-value is 0.021 which is considered statistically significant (assumed I set the threshold of the p-value as 0.05). In the first step of FI calculation, I convert one participant from not having events to having events in the intervention group. Therefore, I have 15 participants with events in the intervention group with the total participants identical (1,372 participants). The recalculated p-value after the replacement is 0.033. In the next step, I keep converting one participant from not having events to having events in the intervention group which changes the total number of people with events in the intervention group is 16. The recalculated p-value is 0.051 which is considered statistically not significant. The FI in this example is 2 indicating that if 2 patients in the intervention group were converted from not having events to having events, the study would lose statistical significance ($p > 0.05$).



Student's role

With the encouragement, support, and guidance of my academic supervisor (Dr. Florian) and my colleague (Ms. Ha-Linh, and my best friend), I, for the first time, did conduct a whole systematic review (SR) and meta-analysis (MA) followed COCHRANE and PRISMA guidelines. The idea for this study came coincidentally when I read about FI in an online workshop. After discussing and sharpening this idea with Dr. Florian, we have tried to invite other authors who published articles on FI into our study, but unfortunately, the collaboration was not succeeded.

I registered the protocol of this study in the International Prospective Register of Systematic Reviews (PROSPERO) prior to commencing data collection (protocol number CRD42021258455). This project gave me an opportunity to approach and practice a new software – COVIDENCE, which is very helpful for screening and extracting data for an SR. After extracting, cleaning, and analyzing the data, I prepared a draft manuscript and finalized it with Dr. Florian.

Achievement

This chapter contains materials of an advanced manuscript to submit for peer-review publication that is under review by the Eurosurveillance journal. The abstract of this work was accepted for an oral presentation to the European Scientific Conference on Applied

Infectious Disease Epidemiology (ESCAIDE) which will take place on 23-25 November 2022 as a hybrid event in Stockholm and online.

Abstract

Background

Vaccines against SARS-CoV-2 have become the most important intervention against the ongoing COVID-19 pandemic, and good efficacy profiles have been reported from several randomized controlled trials (RCTs). However, no evidence exists to date about how robust these reported SARS-CoV-2 vaccine trial results are.

Methods

We conducted a COCHRANE and PRISMA-compliant systematic review and meta-analysis of all SARS-CoV-2 trials published worldwide until 26 April 2022. We calculated the fragility index (FI) and fragility quotient (FQ) incl. interquartile ranges (IQR) for all primary outcomes of included studies and investigated their associations with selected trial characteristics (risk of bias, blinding type, vaccine efficacy [VE], trial phase, sample size, and loss to follow up [LTFU]) using Wilcoxon rank sum tests and Kruskal-Wallis H tests. We used Spearman's correlation coefficients and scatter plots to quantify and visualize the associations between FI and FQ with trial sample size, LTFU, and VE.

Results

We included 29 studies out of 4,191 screened records. The median sample size for all outcomes was 15,506 (IQR: 8,950 – 27,210). The overall median FI and FQ was 53.5 (IQR: 17-124) and 0.41% (IQR: 0.18-0.8%), respectively. While FI was positively associated with trial sample size (p-value <0.001), FQ was positively associated with VE (p-value 0.01). The Spearman correlation coefficient for FI with sample size was moderately strong (0.618), and weakly positive for FI and FQ with VE (0.126 and 0.353, respectively). The FI exceeded the number LTFU in 38 (95%) outcomes.

Conclusions

SARS-CoV-2 VE trial results were prone substantially high robustness levels compared to previous FI reviews. While the trial robustness increased with sample size, both FI and FQ showed considerable variation, suggesting the need for careful contextualization of results, particularly for RCTs with high VE and low percentage LTFU. We recommend the inclusion of FI and FQ in the Cochrane Handbook for Systematic Reviews of Interventions as an additional measure to improve interpretation of trial results, in particular for interventions as pivotal as SARS-CoV-2 vaccines in the midst of a global pandemic.

Lesson learned

This study is my first time involved in and leading an SR and MA. I have learned how to conduct an SR and MA step by step that followed some standard guidelines, such as COCHRANE and PRISMA. I considered it the hardest study because its findings bring the highest level of evidence. I actually feel beyond myself after this project. I am more confident about my intellectual elite for my future work and career.

Public health impact

My study constitutes the largest assessment to date of the robustness of SARS-CoV-2 vaccine trials. Given how crucial vaccines have become in the fight against COVID-19, my research closes a major, highly topical evidence gap. I was able to draw important conclusions for COVID-19-related public health policy and the interpretation of vaccine trial results more generally.

Results from SARS-CoV-2 vaccine efficacy trials were substantially more robust than from trials in other areas and other types of interventions. While robustness increased with trial size, both the FI and FQ showed considerable variability across several important trial characteristics. While the absence of other similarly large FI reviews, in particular of methodologically sound FI reviews of vaccine trials, limits a meaningful contextualization of our results, I believe that the overall high FI found in this study truly reflects substantially higher robustness levels of SARS-CoV-2 vaccine efficacy trials compared to other interventions for which FI have been calculated before.

Recommendation

The FI and FQ provide important insights for the interpretation of vaccine trials in particular. From these findings, I recommend their reporting alongside established parameters as a complementary indicator of how fragile results are to changes in outcome events. This is specifically relevant for interventions as pivotal as SARS-CoV-2 vaccines in the midst of a global pandemic.

Appendix. Advanced Manuscript

Hoang NA, Quach HL, Hoang VN, Tran VT, Pham QT, Vogt F. **Assessing the robustness of SARS-CoV-2 vaccine efficacy trials: systematic review and meta-analysis.** Under review by Eurosurveillance.

Eurosurveillance

Assessing the robustness of SARS-CoV-2 vaccine efficacy trials: systematic review and meta-analysis

--Manuscript Draft--

Manuscript Number:	
Full Title:	Assessing the robustness of SARS-CoV-2 vaccine efficacy trials: systematic review and meta-analysis
Article Type:	Review
Keywords:	fragility index; fragility quotient; COVID-19; SARS-CoV-2; vaccine efficacy
Corresponding Author:	Ha-Linh Quach Duke-NUS Medical School Centre for Ageing Research and Education Singapore, SINGAPORE
Corresponding Author's Institution:	Duke-NUS Medical School Centre for Ageing Research and Education
First Author:	Ngoc-Anh Hoang
Order of Authors:	Ngoc-Anh Hoang Ha-Linh Quach Ngoc Van Hoang Thien Van Tran Thai Quan Pham Florian Vogt
Abstract:	Background Vaccines are among the most important interventions in the COVID-19 pandemic. Good efficacy profiles have been reported but the robustness of SARS-CoV-2 vaccine trial results has not yet been established. Methods We conducted a Cochrane and PRISMA-compliant systematic review and meta-analysis of SARS-CoV-2 vaccine efficacy (VE) trials published worldwide until 26 April 2022. We calculated the fragility index (FI) and fragility quotient (FQ) incl. interquartile ranges (IQR) for all studies, and assessed their associations with selected trial characteristics using Wilcoxon rank sum tests and Kruskal-Wallis H tests. We also used Spearman correlation coefficients and scatter plots to quantify the strength of correlation of FI and FQ with trial characteristics. Results Out of 4,191 screened records, we included 29 trials with 40 primary outcomes, comprising 720,291 participants with a median sample size per outcome of 15,506 (IQR 8,950-27,210). The median FI and FQ was 53.5 (IQR 17-124) and 0.41% (IQR 0.18-0.8%), respectively. The FI was positively associated with sample size (p-value <0.001), and the FQ was positively associated with VE (p-value 0.01). The Spearman correlation coefficient for FI with sample size was moderately strong (0.618), and weakly positive for FI and FQ with VE (0.126 and 0.353, respectively). Conclusions This was the largest study on trial robustness to date. Robustness increased with sample size and varied considerably across several other important trial characteristics. The FI and FQ are valuable complementary parameters for the interpretation of VE trial results in particular, and should be reported alongside established outcome measures.

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Word count of the text	3009
Has informed consent been obtained from persons whose details are described in your manuscript (or from the persons' guardians) that this information may be published? The authors may be requested to provide proof that patient consent has been obtained before we can publish the article.	Not relevant
If the answer to the above question is no, explain here why informed consent was not obtained.	
Please copy/paste your covering letter here.	Editorial Board Eurosurveillance Dear Editorial Team, On behalf of my co-authors, I would like to submit our original research article titled 'Assessing the robustness of SARS-CoV-2 vaccine efficacy trials: systematic review and meta-analysis' for publication in Eurosurveillance. This submission follows the positive appraisal of our pre-submission inquire and invitation to submit by editor Trevor Grizzel on 4 May 2022. In the meantime, this work has also been accepted as an oral presentation at the European Scientific Conference on Applied Infectious Disease Epidemiology in Stockholm in November 2022. To our knowledge, this is the first comprehensive assessment of the robustness of SARS-CoV-2 vaccine efficacy trials. Given how crucial vaccines have become in the global fight against COVID-19, this study closes a major, highly topical evidence gap. We therefore believe that our work is suitable for your journal and of high interest to your readers. In this systematic review and meta-analysis, which closely follows Cochrane and PRISMA guidance, we use 'trial fragility' to assess the robustness of SARS-CoV-2 vaccine trial results. The concept of trial fragility was developed in the 1990s in response to the recognized shortfalls of p-value based reporting of statistical significance in randomized controlled trials (RCTs), as a way to quantify the robustness of results, or lack thereof. The 'fragility index' (FI) and 'fragility quotient' (FQ) are the main measures used in this approach. Briefly, the FI and FQ represent the minimum number and percentage of trial participants whose outcome event would need to change for the trial result to switch from 'statistically significant' to 'statistically not significant'. The FI and FQ have becoming increasingly recognized concepts in clinical trial methodology and are now being reported frequently for RCTs and in systematic reviews across a wide range of topics. These measures do not aim to replace or invalidate the use of p-values, but rather to provide additional, easily interpretable metrics to gauge the robustness of a trial result.

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	After screening over 4,000 records, we included 29 trials with 40 primary outcomes, comprising a total of 720,291 participants. We found substantially higher levels of trial robustness [median FI 53.5 with inter-quartile range (IQR) 17-124; median FQ 0.41% with IQR 0.18-0.8%] than reported in trials from other areas and other types of interventions. While robustness increased with trial size, both the FI and FQ showed substantial variability across a range of important trial characteristics such as blinding type, percentage loss-to-follow-up and effect size. Our findings have significant implications for the interpretation of vaccine trial results, in particular for interventions as pivotal as SARS-CoV-2 vaccines in the midst of a global pandemic. Given the value of FIs and FQs for the complementary interpretation of trial results, we recommend their reporting alongside established outcome measures of RCT results. We believe that our work is of high scientific value and importance for global medical research and practice with regards to SARS-CoV-2 vaccine trials, arguably the most important emerging infectious disease of our times. We confirm that the manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with the submission to Eurosurveillance. All authors have confirmed that they have no conflict of interest to declare. Thank you for your consideration of our work. Kind regards, Ha-Linh Quach National Centre for Epidemiology and Population Health, College of Health and Medicine, Australian National University, Canberra, Australia Department of Communicable Disease Control, National Institute of Hygiene and Epidemiology, Hanoi, Vietnam Centre for Ageing Research and Education, Duke-NUS Medical School, National University of Singapore, Singapore Email: linh.quach@anu.edu.au
If a collective author is included (e.g. a working group or disease-specific network) and if the persons comprising the group fulfil all four ICMJE authorship criteria and are to be included as collective author in the published article and in PubMed, please list each person here. The list of collective authors can contain only names (not countries, institutions, titles or other words) and should be written in the format FirstName LastName, separated by commas. The contribution of the collective author should be stated in the section Authors' contributions. If the members of the group do not fulfil the ICMJE authorship criteria, such a group is mentioned in the author list as "on behalf of the xxx group" and the	

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names of the group members can be listed under Acknowledgements.	
Authors' contributions: the contribution of each author to the article, including collective author if applicable, should be described here. This information will appear at the end of the published article.	NAH, PQT, and FV conceptualized the study. NAH conducted the data curation. NVH and TVT provided resources and software for the analysis. NAH and HLQ did the initial data cleaning and screening. NAH did the data analysis. FV and PQT supervised and validated the data collection and analysis. NAH and NVH reviewed the application of the methodology. TVT and NVH contributed to the visualization of results. FV was in charge of the funding acquisition. NAH wrote the first draft with input from HLQ and FV. NAH and FV wrote the final draft with revision and editing from all co-authors.
Please include any acknowledgements here. You may acknowledge anyone who has helped you with any aspect of the report, including groups of experts who do not fulfil all four ICMJE authorship criteria but who can be acknowledged in this section. It is always the corresponding author's responsibility to obtain permission from anyone being acknowledged.	This research was conducted as part of the Master of Applied Epidemiology program of the Australian National University. NAH and HLQ are trainees of the program and received scholarships from the ASEAN-Australia Health Security Fellowship by the Commonwealth Department of Foreign Affairs and Trade.
Have these findings already been published or is publication of these findings planned in a different format (e.g.: national or European report)?	A preprint can be found at http://dx.doi.org/10.2139/ssrn.4161714
Do you have any conflicts of interest regarding your manuscript? If yes, please specify. If no, enter 'None'.	None
Author Comments:	

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Title: Assessing the robustness of SARS-CoV-2 vaccine efficacy trials: systematic review and meta-analysis

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Keywords: fragility index, fragility quotient, robustness, randomized controlled trial, COVID-19, SARS-CoV-2, vaccine efficacy

Abstract text:

Background

Vaccines are among the most important interventions in the COVID-19 pandemic. Good efficacy profiles have been reported but the robustness of SARS-CoV-2 vaccine trial results has not yet been established.

Methods

We conducted a Cochrane and PRISMA-compliant systematic review and meta-analysis of SARS-CoV-2 vaccine efficacy (VE) trials published worldwide until 26 April 2022. We calculated the fragility index (FI) and fragility quotient (FQ) incl. interquartile ranges (IQR) for all included studies, and assessed their associations with selected trial characteristics using Wilcoxon rank sum tests and Kruskal-Wallis H tests. We also used Spearman correlation coefficients and scatter plots to quantify the strength of correlation of FI and FQ with trial characteristics.

Results

Out of 4,191 screened records, we included 29 trials with 40 primary outcomes, comprising 720,291 participants with a median sample size per outcome of 15,506 (IQR 8,950-27,210). The median FI and FQ was 53.5 (IQR 17-124) and 0.41% (IQR 0.18-0.8%), respectively. The FI was positively associated with sample size (p-value <0.001), and the FQ was positively associated with VE (p-value 0.01). The Spearman correlation coefficient for FI with sample size was moderately strong (0.618), and weakly positive for FI and FQ with VE (0.126 and 0.353, respectively).

Conclusions

This was the largest study on trial robustness to date. Robustness increased with sample size and varied considerably across several other important trial characteristics. The FI and FQ are valuable complementary parameters for the interpretation of VE trial results in particular, and should be reported alongside established trial outcome measures.

Statements

Ethics statement:

Ethics approval was not necessary since we only collected and synthesized data from already published studies for which informed consent had been obtained.

Funding statement:

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This research was conducted as part of the Master of Applied Epidemiology program of the Australian National University. NAH and HLQ are trainees of the program and received scholarships from the ASEAN-Australia Health Security Fellowship by the Commonwealth Department of Foreign Affairs and Trade.

Conflict of interest:

The authors declare that they have no conflict of interest.

Authors' contributions:

NAH, PQT, and FV conceptualized the study. NAH conducted the data curation. NVH and TVT provided resources and software for the analysis. NAH and HLQ did the initial data cleaning and screening. NAH did the data analysis. FV and PQT supervised and validated the data collection and analysis. NAH and NVH reviewed the application of the methodology. TVT and NVH contributed to the visualization of results. FV was in charge of the funding acquisition. NAH wrote the first draft with input from HLQ and FV. NAH and FV wrote the final draft with revision and editing from all co-authors.

Assessing the robustness of SARS-CoV-2 vaccine efficacy trials: systematic review and meta-analysis

Introduction

Several vaccines against SARS-CoV-2 have been and are being developed, and the scientific evidence about their efficacy is growing rapidly.¹ There are now several SARS-CoV-2 vaccines administered at scale around the world for which good efficacy profiles have been reported.²⁻⁴ However, no solid evidence exists to date about the robustness of SARS-CoV-2 vaccines trial results. Given how crucial SARS-CoV-2 vaccines have become in the global fight against COVID-19, this constitutes a major evidence gap.

Robustness of results from randomized controlled trials (RCT), or lack thereof, has been long recognized as an important issue in medical research.^{5,6} Undue emphasis is often put on p-values, often set at an alpha error level of 0.05 when interpreting trial results,⁷⁻⁹ though it is known that statistical significance in trials can easily be lost by small changes of only a few events in the intervention or control group.¹⁰ In response to this, the concept of 'trial fragility' was developed by Walter et al. in the 1990s as a way to quantify how robust (or fragile) results from RCT's are, with the fragility index (FI) as the main measure.¹¹ In short, the FI constitutes the minimum number of trial participants whose outcome event would need to change for the statistical significance of the entire trial to switch from 'statistically significant' to 'statistically not significant', with smaller FI indicating more fragile results (see details and example calculation for the FI in Supplement File 1).¹² The FI does not aim to replace or invalidate the use of p-values, but rather to provide a complementary, easily interpretable metric to gauge how robust a trial result is.¹³ Since the FI is an absolute measure and does not account for sample size, comparisons across different studies or establishing a set of reference values to categorize fragility levels proved difficult.¹⁴ To overcome this, the fragility quotient (FQ) was proposed by Ahmed et al. in 2016 as a relative measure of trial robustness.¹⁵ The FQ is simply the FI divided by the trial sample size, and thus expresses the proportion of trial participants whose outcome events would need to change to non-events in order to turn a trial result from 'statistically significant' to 'statistically not significant'.

The FI and FQ are increasingly being reported across a range of medical disciplines, including in meta-analyses as part of systematic reviews.¹⁶⁻²⁰ Since vaccines against SARS-CoV-2 are now the single most important public health intervention around the world against the ongoing COVID-19 pandemic, it is of utmost importance to establish how robust results of the underlying vaccine trials actually are. We conducted a systematic review and meta-analysis

of the global evidence with the aim to assess the robustness of SARS-CoV-2 vaccine efficacy (VE) trial results using the FI and FQ methodology.

Methods

Search strategy and selection criteria

This is a systematic review and meta-analysis of SARS-CoV-2 VE trial results. We registered the protocol of this study in the International Prospective Register of Systematic Reviews (PROSPERO) prior to commencing data collection (protocol number CRD42021258455), and followed the Cochrane Handbook for Systematic Reviews of Interventions²¹ as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)²² recommendations where applicable.

We included studies presenting results from RCTs in humans on the vaccine efficacy against SARS-CoV-2 that reported at least one dichotomous outcome based on frequentist statistics and were published in the scientific literature in English language before 26 April 2022. We excluded non-randomized studies, studies on animals, trials where VE was not a primary outcome, and trials that did not have either asymptomatic infection, morbidity (symptomatic infection), or mortality as outcome events. We also excluded publications that were not original research articles presenting new data, such as letters to the editor, viewpoints, and narrative reviews.

We searched the databases Medline (via PubMed), Cochrane Library, and EMBASE (see Supplement File 2 for detailed search statements for each database). References of relevant systematic reviews and of all included articles were also searched. All search results were uploaded into the Covidence software,²³ where they were screened by two researchers (NAH and HLQ) independently for relevance based on their titles and abstracts. Full texts of retained search results were retrieved, and the same pair of reviewers then independently reviewed full texts using a pre-established eligibility criteria checklist (see Supplement File 3). At the titles/abstracts and full text screening stages, discrepancies were first discussed between the two researchers and, if necessary, resolved by a third researcher (FV). The reasons for exclusion were also documented, and a PRISMA flowchart of the selection process was constructed. One of the researchers (NAH) extracted data from all included studies using a pre-established data extraction form (see Supplement File 4). In this form, which we piloted prior to data extraction, data from trials with more than one primary outcome were extracted separately for each outcome. Another researchers (HLQ) reviewed extracted data of a random

sample of the included studies as validity check, and discrepancies were discussed between the two researchers and resolved by a third reviewer (FV) if needed.

Data extraction

The following data were extracted from all included studies and entered into a dedicated study database: general information (authors, journal, month and year of publication); methods (study design, type of blinding, trial phase, allocation unit, randomization ratio); participants (countries of patient enrolment, number of participants randomized, number of participants analyzed); intervention and type of control (vaccine brand name, type of vaccine, type of control); type of outcome event (asymptomatic infection, symptomatic infection [symptomatic disease of any severity], death); effect measure (reported p-value, reported VE incl. 95% confident intervals); type of analysis (intention to treat, per protocol); and data required to calculate the FI and FQ (number of participants with outcome events in the intervention group, number of participants with outcome events in the control group, total number of participants in the intervention group, total number of participants in the control group). Separate records were created for each outcome for trials with more than one primary outcome.

Risk of bias assessment

The risk of bias of included studies was assessed independently by two researchers (NAH and HLQ) using the Cochrane Risk of Bias for Randomized Controlled Trials Tool version 2 (RoB2).²⁴ RoB2 has seven domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias) and produces a summary assessment of the risk of bias categorized as low (low risk of bias in all domains), high (high risk of bias in at least one domain), or unclear (unclear risk of bias in at least one domain).²⁴

Data analysis

We calculated the FI and FQ for each primary outcome of all included studies according to the method described by Walsh et al.¹² In short, the p-value for each outcome was recalculated using a 2-sided Fisher exact test via the web interface of ClinCalc²⁵ by iteratively adding events to the group with the smaller number of events, while subtracting non-events from the same group to keep the total number of participants constant. Events were added one at a time until the calculated p-value became equal to or larger than 0.05. The smallest number of additional outcome events required to obtain a p-value of at least 0.05 constituted the FI for that trial outcome. We then calculated the FQ by dividing the FI by the total number of participants that were included in the analysis (sample size) as described by Ahmed et al,¹⁵ and

presented it as percentage for ease of interpretation.²⁶ All calculations were done by two reviewers (NAH and HLQ) independently to minimize data entry and calculation errors. Using the software package STATA v. 16.0,²⁷ we calculated the median and interquartile ranges (IQR) of FIs and FQs for risk of bias as per RoB2 classification; blinding type (single-blinded; double-or triple-blinded; open-label or not reported); magnitude of effect measure (VE <70%; 70-90%; >90%); trial phase; sample size (<10,000; 10,000-25,000; >25,000); and percentage LTFU (<5%; 5-<10%; 10-<15%; 15-<30%; ≥30%). We assessed the associations of trial characteristics with FI and FQ using Wilcoxon rank-sum tests and Kruskal-Wallis H tests. We produced scatter plots incl. least squares regression lines and used Spearman correlation coefficients to quantify the strength of correlation of the FI and FQ with sample size, percentage LTFU, and VE.

Role of funding source

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Results

A total of 4,191 search results were retrieved from the three databases. After removing 220 duplicates, 3,971 titles/abstracts were screened for relevance, resulting in the exclusion of another 3,708 results. A further 234 records were excluded during the full text review for eligibility, mostly because they were not RCTs or did not have VE as primary outcome. Ultimately, a total of 40 primary outcomes from 29 included studies were identified and their data extracted for analysis (Figure 1). See Supplement File 5 for complete citation details of included studies.

Figure 1 here

Nine (31%) of the 29 included studies reported on more than one primary outcome, resulting in 40 outcomes for our analysis with a total of 720,291 participants (median 15,506 [IQR: 8,950-27,210]). The randomization ratio was 1:1 in 34 (85%) outcomes. Eleven (27.5%) outcomes assessed the efficacy of the BNT162b2 vaccine (Vaccine BioNTech, Pfizer), nine (22.5%) the ChAdOx1 nCoV-19 vaccine (Vaccine Oxford, AstraZeneca), four (10%) the Ad26.COV2.S vaccine (Johnson & Johnson Vaccine) and 16 (40%) other vaccines. Most included outcomes were from studies in trial phase 3 (29/40, 72.5%). Half of the outcomes

(20/40, 50%) were from double-blinded studies. Sixteen (40%) and 15 (37.5%) outcomes were based on sample sizes under 10,000 or over 25,000 participants, respectively. Fourteen (35%) and 16 (40%) outcomes reported a VE of <70% and >90%, respectively. Thirteen (34.2%) outcomes had the percentage LTFU between 5% and 10% (see Table 1, 2 and 3).

Table 1, Table 2, and Table 3 here

Overall, the median FI was 53.5 (IQR 17-124, range 0-692) and the median FQ was 0.41% (IQR 0.18-0.8, range 0-2.19). The FI was positively associated with trial sample size [<10,000: median FI (IQR): 12 (1-48.5); 10,000-25,000: 55 (34-71); >25,000: 139 (83-497), p-value <0.001], but not with other trial characteristics at statistically significant levels. The FQ was associated with blinding type [single-blinded: median FQ (IQR): 0.87 (0.55-1.3); double-or triple blinded: 0.24 (0.13-0.55); open-label/not reported: 0.40 (0.33-1.24), p-value 0.005] and VE [<70%: median FQ (IQR): 0.20 (0.06-0.60); 70-90%: 0.31 (0.17-0.43); >90%: 0.62 (0.36-1.26), p-value 0.010] at statistically significant levels (see Table 2). The number of patients LTFU exceeded the FI in 38 (95%) outcomes (see Table 3).

The Spearman correlation coefficient was moderately positive for FI and sample size (0.618), and weakly positive for FQ and sample size (0.233), with considerable variability among both small and large trials (Figure 2). Both FI and FQ were weakly negatively correlated with the percentage LTFU (Spearman correlation coefficient -0.207 and -0.275, respectively) and showed particularly large variability in trials with low percentage LTFU (Figure 3). Both the FI and FQ showed a weak positive correlation with VE, with Spearman correlation coefficients of 0.126 and 0.353, respectively, and considerable variability among trials with high VE (Figure 4).

Figure 2, Figure 3, and Figure 4 here

Based on the RoB2 scale, we assessed one study to be at low risk of bias and nine at unclear risk of bias, while the majority of studies (19/29, 65.5%) were classified as at high risk of bias (Figure 5).

Figure 5 here

Discussion

To our knowledge this was the first comprehensive assessment of the robustness of SARS-CoV-2 vaccine trial results. After reviewing the global evidence and based on an analysis of 720,291 participants across 40 primary outcomes from 29 included trials, we found the median FI and FQ of SARS-CoV-2 VE trials to be 53.5 (IQR 17-124) and 0.41% (IQR 0.18-0.8), respectively. Trial robustness increased with sample size and showed substantial

variability across a range of other trial characteristics such as blinding type, percentage LTFU and VE.

We found substantially higher robustness levels for COVID-19 VE trials than reported in previous FI reviews of other types of interventions. For example, among the five biggest previous FI reviews,^{12,16,17,28,29} covering a wide range of interventions and areas, FIs ranged between 8 and 26. However, as it is known that FI is prone to increase with sample size,¹⁵ it is important to note that the median number of study participants in those reviews ranged between 682 to 2548, compared to 15,506 (IQR: 8,950-27,210) in our study. In seven reviews reporting FQ estimates since 2020, FQs ranged between 0.7% and 19%, and the percentage of studies where the number LTFU exceeded the FI ranged between 11% and 50%.^{16,18,19,26,30-32} Most of these reviews assessed treatments in non-infectious internal medicine or surgical interventions, and none of them was on vaccines. With regards to COVID-19, a systematic review of FIs reported in trials that assessed the use of corticosteroids to treat acute respiratory distress syndrome in COVID-19 patients found only two out of five RCTs, comprising a total of 7,692 patients, to have a FI above 0 (median FI 6).³³ Another recently published study attempted to assess FIs in therapeutic interventions and vaccines for COVID-19, and found 47 studies, five of which were vaccine trials.³⁴ The median FI reported for these five studies was 119 (IQR 61-139), compared to 2.5 (IQR 1-6) in the 36 included drug trials; FQs were not reported. While this is more than double the FI compared to our results, there are a number of methodological issues that make a comparison of results difficult and question the validity of those findings more generally: study-specific FIs and sample sizes were not presented, and it is not clear which RCTs were actually included in that review as these were not explicated listed. This make that review non-reproducible. The search was restricted to one database only and dates back to early August 2021, which might explain the low number of included vaccine studies. However, virtually all COVID-19 vaccine trials that informed the rollout of vaccines worldwide were published thereafter. Lastly, no risk of bias assessment was done and good practice guidelines like PRISMA or Cochrane did not seem to have been followed neither, putting in doubt the validity of the overall findings of that review.

While the absence of other similarly large FI reviews, in particular of methodologically sound FI reviews of vaccine trials, limit a meaningful contextualization of our results, we believe that the overall high median FI found in our study truly reflects substantially higher robustness levels of SARS-CoV-2 VE trials compared to other interventions for which FIs have been calculated before. Of note, the ability of the FI has been questioned in particular with regards to its ability to provide sufficient additional value to allow for an enhanced

1 interpretation of trial results beyond what p-values can offer.^{35–37} While the shortfalls of p-
2 values are widely accepted, confidence intervals and minimal clinically important differences
3 are sometimes proposed as more informative than the FI.^{13,38} In our included RCTs, however,
4 p-values were only reported for nine (22.5%) of the 40 included outcomes in addition to VE.
5 This makes our review on SARS-CoV-2 vaccine trials particularly valuable regardless of these
6 considerations. In any case, the FI should always be seen as a complementary metric for trial
7 robustness and trustworthiness alongside other established criteria like relative and absolute
8 effect size differences, confidence intervals, p-values, clinical significance, and trial design.¹³
9 We closely followed best practice during the conduct and reporting of this study as per
10 Cochrane and PRISMA guidelines wherever applicable; used comprehensive search statements
11 fitted for the three most relevant databases (see Supplementary File 2); covered the three most
12 frequently used, clinically relevant outcomes for SARS-CoV-2 vaccine trials; and provided in-
13 depth analyses separately for all eligible primary outcomes of included studies. We do,
14 however, acknowledge certain limitations. First, the FI and FQ can only be calculated for
15 studies with randomized allocation of interventions.³⁹ This led to the exclusion of 116/234
16 (49.6%) studies at the full text screening stage in our study (see Figure 1). While this might
17 have introduced some selection bias, public health practice concerning SARS-CoV-2 vaccines
18 has nearly exclusively been based on RCTs.^{40,41} As we are not aware of a non-randomized
19 study that substantially impacted public health decision making with regards to the roll out of
20 COVID-19 vaccines, we believe that this issue did not affect the validity and public health
21 relevance of our study substantially. Second, the FI and FQ can only measure robustness in
22 RCTs with a dichotomous outcome, and cannot be applied to continuous or time-to-event
23 outcomes due to its underlying principles and methodology. However, since the vast majority
24 of SARS-CoV-2 VE trials have dichotomous outcomes, with only one of our identified studies
25 being excluded for this reason (see Figure 1), this did not affect our findings. Third, there is no
26 commonly agreed cut-off value for the FI or FQ to classify an outcome as ‘robust’ or not,
27 making the interpretation of any FI review difficult. Forth, we only searched for trials published
28 in English language. Given the dominance of the English-speaking literature in the global
29 evidence on SARS-CoV-2 VE, we do not believe that this caused major problems for our main
30 findings.

31 Conclusions

32 This was the largest study on trial robustness to date. Results from SARS-CoV-2 VE
33 trials were substantially more robust than from trials in other areas and other types of
34

interventions. While robustness increased with trial size, both the FI and FQ showed considerable variability across several important trial characteristics. The FI and FQ provide important insights for the interpretation of vaccine trials in particular, and we recommend their reporting alongside established parameters as a complementary indicator how fragile results are to changes in outcome events. This is specifically relevant for interventions as pivotal as SARS-CoV-2 vaccines in the midst of a global pandemic.

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Table 1. Characteristics of primary outcomes (n=40) of included studies (n=29)

Outcome	Authors	Journal of Publication	Time of Publication	Study design	Blinding type	Trial Phase	Randomization ratio (Allocation Unit)	Countries of enrolment	Vaccine name	Vaccine type/ Control type	Type of outcome	Reported p-value	Reported Vaccine Efficacy (95% CI)	Type of analyses
27.1	Voysey et al.	Lancet	February 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	1/2, 2/3, 3	1:1 (Individual)	United Kingdom (UK), Brazil, South Africa	ChAdOx1 nCoV-19 (AstraZeneca COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	66.7 (57.4-74.0)	per protocol
30.1	Kaabi et al. ⁷	JAMA	May 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	United Arab Emirates (UAE), Bahrain	SARS-CoV-2 WIV04 vaccine (Wuhan COVID-19 Vaccine)	inactivated/ placebo	symptomatic infection	<0.001	72.8 (58.1-82.4)	per protocol
32.2	Kaabi et al. ⁸	JAMA	May 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	UAE, Bahrain	HB02 vaccine (Wuhan COVID-19 Vaccine)	inactivated/ placebo	symptomatic infection	<0.001	78.1 (64.8-86.3)	per protocol
34.3	Baden et al.	NEJM	February 2021	Superiority with parallel groups	Clinician-blinded	3	1:1 (Individual)	United States of America (USA)	mRNA-1273 vaccine (Moderna COVID-19 vaccine)	mRNA/ placebo	symptomatic infection	<0.001	94.1 (89.3-96.8)	per protocol
37.4	Emery et al.	Lancet	March 2021	Superiority with parallel groups	Patient-blinded	2/3	1:1 (Individual)	England, Wales, Scotland	ChAdOx1 nCoV-19 (AstraZeneca COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	72.3 (63.1-79.3)	not reported
39.4	Frencik et al. ⁷	NEJM	May 2021	Superiority with parallel groups	not reported	3	1:1 (Individual)	USA	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	100 (75.3-100)	not reported
42.2	Frencik et al. ⁸	NEJM	May 2021	Superiority with parallel groups	not reported	3	1:1 (Individual)	USA	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	100 (78.1-100)	not reported
44.4	Heath et al.	NEJM	June 2021	Superiority with parallel groups	not reported	3	1:1 (Individual)	UK	NVX-CoV2373 vaccine (Novavax COVID-19 vaccine)	recombinant/ placebo	symptomatic infection	not reported	89.7 (80.2-94.6)	per protocol
47.4	Logunov et al.	Lancet	February 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	3:1 (Individual)	Russia	Gam-COVID-Vac (Sputnik V)	viral vector/ placebo	asymptomatic or symptomatic infection	<0.0001	91.6 (85.6-95.2)	per protocol
50.5	Madhi et al.	NEJM	May 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	1b-2	1:1 (Individual)	South Africa	ChAdOx1 nCoV-19 (AstraZeneca COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	21.9 (-49.9-59.8)	per protocol
51.1	Polack et al. ⁷	NEJM	December 2020	Superiority with parallel groups	not reported	2/3	1:1 (Individual)	USA, Argentina, Brazil, South Africa, Germany, Turkey	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	95 (90.3-97.6)	not reported
55.2	Polack et al. ⁸	NEJM	December 2020	Superiority with parallel groups	not reported	2/3	1:1 (Individual)	USA, Argentina, Brazil, South Africa, Germany, Turkey	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	94.6 (89.9-97.3)	not reported
58.1	Sadoff et al. ⁷	NEJM	April 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA	Ad26.COV2.S vaccine (Johnson & Johnson COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	66.9 (59.7-73.4)	per protocol

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22.2	Sadoff et al. ⁷	NEJM	April 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA	Ad26.COV2.S vaccine (Johnson & Johnson COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	66.1 (55.7-74.8)	per protocol
25.1	Shinde et al.	NEJM	May 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	2a-b	1:1 (Individual)	South Africa	NVX-CoV2373 vaccine (Novavax COVID-19 vaccine)	recombinant/ placebo	symptomatic infection	not reported	49.4 (6.1-72.8)	per protocol
27.2	Tanriover et al.	Lancet	July 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	2:1 (Individual)	Turkey	CoronaVac (Sinovac CoronaVac COVID-19 vaccine)	inactivated/ placebo	symptomatic infection	<0.0001	83.5 (65.4-92.1)	per protocol
30.3	Voysey et al.	Lancet	December 2020	Superiority with parallel groups	Patient-blinded & Clinician-blinded	1/2, 2/3, 3	1:1 (Individual)	UK, Brazil, South Africa	ChAdOx1 nCoV-19 (AstraZeneca COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	70.4 (54.8-80.6)	per protocol
32.3	Thomas et al.	NEJM	September 2021	Superiority with parallel groups	Open-label	2/3	1:1 (Individual)	USA, Argentina, Brazil, South Africa, Germany, Turkey	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	91.3 (89.9-92.2)	not reported
35.1	Sadoff et al. ⁷	NEJM	September 2021	Superiority with crossover groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA	Ad26.COV2.S vaccine (Johnson & Johnson COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	56.3 (51.3-60.8)	per protocol
38.2	Sadoff et al. ⁸	NEJM	September 2021	Superiority with crossover groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA	Ad26.COV2.S vaccine (Johnson & Johnson COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	52.9 (47.1-58.1)	per protocol
41.2	Kremsner et al.	Lancet Infectious Diseases	November 2021	Superiority with parallel groups	Clinician-blind & Statistician-blind	2/3	1:1 (Individual)	Belgium, Germany, the Netherlands, Spain, Argentina, Colombia, Dominican Republic, Mexico, Panama, Peru	CvVacV (CureVac N.V. and the Coalition COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	0.016	48.2 (95.826/CI: 31-61.4)	per protocol
46.2	Khobragade et al.	Lancet	April 2022	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	India	ZyCoV-D (Zydus Cadila's COVID-19 Vaccine)	DNA-based/ placebo	symptomatic infection	not reported	66.6 (47.6-80.7)	per protocol
49.3	Falsety et al.	NEJM	September 2021	Superiority with parallel groups	not reported	3	2:1 (Individual)	USA, Chile, Peru	ChAdOx1 nCoV-19 (AstraZeneca COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	<0.001	74 (65.3-80.5)	not reported
51.3	Fadlyana et al.	Vaccine	September 2021	Superiority with parallel groups	not reported	3	1:1 (Individual)	Indonesia	CoronaVac (Sinovac CoronaVac COVID-19 vaccine)	inactivated/ placebo	symptomatic infection	not reported	65.3 (CI not reported)	not reported
54.4	Ella et al.	Lancet	November 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	India	BBV152 (Bharat Biotech COVID-19 vaccine)	inactivated/ placebo	symptomatic infection	not reported	77.8 (65.2-86.4)	per protocol
56.5	ElSahly et al.	NEJM	September 2021	Superiority with parallel groups	Clinician-blind	3	1:1 (Individual)	USA	mRNA-1273 vaccine (Moderna COVID-19 vaccine)	mRNA/ placebo	symptomatic infection	not reported	93.2 (91.9-94.8)	per protocol
59.1	Clemens et al. ⁷	Nature	October 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	Brazil	ChAdOx1 nCoV-19 (AstraZeneca COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	88.2 (5.4-98.5)	not reported

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22.2	Clemens et al. ²	Nature	October 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	Brazil	ChAdOx1 nCoV-19 (AstraZeneca COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	72.6 (46.4-86)	not reported
22.3	Clemens et al. ²	Nature	October 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	Brazil	ChAdOx1 nCoV-19 (AstraZeneca COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	68.7 (54.9-78.3)	not reported
22.4	Clemens et al. ²	Nature	October 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	Brazil	ChAdOx1 nCoV-19 (AstraZeneca COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	not reported	63.6 (-2.1-87)	not reported
29.1	Walter et al. ³	NEJM	November 2021	Superiority with parallel groups	Patient-blind	2/3	2:1 (Individual)	USA, Spain, Finland, Poland	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	90.7 (67.7-98.3)	not reported
32.2	Walter et al. ³	NEJM	November 2021	Superiority with parallel groups	Patient-blind	2/3	2:1 (Individual)	USA, Spain, Finland, Poland	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	90.7 (67.4-98.3)	not reported
34.1	Thomas et al. ⁴	Vaccine	December 2021	Superiority with parallel groups	not reported	3	1:1 (Individual)	USA, Argentina, Brazil, South Africa, Germany, Turkey	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	94.4 (85.1-98.5)	not reported
34.2	Thomas et al. ⁴	Vaccine	December 2021	Superiority with parallel groups	not reported	3	1:1 (Individual)	USA, Argentina, Brazil, South Africa, Germany, Turkey	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	94.4 (85.2-98.5)	not reported
39.5	Pajon et al.	Nature Medicine	April 2022	Superiority with parallel groups	Clinician-blind	3	1:1 (Individual)	USA	mRNA-1273 vaccine (Moderna COVID-19 vaccine)	mRNA/ placebo	symptomatic infection	not reported	93.2 (91-94.8)	per protocol
42.1	Moreira et al. ⁵	NEJM	March 2022	Superiority with parallel groups	Patient-blind	3	1:1 (Individual)	USA, South Africa, Brazil	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	95.3 (89.5-98.3)	not reported
44.2	Moreira et al. ⁵	NEJM	March 2022	Superiority with parallel groups	Patient-blind	3	1:1 (Individual)	USA, South Africa, Brazil	BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)	mRNA/ placebo	symptomatic infection	not reported	94.6 (88.5-97.9)	not reported
47.8	Halperin et al.	Lancet	December 2021	Superiority with parallel groups	Patient-blinded & Clinician-blinded	3	1:1 (Individual)	Argentina, Chile, Mexico, Pakistan, Russia	Ad5-nCoV vaccine (CanSino's COVID-19 Vaccine)	viral vector/ placebo	symptomatic infection	0.0026	57.5 (39.7-70)	Intention to treat
49.8	Dunkle et al.	NEJM	December 2021	Superiority with parallel groups	Clinician-blind	3	2:1 (Individual)	USA and Mexico	NVX-CoV2373 vaccine (Novavax COVID-19 vaccine)	recombinant/ placebo	symptomatic infection	<0.001	90.4 (82.9-94.6)	per protocol
52.9	Bravo et al.	Lancet	January 2022	Superiority with parallel groups	Patient-blind & Statistician-blind	3	1:1 (Individual)	Belgium, Brazil, Colombia, Philippines, South Africa	SCB-2019 (Clover Biopharmaceuticals' COVID-19 vaccine)	recombinant/ placebo	asymptomatic or symptomatic infection	not reported	67.2 (95.72%CI: 54.3-76.8)	per protocol

² This study assessed two interventions.
³ These studies had more than one primary outcome.

Characteristics	Number of outcomes n (%)	Median FI (IQR)	p-value ^o	Median FQ% (IQR)	p-value ^o
Total	40	53.5 (17-124)		0.41 (0.18-0.8)	
Risk of bias			0.217		0.068
Low risk	2 (5)	46.5 (44-49)		0.18 (0.17-0.19)	
High risk	25 (62.5)	92 (12-144)		0.49 (0.33-1.24)	
Unclear	13 (32.5)	37 (22-71)		0.29 (0.16-0.6)	
Blinding type			0.272		0.005
Single-blinded	9 (22.5)	87 (83-139)		0.87 (0.55-1.3)	
Double-or triple-blinded	21 (52.5)	45 (22-92)		0.24 (0.13-0.55)	
Open-label or not reported	10 (25)	53 (8-125)		0.40 (0.33-1.24)	
Vaccine efficacy			0.328		0.010
<70%	14 (35)	44.5 (1-123)		0.20 (0.06-0.60)	
70-90%	10 (25)	47 (29-61)		0.31 (0.17-0.43)	
>90%	16 (40)	86.5 (28.5-132)		0.62 (0.36-1.26)	
Trial phase[†]			0.082		0.073
1/2 or 2	2 (5)	0.5 (0-1)		0.02 (0-0.04)	
2/3	7 (17.5)	111 (12-125)		0.55 (0.31-1.3)	
3	29 (72.5)	55 (29-125)		0.43 (0.19-0.87)	
Sample size			<0.001		0.594
<10,000	16 (40)	12 (1-48.5)		0.46 (0.05-0.9)	
10,000-25,000	9 (22.5)	55 (34-71)		0.39 (0.29-0.6)	
>25,000	15 (37.5)	139 (83-497)		0.47 (0.24-1.28)	
Percentage of loss to follow up[*]			0.789		0.372
<5%	8 (21.0)	37 (10-355)		0.71 (0.33-1.44)	
5-<10%	13 (34.2)	52 (44-125)		0.43 (0.17-0.63)	
10-<15%	7 (18.4)	92 (12-380)		0.47 (0.24-1)	
15-<30%	5 (13.2)	119 (83-123)		0.33 (0.33-0.55)	
≥30%	5 (13.2)	37 (34-55)		0.16 (0.15-0.32)	

[†]We excluded two outcomes from two studies that could not be categorized into any of the trial phases.
^{*}We excluded two outcomes from two studies because they did not report the denominator of percentage LTFU i.e., the number of participants randomized.
^op-values from Wilcoxon rank sum test and Kruskal-Wallis H test.

Table 3. Parameters of primary outcomes (n=40) of included studies (n=29) needed to calculate the fragility index and fragility quotient

Outcome #	Authors	Participants randomized	Participants analysed	Loss to Follow-up	Participants with outcome events in intervention group	Participants with outcome events in control group	Total participants in intervention group	Total participants in control group	Recalculated p-value	FI	FQ	FQ (%)
1	Voysey et al.	24422	17178	7244	84	248	8597	8581	<0.001	123	0.0072	0.72
2	Kaabi et al. [#]	26941	25536	1405	26	95	12769	12767	<0.001	44	0.0017	0.17
2.2	Kaabi et al. [#]	26941	25519	1422	21	95	12752	12767	<0.001	49	0.0019	0.19
3	Baden et al.	30420	28207	2213	11	185	14134	14073	<0.001	139	0.0049	0.49
4	Emery et al.	not reported	8534	--	59	210	4244	4290	<0.001	111	0.013	1.3
5.1	Frencik et al. [*]	2264	1983	281	0	16	1005	978	<0.001	7	0.0035	0.35
5.2	Frencik et al. [*]	2264	2229	35	0	18	1119	1110	<0.001	8	0.0036	0.36
6	Heath et al.	15187	14039	1148	10	96	7020	7019	<0.001	61	0.0043	0.43
7	Logunov et al.	21977	19866	2111	16	62	14964	4902	<0.001	125	0.0063	0.63
8	Madhi et al.	2026	1467	559	19	23	750	717	0.532	0	0	0
9.1	Polack et al. [*]	43548	36523	7025	8	162	18198	18325	<0.001	119	0.0033	0.33
9.2	Polack et al. [*]	43548	40137	3411	9	169	19965	20172	<0.001	125	0.0031	0.31
10.1	Sadoff et al. [*]	44325	39058	5267	116	348	19514	19544	<0.001	182	0.0047	0.47
10.2	Sadoff et al. [*]	44325	38484	5841	66	193	19306	19178	<0.001	92	0.0024	0.24
11	Shinde et al.	4406	2684	1722	15	29	1357	1327	0.033	1	0.0004	0.04
12	Tanriover et al.	10218	10029	189	9	32	6559	3470	<0.001	29	0.0029	0.29
13	Voysey et al.	not reported	11636	--	30	101	5807	5829	<0.001	45	0.0039	0.39
14	Thomas et al. [*]	44165	42094	2071	77	850	20998	21096	<0.001	692	0.0164	1.64
15.1	Sadoff et al. [*]	43788	38798	4990	484	1067	19400	19398	<0.001	497	0.0128	1.28
15.2	Sadoff et al. [*]	43788	38037	5751	433	883	19113	18924	<0.001	380	0.01	1
16	Kremsner et al.	39680	25062	14618	83	145	12851	12211	<0.001	37	0.0015	0.15
17	Khobragade et al.	27703	24670	3033	20	61	12350	12320	<0.001	22	0.0009	0.09
18	Falsey et al.	32451	26212	6239	73	130	17662	8550	<0.001	144	0.0055	0.55
19	Fadlyana et al.	1620	1620	0	7	18	811	809	0.028	1	0.0006	0.06
20	Ella et al.	25798	16973	8825	24	106	8471	8502	<0.001	55	0.0032	0.32

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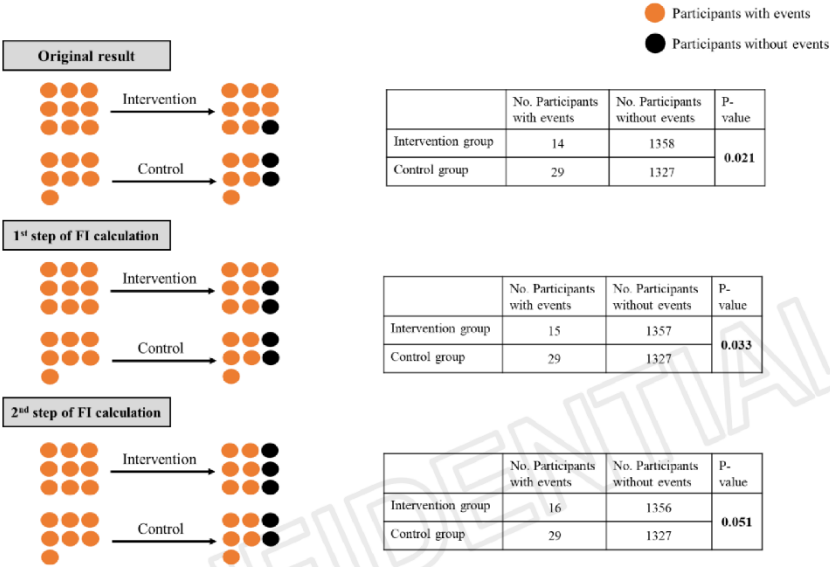
21	EISahly et al.	30415	28451	1964	55	744	14287	14164	<0.001	623	0.0219	2.19
22.1	Clemens et al. [*]	10416	9433	983	1	8	4772	4661	0.02	1	0.0001	0.01
22.2	Clemens et al. [*]	10416	9433	983	11	38	4772	4661	<0.001	12	0.0013	0.13
22.3	Clemens et al. [*]	10416	9433	983	38	115	4772	4661	<0.001	52	0.0055	0.55
22.4	Clemens et al. [*]	10416	9433	983	5	13	4772	4661	0.061	0	0	0
23.1	Walter et al. [*]	2285	1968	317	3	16	1305	663	<0.001	12	0.0061	0.61
23.2	Walter et al. [*]	2285	2186	99	3	16	1450	736	<0.001	12	0.0055	0.55
24.1	Thomas et al. [*]	3813	3538	275	4	71	1750	1788	<0.001	45	0.0127	1.27
24.2	Thomas et al. [*]	3813	3636	177	4	71	1802	1834	<0.001	45	0.0124	1.24
25	Pajon et al.	28451	28451	0	55	744	14287	14164	<0.001	623	0.0219	2.19
26.1	Moreira et al. [*]	10136	9366	770	6	123	4695	4671	<0.001	86	0.0092	0.92
26.2	Moreira et al. [*]	10136	9945	191	7	124	4993	4952	<0.001	87	0.0087	0.87
27	Halperin et al.	36982	21250	15732	45	105	10660	10590	<0.001	34	0.0016	0.16
28	Dunkle et al.	29949	25452	4497	14	63	17312	8140	<0.001	83	0.0033	0.33
29	Bravo et al.	30174	11741	18433	52	155	5935	5806	<0.001	71	0.006	0.6

[#] This study assessed two interventions.^{*} These studies had more than one primary outcome.

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Supplement File 1: Example of fragility index calculation

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Supplement File 2: Search statements by database

DATABASE
PubMed
#1: "corona virus"[tw] OR coronavirus[tw] OR coronavirinae[tw] OR coronaviridae[tw] OR betacoronavirus[tw] OR "beta coronavirus" [tw]
#2: COVID19[tw] OR "COVID 19"[tw] OR COVID2019[tw] OR "COVID 2019"[tw]
#3: nCoV[tw] OR "CoV 2"[tw] OR CoV2[tw] OR 2019nCoV[tw] OR "2019 nCoV"[tw] OR "severe acute respiratory syndrome coronavirus 2"[tw] OR "SARS CoV 2"[tw] OR sarscov2
#4: #1 OR #2 OR #3 (177,303 results)
#5: "COVID-19 Vaccines"[Mesh]
#6: vaccin*[tw]
#7: immuniz*[tw]
#8: inocul*[tw]
#9: "COVID19 vaccin*" [tw] OR "anti-sars-cov-2 agent" [tw] OR anti-sarscov2 agent[tw] OR sarscov-2 vaccine[tw]
#10: #5 OR #6 OR #7 OR #8 OR #9 (632,228 results)
#11: #4 AND #10 (19,484 results)
#12: Humans[Mesh] OR human*[tw] OR volunteer*[tw] OR participant*[tw] OR subject*[tw] OR people[tw]
#13: (clinical[tw] AND trial[tiab]) OR clinical trials as topic[Mesh] OR "random allocation"[Mesh] OR clinical trial[tw] OR random*[tw]
#14: #12 AND #13 (1,688,919 results)
#15: #11 AND #14 (1,254 results)
Filters applied: English (for language) and Humans (for species) (1,054 results)
Cochrane Library
#1: MeSH descriptor: [Coronavirus] explode all trees
#2: MeSH descriptor: [Coronaviridae] explode all trees
#3: MeSH descriptor: [Coronavirus Infections] explode all trees
#4: MeSH descriptor: [SARS-CoV-2] explode all trees
#5: MeSH descriptor: [Betacoronavirus] explode all trees
#6: coronavir* OR corona virus OR betacoronavir* OR beta coronavirus
#7: COVID19 OR COVID 19 OR COVID 2019 OR nCoV OR CoV 2 OR CoV2 OR 2019 nCoV OR severe acute respiratory syndrome coronavirus 2 OR SARS CoV 2 OR sarscov2
#8: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 (7,237 results)
#9: MeSH descriptor: [Vaccines] in all MeSH products
#10: MeSH descriptor: [Immunity] in all MeSH products
#11: (vaccin*):ti,ab,kw OR (immuniz*):ti,ab,kw OR (inocul*):ti,ab,kw
#12: #9 OR #10 OR #11 (32,018 results)
#13: #8 AND #12 (758 results)
#14: MeSH descriptor: [COVID-19 Vaccines] explode all trees
#15: COVID19 Vaccin* OR COVID 19 Vaccin* OR anti sars cov 2 agent OR anti sarscov2 agent OR sars cov 2 vaccin* OR sarscov2 vaccin*
#16: #14 OR #15 (711 results)
#17: #13 OR #16 (822 results)
#18: (human*):ti,ab,kw OR (volunteer*):ti,ab,kw OR (participant*):ti,ab,kw OR (subject*):ti,ab,kw OR (people*):ti,ab,kw
#19: ("clinical trial"):ti,ab,kw OR (random*):ti,ab,kw OR (clinical trial):ti,ab,kw
#20: #17 AND #18 AND #19 (672 results)
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#1: corona virus.mp. or exp Coronavirinae/
#2: Coronaviridae/ or exp coronavirus disease 2019/ or exp Severe acute respiratory syndrome coronavirus 2/
#3: exp Betacoronavirus 1/ or exp Betacoronavirus/
#4: ('Betacoronavirus' or 'beta coronavirus').mp.
#5: coronavirus disease 2019.mp. or exp coronavirus disease 2019/
#6: ('coronavirus disease 2019' or 'coronavirus disease 2019' or 'COVID-19' or COVID19 or sarscov2 or 'COVID-2019' or COVID2019).mp.
#7: exp severe acute respiratory syndrome/ or exp coronavirus disease 2019/ or exp Severe acute respiratory syndrome coronavirus 2/ or exp SARS coronavirus/
#8: ('nCoV' or 'SARS-CoV-2' or 2019nCoV or CoV2).mp.
#9: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 (188,806 results)
#10: anti-sars-cov-2 agent.mp. or exp anti-SARS-CoV-2 agent/
#11: 'sars-cov-2 vaccine.mp. or exp SARS-CoV-2 vaccine/
#12: ("covid19 vaccin*" or "covid 19 vaccin*").mp.
#13: #10 OR #11 OR #12
#14: #9 AND #13 (6,645 results)
#15: exp immunization/ OR exp randomization/ OR exp human/
#16: exp clinical trial/ or exp "controlled clinical trial (topic)"/ or exp controlled clinical trial/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/
#17: #14 AND #15 AND #16 (455 results)
Filters applied: English (for language) (451 results)

Supplement File 3: Eligibility criteria checklist for full text screening

General Information

Study ID (unique assigned number on Covidence)	
Study title	
Notes	

Study eligibility

Study Characteristics	Eligibility criteria	Eligibility criteria met?			Location in text or source (pg/fig/table/other)
		Yes	No	Unclear	
Type of study	Randomised controlled trial	☐	☐	☐	
	Frequentist statistical method	☐	☐	☐	
Participants	Humans	☐	☐	☐	
Types of intervention	Any SARS-CoV-2 vaccines	☐	☐	☐	
Types of comparison	Placebo, active control or standard care	☐	☐	☐	
Types of outcome measures	Dichotomous outcomes	☐	☐	☐	
	Efficacy of vaccine: reduction the infections	☐	☐	☐	
	Efficacy of vaccine: reduction in morbidity	☐	☐	☐	
	Efficacy of vaccine: reduction in mortality	☐	☐	☐	
INCLUDE ☐		EXCLUDE ☐			
Reason for exclusion					
Notes:					

Supplement File 4: Data extraction form for included studies

General Information

Study ID (unique assigned number on Covidence)	
Study title	
Protocol registration (<i>yes/no</i>)	
Journal name	
Publication year	
Journal impact factor (<i>in the year of publication</i>)	
Type of funding (<i>no funding/government/private</i>)	
Notes	

Methods

	Descriptions as stated in the article	Location in text or source (pg & ¶/fig/table/other)
Aim of study (<i>e.g. superiority, non-inferiority, adaptive</i>)		
RCT design type (<i>e.g. parallel groups, crossover, factorial, randomized withdrawal</i>)		
Type of blinding (<i>e.g. single, double, triple</i>)		
Number of sites (<i>single-site, if multi-centre: no of sites</i>)		
Phase of trials (<i>II/III, III, IV</i>)		
Sample size calculation prior to enrolment (<i>yes/no</i>)		
Unit of allocation (<i>by individuals, cluster/groups</i>)		
Reported to have obtained ethical approval	☐ Yes ☐ No ☐ Unclear	

Participants

	Descriptions as stated in the article	Location in text or source (pg & ¶/fig/table/other)
Population description (from which study participants are drawn, including inclusion, exclusion)		
Country(ies) (where participants enrolled)		
Time (details time range)		
Informed consent obtained	☐ Yes ☐ No ☐ Unclear	
Total no. randomised		
Total no. analysed		
Total no. lost to follow-up		
No. lost to follow-up in intervention group		
No. lost to follow-up in control group		
Notes:		

Intervention & Control groups

Copy and paste table for each intervention and comparison group

	Descriptions as stated in the article	Location in text or source (pg & ¶/fig/table/other)
Name of vaccine (vaccine brand name)		
Type of vaccine used (viral vector, genetic – nucleic acid, inactivated, attenuated, or protein)		
Name/type of control used (placebo/active control/standard of care)		

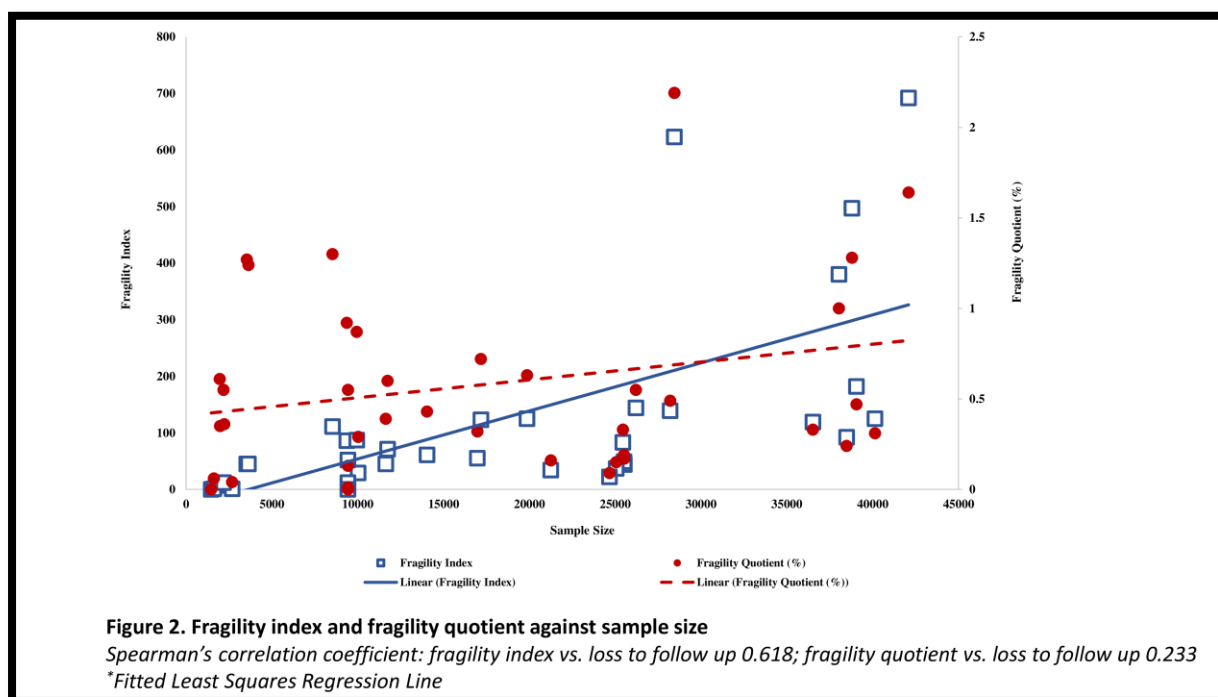
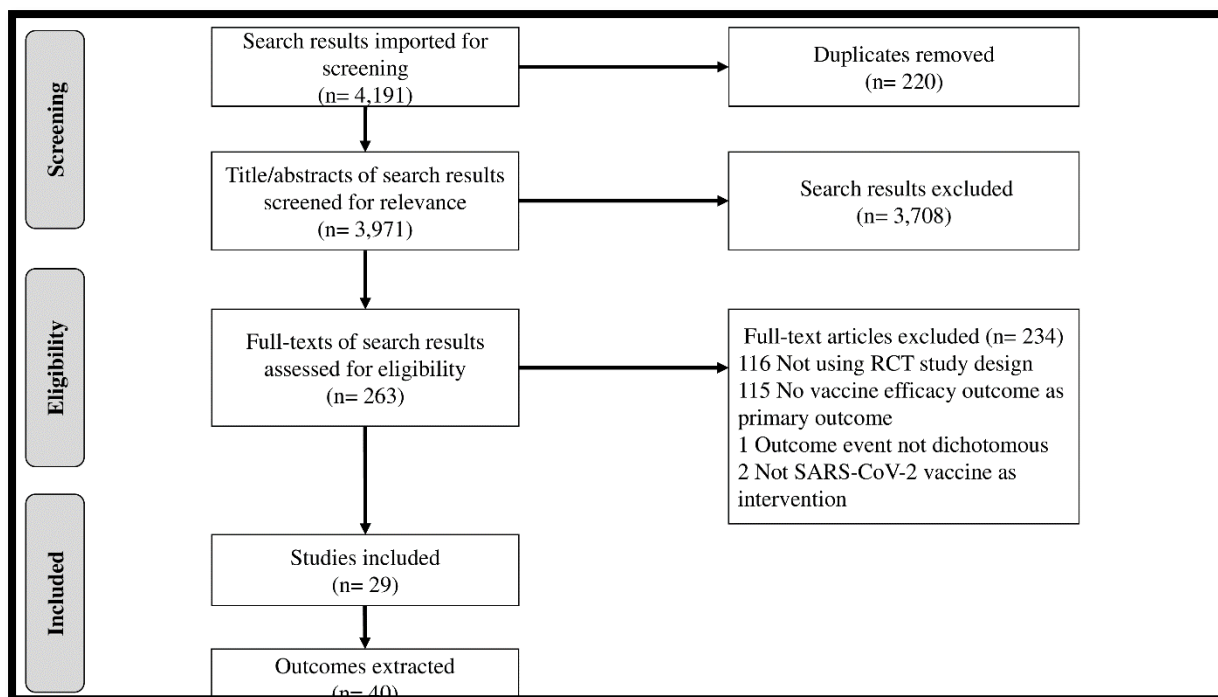
Outcomes (Copy and paste table for each efficacy outcome)

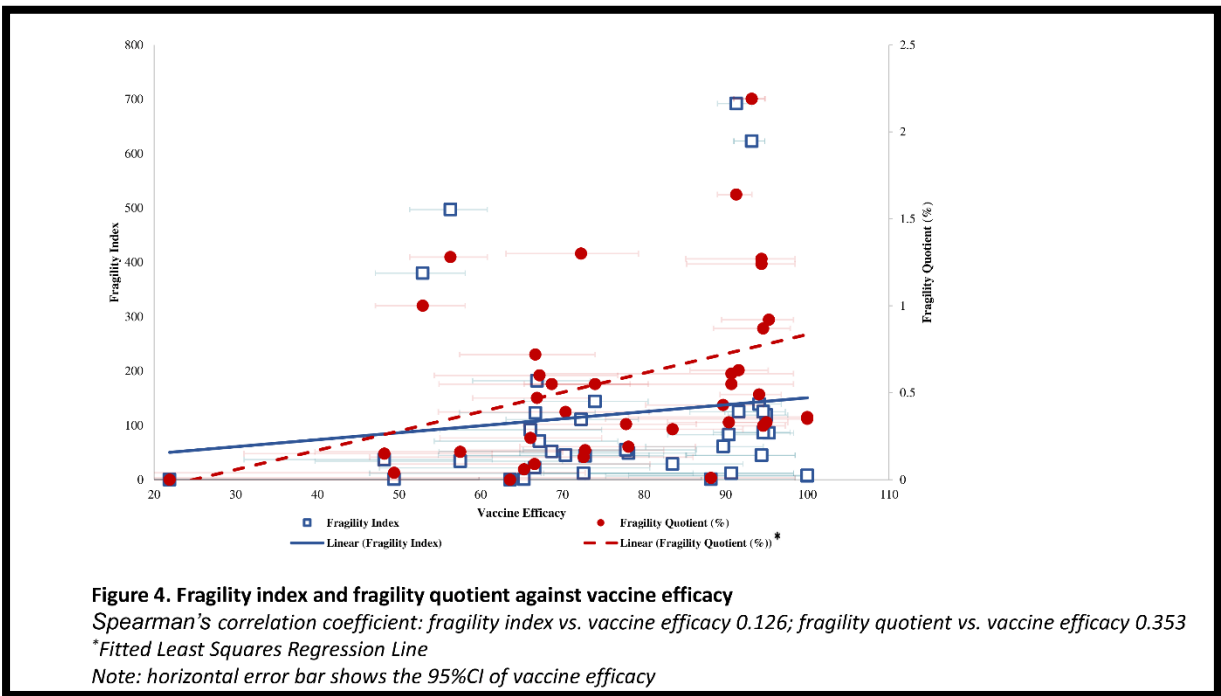
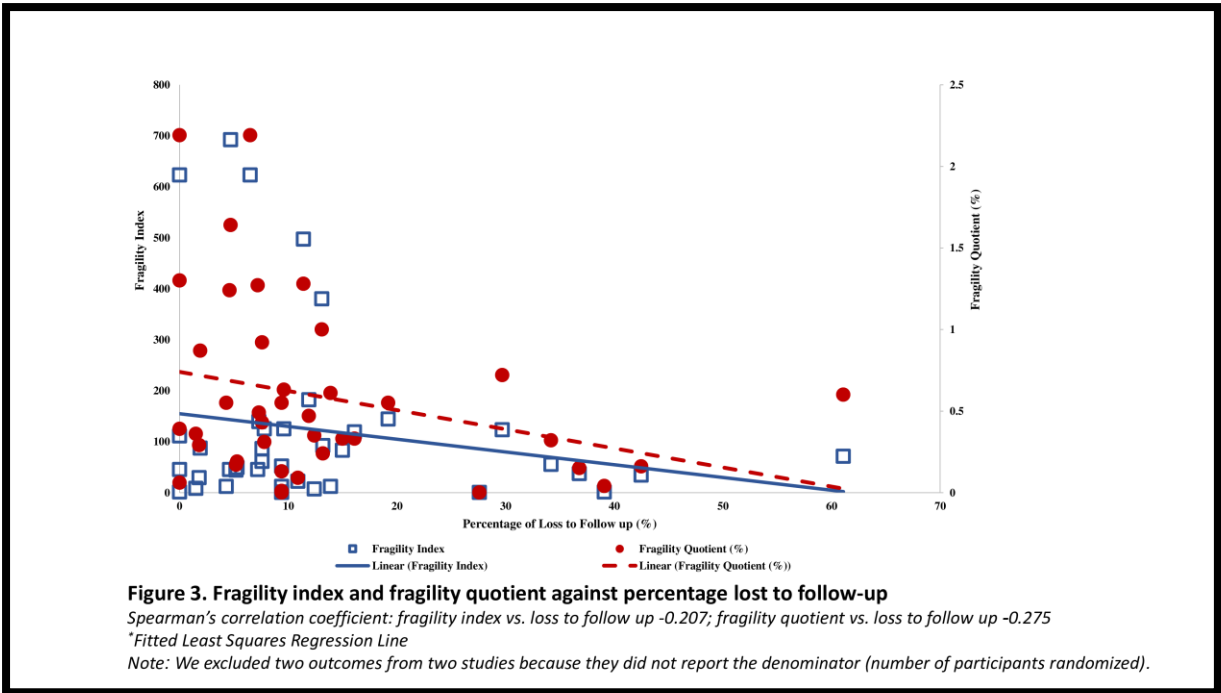
	Descriptions as stated in the article	Location in text or source (pg & ¶/fig/table/other)
Outcome name		
Types of outcome (primary/ secondary/ tertiary)		
Outcome definition (with diagnostic criteria if relevant)		
Reported the threshold for determining statistical significance (yes/no, if yes, specify)		
Reported statistical significance (yes/no)		
Reported p-value (yes/no, if yes, specify value and the statistical test used)		
Effect size measure and value (e.g. RR, OR, IRR, and 95%CI)		
Type of analysis (intention to treat/per protocol)		
Missing data management (e.g. assumptions made for ITT analysis)		
Power calculation (Yes/no, if yes, level of power achieved)		
Notes:		
Fragility Index Calculation		
The number of outcome events in experimental group		
The number of outcome events in control group		
The total number of people in the experimental group included in the analysis		
The total number of people in the control group included in the analysis		
Notes:		

Supplement File 5: Citation details of included studies

1. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* (London, England). 2021;397(10277):881-891. doi:10.1016/S0140-6736(21)00432-3
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Voysey 2021	−	−	?	+
Kaabi 2021	−	−	−	−
Baden 2021	−	−	+	+
Emary 2021	?	−	+	+
Frenck 2021	−	?	+	+
Heath 2021	−	?	+	+
Logunov 2021	−	−	−	?
Madhi 2021	?	−	−	+
Polack 2020	−	?	+	+
Sadoff 2021	−	?	?	+
Shinde 2021	?	?	−	+
Tanriover 2021	−	−	?	−
Voysey 2020	−	?	?	+
Thomas 2021	−	?	+	+
Sadoff 2021	−	?	−	?
Kremsner 2021	−	?	−	−
Khobragade 2022	−	−	−	−

Falsey 2021	?	+	?	?
Fadlyana 2021	-	?	+	?
Ella 2021	-	-	-	-
EISahly 2021	?	+	+	+
Clemens 2021	-	?	-	?
Walter 2021	-	?	-	?
Thomas 2021	?	+	+	+
Pajon 2022	?	+	+	+
Moreira 2022	-	?	-	?
Halperin 2021	-	?	-	?
Dunkle 2021	-	?	+	+
Bravo 2022	-	-	-	-

Random sequence generation

Allocation concealment

Blinding of participants and personnel

Blinding of outcome assessment

+	-	-	+
-	-	-	-
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-  High risk of bias
 Low risk of bias
 Unclear risk of bias

AL

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Incomplete outcome data

Selective reporting

Other bias

OVERALL ASSESSMENT

AL



For the benefit of our readers with different professional backgrounds, we include a box at the top of the published article that is intended to bring out the key public health message of your work in a clear, accessible way. When preparing the text for this particular section, please avoid jargon and imagine a broad target audience, including for example public health policy makers and science journalists. Plain language should be used, avoiding scientific jargon.

Key public health message

What did you want to address in this study?

- [max 3-5 lines of text]

We aimed to investigate the robustness of SARS-CoV-2 vaccine efficacy trials synthesizing all published studies worldwide. 'Trial robustness' is an important yet underutilized concept to interpret results from randomized controlled trials (RCT). While good efficacy profiles have been reported for several COVID-19 vaccines, the robustness of the underlying trial results has not yet been established.

What have we learnt from this study?

- [max 3-5 lines of text]

We found high levels of trial robustness overall, however, there was substantial variation across several important trial characteristics such as sample size, blinding type, percentage loss to follow-up, and effect size. Rigorous methodological standards for trial conduct are crucial to ensure high robustness of results.

What are the implications of your findings for public health?

- [max 3-5 lines of text]

Results from SARS-CoV-2 vaccine trials are overall very trustworthy, which is important data in times of rising vaccine hesitancy and scepticism towards medical research methods. Only reporting effect sizes and p-value based 'statistical significance' does not capture the complexities of trial results sufficiently well. We recommend to make the reporting of trial robustness standard practices for vaccine efficacy RCTs more generally alongside established trial outcome measures.