Viability of local vaccine production in developing countries: An economic analysis of cost structures, revenue sizes, market shares and vaccine prices

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February 2017

A thesis submitted for the degree of Doctor of Philosophy of

The Australian National University

Statement of Originality

I declare that this thesis is the result of original research, and has not been submitted in whole or in part to this, or any other university, for the attainment of a formal qualification. The questionnaire in the appendix of Chapter 3 was developed by the author under close supervision of two senior vaccine experts in WHO. Except where otherwise acknowledged in the text, this thesis represents my own original work.

Signed:____

Acknowledgements

Each PhD journey is unique. Mine is coloured by continuous changes that one would perhaps expect yet not fully anticipate from committing to a journey of four years. The completion of this thesis owes greatly to the support and assistance of many people, which I would like to acknowledge.

Not often is a PhD bestowed with two different Chair supervisors, and I am deeply indebted to both. During the first half of my PhD candidature, my Chair supervisor was Professor James R.G. Butler, who had given me the grounding, support and flexibility which laid the foundation of my research. For the second half of my candidature, my Chair supervisor was Professor Archie Clements. His encouragement, dedication and patience is what led the completion of my PhD research. I am so grateful for his support, careful eye and insightful feedback. I feel my thesis has had the best of two worlds, for this I am truly blessed.

This thesis has benefitted greatly from the members of my PhD supervisory panel, Dr Martin Friede, Louise Carter, Dr Ines Atmosukarto and Dr Yijuan Chen. I am grateful for their timely advice, vast experience and constructive feedback which shaped the thesis analysis. A special thank you to Mba Ines for the many discussions and encouragements that she provided; and to Martin for allowing me to work with his TTi team at WHO/HQ. His team housed my internship and research visit, and allowed me to tap into their network. In particular is Dr.Jan Hendriks, who had kindly co-supervised my visit at WHO/HQ given the challenges of the Ebola pandemic needing Martin's attention at the time.

I would like to acknowledge the financial and technical support provided by the Australian government through the Australian Leadership Awards scholarship and research grant of the Allison Sudradjat Prize that has allowed me to pursue my PhD research and attend a number of research-related travels. I would also like to acknowledge the supplemental stipend provided by the ANU, the PhD research funding provided by RSPH, the ANU Vice-Chancellor's travel grant and a travel sponsorship from WHO/HQ. The administrative support provided by the DFAT/Australia Awards liaison team at the ANU under the leadership of Gina Abarquez is greatly acknowledged. I would also like to thank the RSPH administrative team, in particular Jaimee Bell, Laura Vitler, Peter Ward, Helen Wong, Bec Moss and Greg Rathbone.

Research requires data, yet not all data is available publicly. I would like to thank the participation of the ten questionnaire respondents as well as the four vaccine manufacturers that I interviewed. I am grateful for the kind support and assistance from Laure Dumolard at WHO-HQ and Dr Valentin Todorov from UNIDO by providing me access to data that my PhD has drawn its analysis from. I am grateful for the kind support of the staff, consultants and partners in WHO, GAVI, UNIDO, PATH that I had communicated with during the three month fieldwork in Geneva and afterwards. Their time, insight and suggestions have helped sharpen my analysis and understanding of developing country vaccine manufacturing.

During the course of my PhD I have drawn upon numerous insights from the conferences that I attended and presented, as well as a Summer course on vaccines at the LSHTM where I was fortunate to consult with Professor Anne Mills, Professor Kim Mullholland, and Dr Ulla Griffiths. I am particularly grateful for the many mentors, past and present, which lent their support and generous feedback during the formation and conduct of the thesis research. In particular are Dr Julie Milstien, Dr Sarah Barber, and Professor Hal Hill. Many field experts have also been generous in lending their insights. Among them are Dr Raymond Hutubessy, Dr Miloud Kaddar, Alastair West and Dr Robert Sparrow. I would also like to thank Dr Alice Richardson and Dr Pauline Ding for their consultations on the statistical aspects of my data analysis; Dr Shea Andrews for providing a better understanding of multilevel and mixed-model regression models, Dr Jane Desborough for introducing me to the convergent design method as well as the Research Training team, and ASLC at ANU for their research skills and trainings.

A PhD is said to be a lonely journey – but no journey is ever silent, even when it is done in essence, alone. I am grateful for the many friendships and communities that I have found in Canberra. The friendships I've developed at the ANU campus and off-campus mostly through my son's friendships from the three childcare centres and the primary school that he attended in Canberra. I am especially grateful for the friendships at RSPH, Graduate House, SUAW sessions and the ANU Thesis Boot Camp. The Indonesian community in Canberra has also been a source of comfort and support, providing a feel of home away from home, which I appreciate dearly. I am also incredibly grateful for the friends in Geneva whom I reconnected with as well as developed new friendships – they provided an incredible supportive environment during my three month fieldwork at WHO headquarters.

To my family, particularly to my two pillars of strength, Bunda and Abah, I owe the world over. My dad's own PhD journey is a source of inspiration that I have drawn upon throughout my PhD. My mother, I cannot thank enough for each and every day that I would draw upon her wisdom, prayers, patience and love. She is a source of inspiration and strength. I do not have enough words to thank them both. I am most humbled by the support and encouragement from my siblings, Abang, Taufik, Ayed and their families, as well as my mother in law, Mama Nahdiar. Though we are all geographically spread, their love and support has been very much felt.

I would like to acknowledge my husband Kiki, and thank him for his incredible faith, continuous encouragement and full support in me pursuing my research. This PhD thesis would definitely not have materialised otherwise. My husband and I had planned our PhDs to be done one after the other. Though the process may have skewed a bit from what we had envisioned it to be, I feel that the 7.5 year PhD journey we've had in total, has certainly taught us greatly. Knowing that I have another researcher's back, especially one with love, has been a powerful source of strength. I am eternally grateful for his support. To my thoughtful and inquisitive son, Omar. I am thankful beyond words for your support and companionship. Arriving in Canberra at the tender age of 2, braving the childcare system cold turkey, in an even more foreign country than your birthplace. You have taught me the meaning of unconditional love and having faith in me despite not knowing what a PhD or thesis actually means. I hope that one day you may understand why at times I was not there to accompany you.

Finally, this thesis is dedicated to my mother, Syarifah Halimah and the brave women in my lineage, who inspire me to believe that all things are possible.

Abstract

Over half of the vaccines used in developing countries' immunisation programs are supplied by developing country manufacturers. The viability of vaccine production in developing countries play a significant role in securing the global capacity of vaccine supplies. These producers however, face challenges in balancing between meeting the needs of the large population sizes and high disease burden typically found in developing country markets with uncertainties in demand forecasting and low profitability. Economic studies on the viability of vaccine production in developing countries are limited. An identification and better understanding of the critical elements influencing local vaccine production is crucial and timely, given the present need to secure and enhance the capacity of global vaccine supplies in the face of emerging and re-emerging diseases.

This thesis focuses on the viability of local vaccine production in developing countries by conducting three assessments on cost structures, revenue sizes and percent market shares, and vaccine prices. The objective of the first assessment, cost structure, is to address the supply-side barriers of local vaccine production. In the second assessment, the research utilises revenue sizes and percent market shares as a proxy of viability and quantifies the influence of vaccine viability factors on developing country vaccine production. The third assessment on vaccine prices addresses the demand side barriers to vaccines produced by developing countries and observes the influence of procurement factors on prices of vaccines produced by developing countries.

For the first assessment, on cost structures, primary data were collected from existing vaccine producers in developing countries and analysed using a cost-analysis method. Three hypothetical scenarios using different production scale and scope were applied to estimate the costs-per-dose of vaccines. The findings showed that the scale and

scope of production are essential in achieving and sustaining viability. The findings also showed that the main factors influencing viability were strong domestic sales and consistent supply, this also holds for companies planning to expand into export markets. Further, a step-cost characteristic for fixed costs, and failure rates ranging between 2% to 45%, were identified.

In the second assessment, factors were assessed for their influence on revenue sizes and percent market shares of vaccine products supplied by developing country manufacturers for immunisation programs. A multilevel regression model was built using a hierarchical dataset for years 2012 – 2014, for the overall global market as well as the domestic and export markets specifically. The findings showed that revenue sizes were influenced by national income levels, consistent production supplies and the ability to meet the needs of immunisation programs in procuring countries. While factors identified as influencing percent market share were: having consistent production, the ability to meet the needs of immunisation programs in procuring countries as well as having vaccines with prequalification status. The third assessment, on vaccine prices, was based on a mixed effects regression on a panel dataset of vaccine prices for years 2005 to 2015. The analysis found that procurement volume, method and size of vaccine formulation were influential in determining vaccine prices, for both traditional and modern technology types.

The overall findings suggest that the cost of producing vaccines in developing countries are an average of $2.05 per dose ranging between US$0.92 and $4.40. These estimates are within the cost range suggested for multinational companies (Mercer Management Consulting (2002): $0.05 to $3-4 per dose). Whilst the vaccine markets that developing country producers face are not premium markets like those found in high-income countries, this is likely compensated by the vast size of these markets and the lack of domestic competition. Their production viability however becomes challenged once they expand their production into export markets and when they produce newer technology vaccines. It is in these situations where knowledge of critical factors becomes important.

This thesis not only adds to what is known about the viability of vaccine production in developing countries, but also provides robust evidence for developing countries and global health advocates to understand better the factors driving viability in regards to costs, revenue sizes and percent market shares as well as prices. This may allow policymakers to navigate and develop policies that can further support local vaccine producers and other developing countries that are considering investing into local vaccine production.

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List of Acronyms and Abbreviations

AMC	Advance market commitment
BCG	Bacillus Calmette–Guérin
BMFG	Bill and Melinda Gates Foundation
BMBF	Federal Ministry of Education and Research, Germany
CAPEX	Capital expenditure
CIPIH	Commission on Intellectual Property Rights, Innovation and Public Health
CVI	Children's Vaccine Initiative
DALY	Disability Adjusted Life Years
DCVM	Developing country vaccine manufacturers
DCVMN	Developing Country Vaccine Manufacturers Network
DTP	Diphtheria tetanus pertussis
EPI	Expanded Program on Immunisation
GAVI	Global Alliance for Vaccines and Immunization
GFCF	Gross fixed capital formation
GMP	Good manufacturing practices
GNI	Gross National Income
GSPA-PHI	Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property
GVAP	Global Vaccine Action Plan
Hib	Haemophilus influenzae type b
HIC	High-income countries
HPV	Human papillomavirus
ICVM	Industrialised/developed country vaccine manufacturers
IPV	Inactivated poliomyelitis vaccine
IVI	International Vaccine Institute
JRF	Joint Reporting Form
LMIC	Lower-middle income country
Men-A	Meningococcal strain A
MIC	Middle income countries
MNC	Multinational companies
MVA	Manufacturing value added
NRA	National Regulatory Authority
NUV	New and underused vaccines

OPV	Oral poliomyelitis vaccine
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcal conjugate vaccine
PDVI	Pediatric Dengue Vaccine Initiative
PPS	Pneumococcal polysaccharide vaccine
PQ	Prequalification
QC	Quality control
R4D	Results for Development
UMIC	Upper-middle income country
UN	United Nations
UNICEF	United Nations Children's Fund
UNIDO	United Nations Industrial Development Organization
V3P	Vaccine Product, Price and Procurement
WHO	World Health Organization

Chapter 1 Introduction

1.1. Overview

Vaccines have been commended as one of the most cost-effective breakthroughs in public health, only second to provision of clean water (WHO, 2003). Launched in 1974 to deliver vaccines against diphtheria, tetanus, pertussis, polio, measles and tuberculosis, the expanded program for immunization (EPI) has saved approximately 20 million lives in the two decades that followed its launch (World Bank, 1993). Since then, with the advances in biotechnology and immunology, increasing numbers of vaccines are being developed and have become available. The adoption of these new and underused vaccines (NUVs) into national immunisation programs however, has not taken place in as timely a manner as expected.

The World Health Organization (WHO) estimates that to date 2 to 3 million deaths each year are currently prevented through immunisation programs (WHO, 2016b) and that there is increased access to new vaccines for low and middle income countries[1]. However, despite these impressive achievements, the immunisation programs still face major challenges, both in sustaining vaccination coverage levels as well as in ensuring equal access to new and underused vaccines (NUV) in populations that need them most, as much as 1.5 million vaccine-preventable deaths are still recorded (WHO, 2012, 2016b).

The WHO midterm review of the Global Vaccine Action Plan (GVAP) found that though many countries have achieved the 2015 global immunisation target of 90%, the average global immunisation coverage still falls short from achieving this target. These coverage rates have only risen by 1% since 2010. Whilst 16 countries recorded

[1] In 2015, 99 low and middle-income countries were recorded introducing one or more NUVs, exceeding the target of 90 countries set by the WHO Global Vaccine Action Plan (WHO, 2016a).

increases in their coverage levels, 26 countries reported no change and 25 countries experienced a net decrease from their coverage levels in 2010 (WHO, 2016a).

Global vaccine supplies are essential in ensuring that the aims of immunisation programs continue to be achieved, and in increasing accessibility to all populations around the world. The UNs Sustainable Development Goals (SDGs) promote the research and development of vaccines as a means to achieve universal health coverage, and enable access to affordable quality medicines and vaccines (UNDP, 2016).

The vaccine markets in developing and developed countries are quite distinct in terms of profitability, size and epidemiological needs. This poses a considerable challenge for vaccine manufacturers to fulfil public health needs for both developing and developed country markets in an equitable manner. WHO data show that profits and revenues are mostly generated from vaccine markets in industrialised countries. However, it is in developing country markets that population sizes and burdens of disease are highest. If left to market forces, manufacturers will most likely opt to produce vaccines for developed countries where profits are highest. This was demonstrated in a 1990 report by the Commission on Health Research for Development where a 10/90 gap was shown to exist (Milstien, Kaddar, & Kieny, 2006); in that only 10 percent of the global budget for health research is allocated to research and development (R&D) for 90 percent of the global health burden. Children in developing countries therefore are not benefitting from vaccine technology advances that have been accessible to those in developed countries.

Both policy-makers and manufacturers must address a mix of technological, political, financial, and logistical issues that affect sustainable production in many developing countries. This includes the impact of multilateral and bilateral trade agreements on the economic and public health situation of countries, such as the impact of removal of trade barriers for national manufacturers. The development of a skilled local workforce, through governmental incentives and education policies to prevent brain drain is another consideration.

This thesis examined the supply and demand side barriers of vaccine production, which are vaccine production costs and vaccine prices; and further, using revenue sizes and percent market shares as proxies for viability, to assess the factors that are critical to viability. This thesis applies economic concepts and methods in its assessments.

This research on the economic aspects of existing local vaccine producers will help developing countries and global health advocates to better understand the factors driving viability in regards to costs, revenue sizes and percent market shares as well as prices. This may allow policymakers to navigate and develop policies that can further support existing local vaccine producers and might assist other developing countries that are considering investing into new local vaccine production.

1.2. Aims of the thesis

The overarching aim of this thesis was to investigate how existing vaccine manufacturers in developing countries remain viable and what are the factors that are critical for them to gain and sustain viability in the face of changes within global vaccine markets. Critical factors for the viability of local vaccine production in developing countries were assumed to encompass three areas related to commercial production (McElliogott, 2009), these were: cost structures; revenue sizes and percent market shares; and prices.

Several research questions need to be addressed in order to examine the aspects surrounding viability of local vaccine production. These are:

- *Cost structure* - What are the cost structures in establishing vaccine manufacturing facilities in developing countries?;

- *Percent market size and shares* - How do vaccine viability factors influence the revenue sizes and percent market share of DCVMs?;
- *Vaccine prices* – How do procurement factors influence the prices of vaccines supplied by developing countries?.

1.3. Background

Local producers supply over half of the vaccines used in developing countries' immunisation programs and are recognised as important players in the industry (CVI & WHO, 1999; Jadhav, Gautam, & Gairola, 2014). These vaccine manufacturers have made huge strides over the past 30 years, expanding their production and switching their focus from primarily domestic markets and traditional vaccines to becoming a supplier of the global market by increasing capacity, improving facilities and developing NUVs.

Public health advocates are highlighting DCVMs as a central part of their strategic agenda in securing the global supply of vaccines (Hendriks, Holleman, de Boer, de Jong, & Luytjes, 2011). They are seen not only as a means to ensure adequate supply but also acknowledged for their important impact in influencing access to NUVs (WHO, 2011a). Much has changed from 30 years ago when the debate focused on whether or not supplying vaccines produced in developing country facilities was a good idea (UNIDO, 1986) (Muraskin, 1998).

A turning point in the prioritisation of DCVMs was during the emergence of the H5N1 influenza pandemic (Hendriks et al., 2011). In 20015, as requested by the World Health Assembly[2], the WHO together with its international and national partners developed strategies to expand global vaccine manufacturing capabilities, particularly in developing countries (Kieny et al., 2006). Among its strategies was the creation of a

[2] The World Health Assembly is the decision-making body of WHO. It is an annual assembly of WHO's member states which make decisions and determine the policies and priorities for WHO's mandate and agenda.

hub model, which in contrast to a typical bilateral technology transfer arrangement, has a single technology donor that transfers to multiple numbers of technology recipients. The hub model managed to boost the global capacity of influenza vaccines, in an unprecedented timeframe (Friede et al., 2011).

The importance of building capacity in developing countries to secure global supply of vaccines has been increasingly high on the global health agenda. A large part of this has been achieved through technology transfer projects (Friede et al., 2011). Some examples of technology transfer projects include the NIH dengue vaccine technology to local manufacturers like Instituto Butantan, São Paulo, Brazil, Vabiotech, Hanoi, Vietnam and Panacea Biotec Inc., New Delhi, India, Serum Institute, Puna India.

1.4. Scope of the research

The overall scope of this thesis was the human vaccines[3] market accessible to DCVMs within the context of public health programs[4]. This includes both production and sales of vaccines by DCVMs, limited to those used for immunisation programs[5]. These include immunisation programs in developing countries and elsewhere.

The research questions examined by this thesis are specific to the viability of public-market vaccine production that is owned[6] by developing countries – and more specifically, the critical factors influencing costs, revenue sizes and percent market shares as well as vaccine prices. The critical factors relating to these three aspects are analysed separately.

[3] further referred to as 'vaccines'
[4] This will be referred to as national immunisation programs in this thesis.
[5] Two markets exist for vaccines: public and private market. Public market vaccines are those procured by governments and used in immunisation programs, while private market vaccines are procured by individuals and administered privately by health personnel. This thesis focuses on public-market vaccines only.
[6] This thesis takes on production based on ownership as opposed to a location basis, where the latter may include production facilities owned by multinational manufacturers and based in developing countries.

This thesis refers to two groups of vaccine manufacturers, based on their country of origin and income levels. These two groups are developing country vaccine manufacturers (DCVMs)[7] and developed/industrialised country vaccine manufacturers (ICVMs). This thesis focuses on the vaccines market relevant to DCVMs only. Therefore, though local producers[8] also exists in developed countries[9], the term local production/local producers in this thesis refers only to DCVMs.

In this thesis, classification of countries follows the World Bank's classifications based on Gross National Income (GNI) per capita, using the Atlas method[10] (Appendix 2.1). These are: high income countries (HIC) ($12,736 or more), middle income countries (MIC) (more than $1,045 but less than $12,736) and low income countries (LIC) ($1,045 or less). The term 'developing countries' refers to the latter two, while 'developed countries' refers to those in the HIC bracket. MIC countries are further segregated by lower-middle (LMIC) and upper middle (UMIC) with a GNI per capita threshold of $4,125. This thesis was not intended to study the difference between the lower and upper middle groups in the middle income bracket but may refer to these classes when needed. Furthermore, a network of DCVMs does exist, also known as the Developing Country Vaccine Manufacturers Network (DCVMN), yet this thesis refers to DCVMs based on their country status and not membership of the DCVMN[11] because some DCVMN members include those that are no longer categorised as developing countries.

[7] DCMs are also often referred to as local producers and emerging suppliers.

[8] Refers to manufacturers based in a country and majority of ownership is by an entity of that country, either public or privately owned

[9] Many local producers in developed countries however have become privatised, acquired or dissolved, such as those in the Netherlands (RVIM/Bilthoven), Italy (Sclavo SpA), etc.

[10] Using the Atlas methodology in calculating GNI reduces the impact of exchange rate fluctuations caused by inflation. The Atlas conversion factor is based on the a country's exchange rate, taken as an average of a given year and its two preceding years, and then adjusts the difference between the inflation rate of the country and at the international level (World Bank data methodology, 2016).

[11] This thesis therefore excludes some DCVMN members that are developing countries which production data may not appear during the study period observed; as well as members that are now high income countries such as Republic of Korea, Taiwan, etc.

An example of this would be the Republic of Korea (hereafter referred to as South Korea). South Korea was classified in the past as a developing country, and is now considered a HIC due to the rise in its national income level[12]. Two of its vaccine manufactures however, are local producers[13]. Studies in the past, including some recent studies have included Korean production when reviewing DCVMs. However, for consistency, the countries included in the research are those that were classified as either low or middle income in 2012 (the start of the study period), thereby excluding South Korea. Of note, Argentina's classification switched from middle income (2012 – 2013) to high income in 2014 but data from Argentina in 2014 were included in this thesis as per the criterion described above. Furthermore, in Chapter 4, the DCVMs that were present in the observed timeframe were all in countries that are classified as middle income. This is partly due to progress and changes in the economic status of these producing countries over time. It is also important to highlight that in Chapter 5 the panel dataset period is longer than mentioned above (2005 – 2015). The observed manufacturers were still consistent however with those included in Chapter 4. As such, the thesis includes DCVMs in countries that were classified as middle-income countries in 2012.

1.5. Organisation of the thesis

Following on from this introductory chapter, which covers the aims and scope of the research, the thesis is comprised of five subsequent chapters:

Chapter 2, presents a review of the existing literature to identify gaps in knowledge and provide context for the research. The literature review focused on local production of vaccines in developing countries, with a particular emphasis on vaccines supplied for immunisation programs globally. The chapter provided the reasoning and background

[12] GNI per capita is often referred to as national income level, while total GNI is referred to as national income size.

[13] One of these producers have now been acquired by a multinational, therefore only one remains a local producers.

as to how local production of vaccines has emerged and contributed to the global supply of vaccines, and discussed the economics and production process of vaccines, providing the foundations on which the analyses in chapters 3, 4 and 5 were established.

Chapter 3, “The cost structures of establishing new vaccine manufacturing facilities in developing countries”, is the first of three analysis chapters. This chapter used a cost analysis method to assess vaccine production costs in developing countries. Given the sensitivity of the topic, the data were derived from a questionnaire with self-reported responses and used cost ranges. The study used three hypothetical scenarios of production scale and scope to enable comparative analysis. Data were generated from eight vaccine manufacturers from different countries, which provided data for 12 vaccine products. The results included estimates of the costs-per-dose from fixed and variable cost components, as well as the patterns of these costs overall and for a number of cost drivers. The cost drivers analysed in this chapter were: production scale and scope, vaccine technology types and vaccine formulations.

Chapter 4, “A multilevel modelling analysis of viability factors for vaccine production in developing countries”, examined the viability determinants of developing country vaccine production. A three-level hierarchical panel dataset[14] for a three-year period (2012 – 2014) was developed for this chapter. The dataset was compiled from disaggregated panel datasets developed by WHO, the World Bank, UNICEF and other relevant sources. Using global, domestic and export revenue sizes as well as global and export market shares as proxies for viability, the influence of a range of determining factors was analysed using multilevel regression.

[14] level one: vaccine type; level two: manufacturer; level three: producing country. The data structure was hierarchical/nested.

Chapter 5, "A mixed-effects model of the association between procurement factors and prices of vaccines produced by developing countries", assessed the influence of procurement factors on vaccine prices from developing country manufacturers. Using a vaccine price database across 11 years (2005 – 2015), a mixed-effects regression was undertaken. The analysis was conducted at the transactional level, and a comparison was made between factors influencing prices of vaccines produced by developing countries in general, as well as by technology level, defined as traditional vaccine types and NUVs.

Chapter 6, "Discussion", interpreted the findings of the analyses presented in chapters 3, 4 and 5 within the context of the overarching aim, examined their implications for global vaccine manufacturing policy and practice, outlined the study limitations and suggested future research work.

Chapter 2 Background

2.1. Introduction

This chapter reviews the existing literature on vaccine production in developing countries, particularly vaccines supplied to immunisation programs. The literature review is organised in nine sections. The next two sections (2.2 and 2.3) provide a historical perspective as well as the landscape of recent developments in vaccine production that have shaped DCVMs. An overview of the economics of vaccines is featured in section 2.4. This is then followed by sections 2.5 and 2.6 that present studies on the merit and challenges of DCVMs and their production viability. The last two sections of the chapter present existing literature on vaccine production costs and vaccine prices. This chapter closes with a summary and rationale of the three specific aims encompassing the thesis.

2.2. Historical perspective

Though there seems to be a clear divide at the present time between vaccine producers in developing countries and those in the industrialised world, vaccine producers before advent of the 21st century had many similarities, primarily in that they were not established for profit gains. Vaccine production in the past was mainly a government activity, and was meant to supply public health programs with newly developed vaccines. Vaccine manufacturers were mostly research institutes, hospitals and universities, while some were public-private, non-profit foundations such as the Mérieux Biological Institute and the Pasteur Institute. (Milstien, Costa, Jadhav, & Dhere, 2009; van Noort, 1992).

As for the production of vaccines in developing countries, this was mainly initiated during the colonial era. During this period, international travel exposed citizens of colonizing countries to tropical diseases (de Knecht-van Eekelen, 1989; Moulin, 1992).

This, along with some non-colonized country requests[15], instigated the Pasteur Institute in France to establish laboratories in various developing countries as early as 1891 (Saigon, Vietnam) (Figure 2.1). Their mission was to research and develop products such as the Bacillus Calmette–Guérin (BCG) and diphtheria–tetanus–pertussis (DTP) vaccines as well as the rabies vaccine, anti-toxins and antivenins (Guénel, 1999) (Milstien et al., 2009). As documented by Dedet (2008) and shown in Figure 2.1, 57 Pasteur Institutes were established world-wide, yet only 22 are still in operation (shown

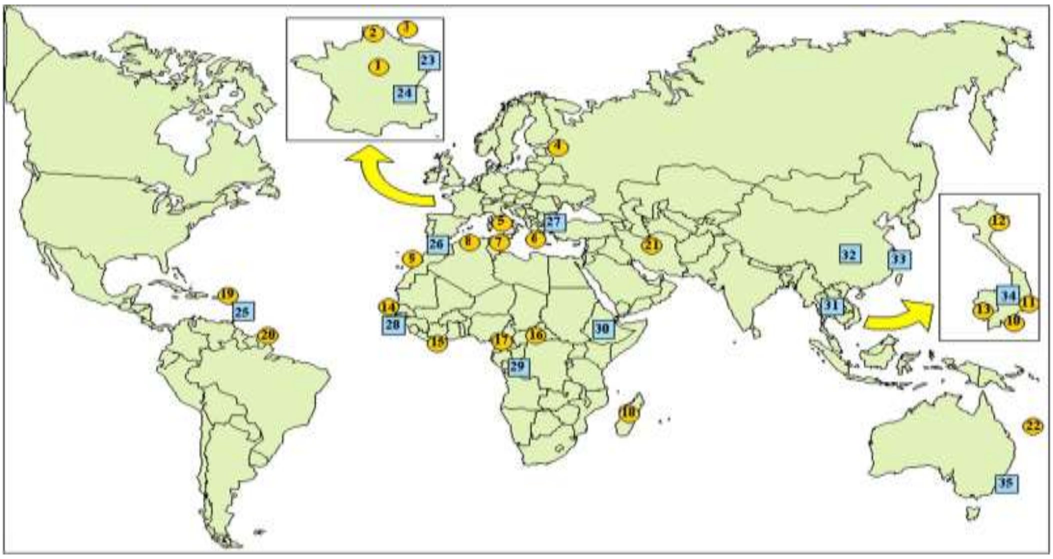

Figure 2.1 Pasteur Institutes worldwide in 2008. Note: (Not shown are associate institutes and recent creations). Round symbols: 22 Pasteur Institutes still in operation: 1: Institut Pasteur (Paris, France); 2: Institut Pasteur de Lille (France); 3: Institut Pasteur du Brabant (now Brussels, Belgium); 4: Institut Pasteur de St. Petersbourg (Russia); 5: Institut Pasteur de Rome (Italy); 6: Institut Pasteur hellénique (Greece); 7: Institut Pasteur de Tunis (Tunisia); 8: Institut Pasteur d'Algérie; 9: Institut Pasteur du Maroc (Casablanca, Morocco); 10: Institut Pasteur de Saigon (now Ho Chi Minh City, Vietnam); 11: Institut Pasteur de Nhatrang (Vietnam); 12: Institut Pasteur d'Hanoi (Vietnam); 13: Institut Pasteur de Phnom Penh (Cambodia); 14: Institut Pasteur de Dakar (Senegal); 15: Institut Pasteur de Côte d'Ivoire (Abidjan, Ivory Coast); 16: Institut Pasteur de Bangui (Central African Republic); 17: Centre Pasteur de Yaoundé (Cameroon); 18: Institut Pasteur de Madagascar; 19: Institut Pasteur de Guadeloupe (French West Indies); 20: Institut Pasteur de Guyane française (French Guiana); 21: Institut Pasteur de Teheran (Iran); 22: Institut Pasteur de Nouvelle Calédonie (New Caledonia) Caledonia. Square symbols: 35 Pasteur Institutes which are no longer in existence: 23: Institut Pasteur de Strasbourg (France); 24: Institut Pasteur de Lyon (France); 25: Institut Pasteur de Martinique (French West Indies); 26: Institut Pasteur de Tanger (Tangiers, Morocco); 27: Institut impérial de Bactériologie de Constantinople (Turkey); 28: Institut Pasteur de Kindia (Guinea); 29: Institut Pasteur de Brazzaville (Congo); 30: Institut Pasteur d'Ethiopie (Addis Ababa, Ethiopia); 31: Institut Pasteur de Bangkok (Thailand); 32: Institut Pasteur de Chengdu (China); 33: Institut Pasteur de Shanghai (China); 34: Institut Pasteur de Dalat (Vietnam); 35: Institut Pasteur d'Australie (Sydney, Australia). Reproduced from Dedet (2008).

[15] Iran, a non-western colony, requested that the Pasteur Institute in Paris establish a laboratory which is now known as the Pasteur Institute of Iran, in the aftermath of the influenza pandemic in 1918-1919. http://www.iranicaonline.org/articles/institut-pasteur-1

as yellow circles in Figure 2.1), and 35 establishments (shown as blue squares in Figure 2.1) no longer exist.

Many of the public manufacturers in Europe and the United States later became privatised as a result of the various challenges faced. These challenges included issues around production management, the need to acquire new technologies, as well as the challenges to fulfil the progressing standards of good manufacturing practices (GMP), where the GMP is a global regulatory standard in vaccine production practices. A number of mergers and acquisitions then took place and have led to the emergence of multinational (MNC) vaccine companies, which have now become the dominant entities of the vaccines industry that we know today.

DCVMs have also evolved. After the 1960s, particularly with political developments regarding sovereignty taking place within many developing countries, the status of vaccine manufacturers such as Pasteur Institutes have changed. As a result of negotiations with the Pasteur Institute in Paris, local institutions have either dissolved, remained linked or continued without the Pasteur affiliation (Brès & Chambon, 1982); (Milstien et al., 2009).

2.3. Landscape of recent developments in the vaccine market

Despite the success of immunisation programs established in the late 1970s, the subsequent advances and discoveries of new vaccines have not been equally accessible to developing countries. Mahoney and Maynard (1999) and Vandersmissen (2001) note that vaccines typically take between 20 – 30 years from first licensing, usually in the private market of developed countries, to reach the public markets in the developing world. Prior to the last 15 years, NUVs were disproportionately available to affluent countries, yet this has now changed thanks to the concerted efforts of public health advocates and international organisations.

2.3.1. Tiered pricing mechanism for vaccines

In 2000, WHO called for a movement towards equity pricing based on income level classifications developed by the World Bank (WHO, 2001). The aim of this proposal was to enable the lowest prices for the poorest countries.

Conceptually, in a tiered pricing mechanism producers charge different prices for different units of the same product, yet not due to the differences in costs. Economic theory suggest that producers are still gaining profit from differentiating prices because it allows them to cater for 1) different buyers that are willing to pay a different amount for the same product, and 2) a buyer who is willing to pay a different dollar amount for different units of the same product. This way, a tiered pricing mechanism allows producers to capture some of the consumers' surplus that would otherwise go to buyers (Figure 2.2).

Figure 2.2 The economic concept of a tiered pricing mechanism.

Multiple prices permit a seller to capture consumers' surplus. As seen in Figure 2.2, with differentiated prices, manufacturers may capture more of the consumers' surplus compared to a condition where it is only restricted to two different price levels.

The operation of tiered pricing is however dependent upon the ability of the producer to segment the markets in which different prices are charged. Since vaccines are a particular product which require certain conditions in their handling, leakage between markets is quite difficult. From an economic efficiency perspective, the more tiers linked to different prices and levels of development the better. Administratively however, the more complicated the system, the more difficult it will be to police any system and prevent parallel importation.

The use of a tiered pricing system allows licensed vaccines to be accessed by the poorest countries without much delay. The rationale is that new vaccines can be made available to developing countries reduced prices, because these are offset by higher prices charged for the same product in more affluent markets. This way, manufacturers can recover their investments while making the product available in developing country markets at the same time.

The development and support for tiered pricing was essential in enabling early introduction of newer vaccines in to the developing world. This mechanism was further advocated and enforced through a body known as the Global Alliance for Vaccines and Immunization (GAVI), which was established in January 2000. This alliance, later known as the GAVI Alliance, focused its efforts on supporting countries to introduce NUVs as well as support countries in strengthening their immunisation systems in coping with the introduction of new vaccines. GAVI procures its vaccines in bulk through UNICEF and PAHO's pooled procurement mechanism. The prices of these vaccine are usually already tiered, and tailored to different markets.

The success of tiered pricing was due to several factors. Firstly, the vaccines procured in the 1980s and 1990s were mostly similar across markets, enabling vaccine manufacturers to recoup their production costs by way of the tiered/differential pricing arrangement whereby they sold the same vaccines at higher prices to developed countries, allowing for cost-recuperation while selling at lower and more affordable prices to developing countries. This was done through the coordination of the United Nations Children's Fund (UNICEF) and Pan American Health Organization (PAHO) (Batson, 2005). Secondly, vaccine manufacturers tended to keep an excess production capacity for many of the traditional vaccines, enabling them to supply vaccines at a low price to developing countries without having to invest in expanding production capacity. Thirdly, until the 1980s, the number of vaccine suppliers was large enough to maintain competition, effectively keeping vaccine prices low. Lastly, as described by Plahte (2005), tiered pricing, though often mistaken for a subsidy, in fact provides economic benefits for all parties involved: consumers in the lower priced market benefit from having access to a product that would not have otherwise been available; producers, who gain a larger revenue and profit; and consumers in the higher-priced market, who benefit from prices being slightly lower than if the tier-price mechanism wasn't introduced.

2.3.2. Market shaping strategies

As advances in biotechnology enabled new and more advanced vaccine products, the demand for vaccines used in developed and developing countries however started to differ, and the dynamics of the market changed even further. Immunization programs in developed countries started to demand newer antigens and technology advancements on existing vaccines, taking them further from the traditional set of vaccines afforded by developing countries (Hausdorff, 1996).

Tiered pricing is very much dependent on homogenous immunization schedules and demand across high and low income countries. Therefore, when vaccine requirements differ between developed and developing countries, it becomes difficult to maintain excess capacities and economies of scale, and in the end, price tiering becomes even more difficult to sustain. This market divergence phenomenon later became more prominent in the vaccine market and highlighted the need for new and longer-lasting strategies (Jarrett, 2008; Levine, Kremer, & Albright, 2005; Milstien, 2010; Milstien et al., 2006).

In response to market divergence between high and low-income countries, a number of market shaping strategies have been devised under the framework of push and pull mechanisms. A push mechanism provides a guarantee (Berkley, 2014) for developers to invest in R&D of a new drug; while pull mechanisms ensure that the product developed will be purchased.

Though Kremer (2000) highlighted that there could be many risks to society in regards to push mechanisms due to adverse selection and moral hazard, some initiatives that have been developed based on the principles of push and pull mechanisms have showed a significant influence in the vaccine market. An example with regards to pull mechanisms is the advance market commitment (AMC), whereby a market is essentially created ahead of time so that vaccine manufacturers are willing to sell their vaccines at a price that would only be available at a much later timeframe. This strategy has been used to support countries in producing the pneumococcal conjugate vaccine, an NUV. The introduction time gap between high and low income countries was around five years (Figure 2.3).

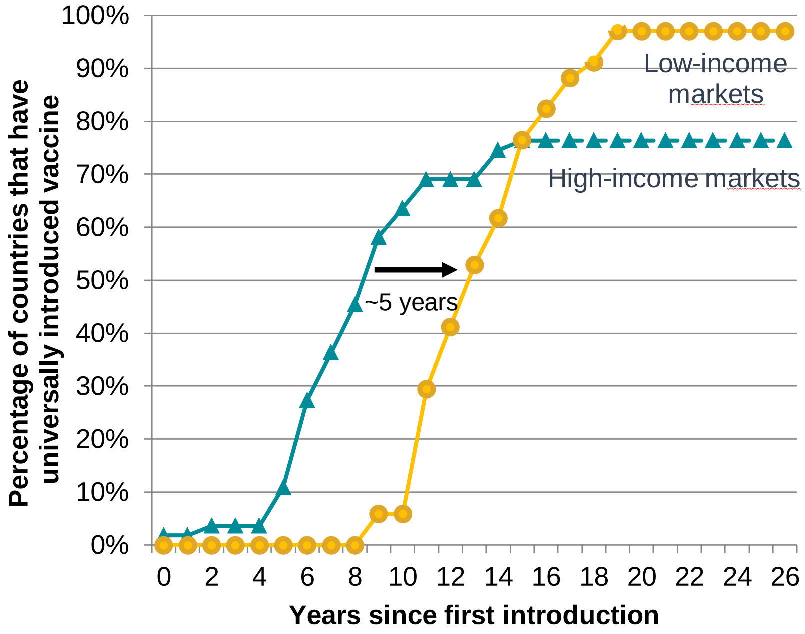

Figure 2.3. Pneumococcal conjugate vaccine (PCV) introduction: high- and low-income markets. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub Global Vaccine Introduction and Implementation Report, June 2016; and Batson (2014).

The practices of push mechanisms have also produced significant results, such as through the development of the meningococcal strain A vaccine (Men-A) by the Serum Institute of India and the more recent dengue vaccine developed by Sanofi Pasteur in partnership with the International Vaccine Institute (IVI)'s Pediatric Dengue Vaccine Initiative (PDVI) (IVI, 2006; Sanofi Pasteur, 2013). The PDVI receives support from the Bill and Melinda Gates Foundation (BMGF), a major financier and investor in public health. While the market-shaping strategy for the Men-A vaccine, which was also supported by the BMGF, in its tendering process attracted many vaccine manufacturers including DCVMs[16].

Vaccines are also procured for the private markets in developing countries. Private markets are estimated to account for 5–10% of total vaccine sales in developing countries (WHO, 2016d). Private-sector demand mainly consists of more affluent

[16] Personal communication with SII representative.

population segments in developing countries that decide to take on responsibility for their own immunization, using preferred presentations not offered by the public sector. The private sector plays a generally small role on the demand side of vaccines except in some populated countries with rapid economic growth, where demand from middle classes for new and non-EPI vaccines can be of significant value.

In recent decades, the importance of building capacity for vaccine production in developing countries has increased, particularly with the re-emergence of a highly pathogenic avian influenza (Hendriks et al., 2011). The Fifty-eighth World Health Assembly in 2005 (resolution WHA58.5) requested WHO to seek ways that would reduce the global shortage of influenza vaccines for both epidemics and pandemics, and encourage more R&D into new and improved vaccines (Friede et al., 2011). Among the resulting efforts, WHO supported the expansion of global manufacturing capability, particularly in developing countries, by creating a hub model for the technology transfer of influenza vaccines, which boosted the global capacity in an unprecedented timeframe. The Bill and Melinda Gates Foundation, a prominent supporter of global health, is in the midst of commissioning studies focusing on developing countries' vaccine production and related costs (Shulman, 2014) (BMGF, 2014). The Federal Ministry of Education and Research (BMBF) in Germany has also invested in developing countries' vaccine production and capacity building, by supporting dengue vaccine production in Brazil and Vietnam (IVI, 2014). In addition, preliminary discussions are also underway to review the potential of increasing the capacity of local production in disproportionately low vaccine-producing regions, through initiatives such as the African Vaccine Manufacturing Initiative (AVMI) (KPMG Africa, 2014; UNIDO, 2014).

2.4. The economics of local vaccine production

To fully understand how changes in the vaccine market have taken effect, it is important to understand the characteristics that make vaccines distinct from other pharmaceutical products.

Vaccines are a type of pharmaceutical product that are of a biological nature and are typically used for disease prevention rather than treatment or cure (Milstien, Batson, & Wertheimer, 2005). Widespread use of certain vaccines has eliminated infectious diseases such as smallpox, and substantially reduced the incidence and mortality of respiratory infections associated with measles and pertussis; vaccines have the potential to protect unvaccinated people by reducing the circulation of infectious agents through a process called herd immunity.

The definition of a vaccine provided by the WHO is as follows: "A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters." These characteristics of vaccines affect their production and the market in which they are supplied, in multiple ways.

First is the vaccine's biological nature and the fact that it is mainly administered to healthy individuals from populations that are often vulnerable[17]. This poses strong imperative on ensuring vaccine safety and efficacy, resulting in strict regulatory

[17] Such as infants, pregnant mothers and elderly individuals.

requirements for license approval that are often more stringent compared to other pharmaceutical products[18].

Second, as a public health instrument, the major purchasers of vaccines are usually governments. The use of public funds therefore, puts much pressure on the prices at which a manufacturer is able to sell its vaccines. These two pressures alone have led many manufacturers in the past to find the vaccine market unattractive, and to decide to leave the market (M. V. Pauly, 2005), leading to a higher level of market imperfection and market concentration (P. Danzon & Pereira, 2005; Hendriks, 2012).

Third, the capital cost in producing vaccines, similar to other pharmaceuticals, is high; while compared to other pharmaceuticals products, the profit margins for vaccines are lower. Further, despite the lower dosage usually required for vaccines, the level of pricing that can be charged, particularly in developing countries, is significantly lower compared to other biologicals (Prifti, 2010; Sinclair, Latham, Wen, Ellis, and Pujar, 2015).

Finally, vaccines with different antigens have different markets that often do not overlap with one another[19] (Arnould & DeBrock, 1996), resulting in high market concentrations within individual vaccine markets. Currently licensed vaccines prevent against up to 25 different diseases, while the number of vaccine products available are much higher given that some are combination vaccines while some are formulated for different age

[18] There is no concept of a true generic product for vaccines. A vaccine made in a new facility is treated as a new vaccine and has to undergo rigorous preclinical and clinical studies to be approved for use, often requiring a dedicated facility for its manufacturing. Unlike drugs, where generics are made and licensed based on chemical equivalence, a simple bioequivalence is not adequate proof that a vaccine will be safe and efficacious. The implication of this is that producing a copy of an existing vaccine is still expensive and time consuming.

[19] Vaccine product that do not overlap with one another are those catered for distinctive diseases such as vaccines for Poliomyelitis and Hepatitis B. However some vaccines may be in competition with one another in the case of similar vaccines perceived as using more advanced methods, such as the oral poliomyelitis (OPV) and inactivated poliomyelitis (IPV) vaccines, also when combination forms are developed such as DTP-Hepatitis B-IPV vaccine.

groups and geographical needs[20] (Smith, Lipsitch, & Almond, 2011) most of which become individual markets that do not compete with one another. Demand for a pentavalent vaccine (DTP, Hepatitis B and Hib) may not be equivalent to the demand for a quadrivalent vaccine (DTP and Hepatitis B only). Further, vaccine production involves a large range of biological agents, which allows very limited standardization of production process and outputs (Wang & Singh, 2013). In manufacturing a vaccine, the goal is to develop a process that can consistently produce vaccines that are safe and efficacious. This starts at the vaccine discovery stage, and up to the clinical study and commercial supply stages in which the requirement is that the vaccine can preserve the defined immunological properties from the discovery stage (Pujar et al., 2014).

Sinclair et al. (2015) suggest that the capital required to produce vaccines is higher than for other pharmaceutical products. They reported that the capital intensity[21] of the biopharmaceutical industry, calculated as a percentage capital expenditure divided by total revenue, was 12.4%, which was much higher than the general pharmaceutical sector at 9%. This high capital intensity might explain the high costs of manufacturing vaccines, whilst indicating that cost reductions will be difficult to achieve. Sinclair et al. (2015) suggested that if manufacturing capital requirements do not change, the capital intensity value will increase further as health care providers and competitive products put increasing pressure on biopharmaceutical and vaccine pricing.

Vaccines can be generally differentiated into three different groups, based on their market structure and characteristics (Table 2.1).

[20] Examples of vaccines for different age groups are the Pneumococcal conjugate (PCV) vaccine for infants and the Pneumococcal polysaccharide (PPS) vaccine for adolescents and adults. While examples of vaccines for different geographical needs are the Meningococcal strain C (Men-C) vaccine for UK and Australia; and the Meningococcal strain A (Men-A) vaccine for the African region.

[21] The level of capital intensity measures the amount of capital required per dollar of revenue generated.

Table 2.1. Vaccines categories, based on market structure and characteristics

	TRADITIONAL VACCINES	NEW AND UNDERUSED VACCINES	VACCINES IN DEVELOPMENT
MARKET STRUCTURE AND CHARACTERISTIC	• Typically 'mature' vaccines - in the market for decades • Saturated market • Off-patent products, • Sold at very low prices • Low marginal rates of return to producers. • Old technology • increasingly efficient to produce: • learning curve (over time) • economies of scale (cost/dose lowers as volume increases) • Limited incentive for R&D investment • Producers mostly local manufacturers in developing countries • Advanced version exist for a divergent market (marketed for developed countries	• Slow adoption in developing countries, despite being available in developed countries for a long time • Though introduced at tiered prices, the price is higher than traditional (EPI) vaccine prices • Many supply chain systems in developing countries not yet adapted to incorporate NUVs • Inadequate national disease burden data • High sunk costs, • More advanced technology • Typically oligopoly (or duopoly) • Still on patent ('product-patent' not 'process-patent') • High incentive for R&D investment • Producers are mostly multinational firms.	• Potential monopoly for first inventors • High incentive for R&D investment • Producers mostly multinational firms and biotechnology companies
EXAMPLES	• Poliomyelitis (OPV), • Tetanus, • Diphtheria, • Pertussis, • Measles, • Hepatitis B, • Haemophilus influenzae type b (Hib), • Meningococcal meningitis • Tuberculosis (BCG), • Yellow Fever	• Cholera • Dengue • Hepatitis A • Hepatitis E • Human papillomavirus (HPV) • Influenza • Japanese encephalitis • Malaria • Mumps • Pneumococcal disease • Rabies • Rotavirus • Rubella • Tick-borne encephalitis • Typhoid • Varicella	• Campylobacter jejuni • Chagas Disease • Chikungunya • Dengue • Enterotoxigenic Escherichia coli • Enterovirus 71 (EV71) • Group B Streptococcus (GBS) • Herpes Simplex Virus • HIV-1 • Human Hookworm Disease • Leishmaniasis • Malaria • Nipah Virus • Nontyphoidal Salmonella Disease • Norovirus • Paratyphoid fever • Respiratory Syncytial Virus (RSV) • Schistosomiasis • Shigella • Staphylococcus aureus • Streptococcus pneumoniae • Streptococcus pyrogenes • Tuberculosis • Universal Influenza Vaccine

Source: Adapted from Batson, Glass, and Seiguer (2003), WHO and other sources.

Manufacturers in developing countries mostly produce vaccines in the first and second category. By contrast, pipeline vaccines in the third category are mostly produced by multinational producers and biotechnology firms.

Economic theory suggests that the supply of a product depends on the market that the producer faces. A limited number of multinational pharmaceutical firms dominate the global vaccine market (Figure 2.4). The role DCVMs in the global vaccine market is relatively small, but it is increasing over time (Figure 2.5).

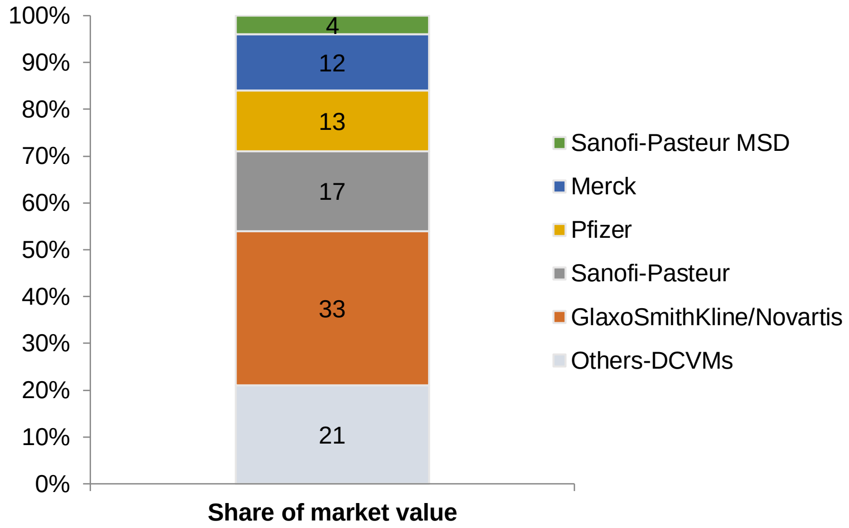

Figure 2.4. Global vaccine sales by supplier (value) in 2012. Source: Batson (2014).

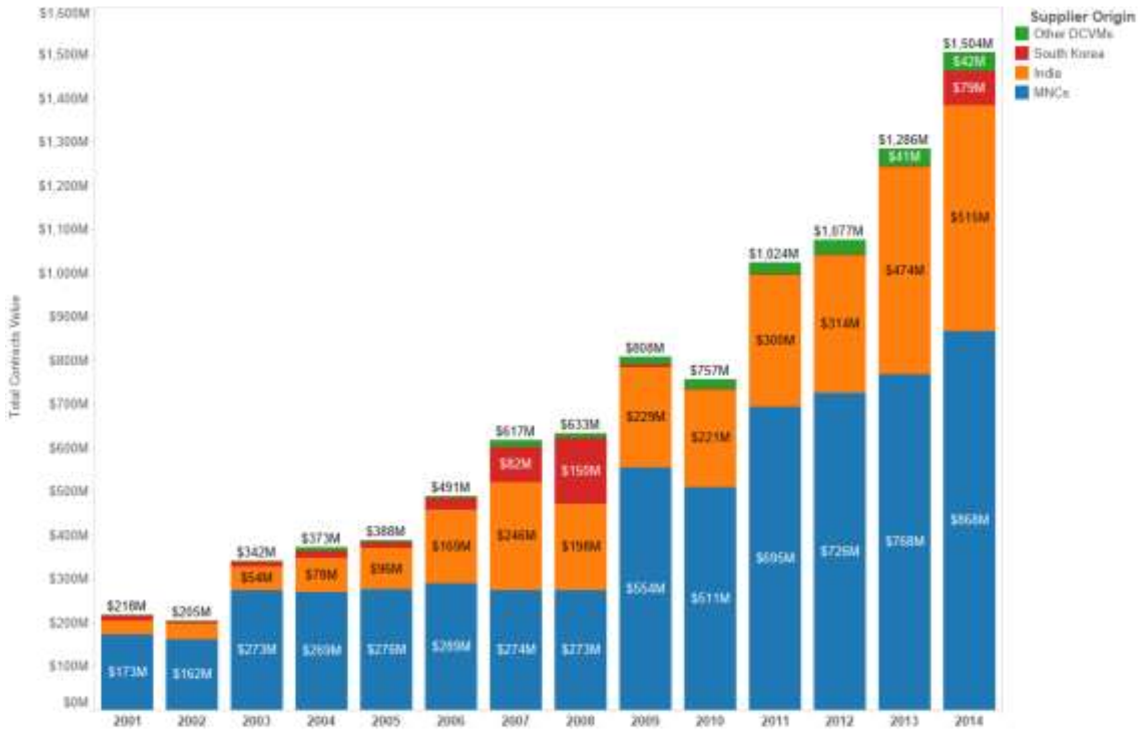

Figure 2.5. Supplier origins and values of UNICEF vaccine purchases over time (2001 – 2014). Source: Reproduced from Batson (2014).

A huge gap however exists between vaccine markets in industrialised and developing countries, where the revenue of vaccine sales is still mainly driven by vaccine markets in industrialised or high-income countries (Figure 2.6) yet the majority of disease burden and global population in need of vaccines is found in developing countries (Figure 2.7). This gap poses a challenge for manufacturers globally, because sustainable production needs to be driven by economic incentives (Robbins & Arita, 1994).

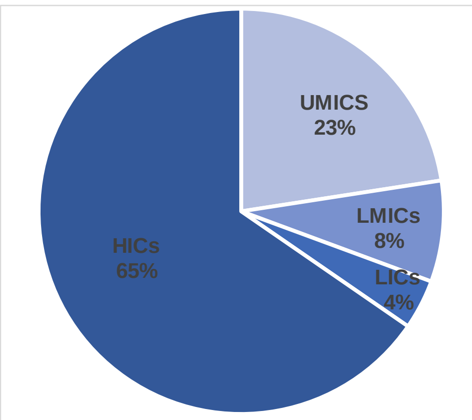

Figure 2.6. Share of global vaccine markets in 2014. US$ approximate value. Source: Reproduced from Batson (2014)

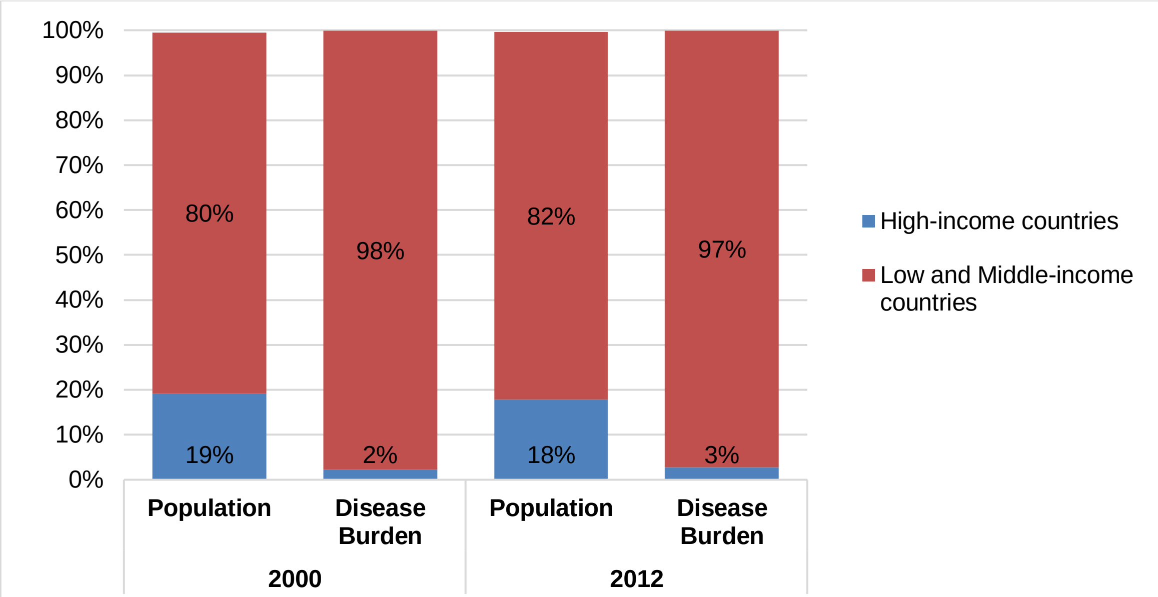

Figure 2.7. Comparison of share of global disease burden and population sizes, in 2000 and 2012. Disease Burden is % of total DALYs for Group I causes (communicable, maternal, perinatal and nutritional conditions). WHO data

Sloan (2012) suggested that there may be an endogenous relationship between a country's economic level, which constrains its ability to pay high vaccine prices, and the high prevalence of infectious diseases that would inhibit its economic growth. He further highlighted the irony that, despite the high social benefit of immunisation programmes, development of new vaccines, particularly those that prevent diseases in low-income countries, is likely to face underinvestment.

2.5. Local vaccine production in developing countries

Hausdorff (1996) suggested that developing countries have three options in obtaining new vaccines. They can either 1) procure the vaccine directly; 2) enter into an arrangement with a foreign manufacturer by having the new vaccine shipped in bulk then bottled and labelled domestically; or 3) make the vaccine entirely locally, perhaps after entering into a joint venture arrangement with another manufacturer.

A survey of policy makers in developing countries conducted by DeRoeck (2004) concluded that local producers of vaccines in several countries have had an important role in locally influencing the introduction of vaccines either by initiating the development of new vaccines or through the attainment of new technologies in vaccinology. Local production is also believed to drive down vaccine prices to a level where governments would be encouraged to consider their use (Muraskin, 1995).

Milstien and Kaddar (2006) noted that an ideal source of R&D for diseases affecting developing countries is the countries where the diseases are endemic. Recent developments have shown an emergence of disease-specific, public-private partnerships stimulating research on vaccines for diseases that disproportionately affect people in developing countries. These partnerships have included efforts in basic research, vaccine development, joint production and clinical trials.

Vaccine production has existed in over 55 countries across all income brackets, including 36 developing countries (Children's Vaccine Initiative, 1999)[22]. In 2014 however, WHO data showed that this number has declined to a total of 33 countries that produce vaccines, of which 16 are developing countries, and specifically within the middle-income bracket (Plotkin, Orenstein, & Offit, 2013) (Figure 2.8). The decline in numbers of vaccine-producing countries has been mainly linked to challenges in production management and access to new technologies, as well as in meeting the continuously strengthened regulatory requirements for producing vaccines (Milstien et al., 2009).

[22] The CVI study reported that the vaccine producing countries were: Argentina, Bangladesh, Brazil, Bulgaria, Chile, China, Colombia, Croatia, Cuba, Czech Republic, DPRK, Ecuador, Egypt, India, Indonesia, Iran, Jordan, Mexico, Myanmar, Nigeria, Pakistan, Philippines, Poland, Romania, Russia, Senegal, Serbia, Slovakia, South Africa, South Korea, Thailand, Tunisia, Turkey, Uruguay, Venezuela and Vietnam.

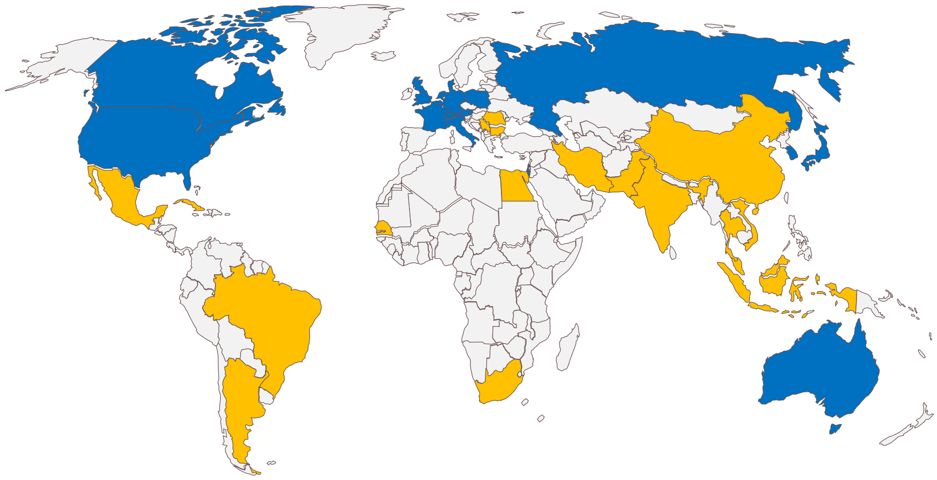

Figure 2.8. Map of vaccine-producing countries in 2014. 16 developing countries[23] that produce vaccines are shaded yellow and 17 industrialised countries that produce vaccines are shaded blue.

Local production of vaccines is of particular interest to developing countries. Among the different arguments behind a government's desire to manufacture new vaccines locally, securing adequate supply of vaccines is known to be a critical factor, mainly in countries with large populations (Munira & Fritzen, 2007; van Noort, 1992). Kaplan and Laing (2005) suggested several industrial policy reasons behind a country's decision to invest in production. These are unmet or unavailable quality specifications produced elsewhere; design and process secrecy needs; existing supply being unreliable; wanting control over production schedules; local employment creation; interest in acquiring and upgrading domestic technology capacity; self-sufficiency in public health interventions; reduced reliance on imports; managing foreign exchange flow; and the desire to enter or expand into export markets.

The need to increase capacity of local producers has also been discussed in the international forums. In 1978, discussions of local production were initiated by the WHO during the International Conference on Primary Health Care (WHO, 1978). The United Nations (UN) agencies also promoted strategies for local production using technology transfer arrangements aimed at acquiring more sophisticated technologies and

[23] Developing countries with national vaccine production as of 2014 are: Brazil, Bulgaria, China, Croatia, Cuba, Egypt, India, Indonesia, Iran, Mexico, Pakistan, Senegal, Serbia, Thailand, Tunisia and Vietnam. In 2014, Argentina moved from an Upper Middle Income country to a High Income Country.

increasing local capacity (UNCTAD, 2002). In 2003, the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) was established during the World Health Assembly. The aims of CIPIH were to "review the interfaces and linkages between intellectual property rights, innovation and public health" and to "examine in depth how to stimulate the creation of new medicines and other products for diseases that mainly affect developing countries" (CIPIH, 2011). In its report in 2006, CIPIH discussed local production as a means to have affordable pharmaceutical products and to strengthen the bargaining position of developing countries for compulsory licencing (WHO, 2006). Some input-related barriers along with potential solutions were also highlighted in the report. Following the CIPIH report recommendations, the negotiations between WHO member states led to the adoption of the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI), in 2008. Through GSPA-PHI, an emphasis on local production was renewed, that it be a "means to contribute to the overall goals of promoting technology transfer, innovation, capacity-building and improving access" (WHO, 2011b).

Local vaccine producers play a crucial role in the establishment and maintenance of the WHO Expanded Program on Immunisation (EPI) (Jadhav et al., 2014; Munira & Fritzen, 2007). Many local producers, especially those that are publicly owned, often have exclusive supply arrangements with their governments, which provide them with a captive market in their respective countries (CVI, 1999; Mahoney & Maynard, 1999). Nevertheless, local production of vaccines is not an easy task, often faced with much scrutiny from the public, particularly with regards to patent issues and quality assurance. Mahoney and Maynard (1999) argued that, despite initiatives to stimulate vaccine research and development and improve public sector vaccine production in developing countries, it is not likely that developing countries will soon become significant players in basic and upstream applied vaccine R&D. This is further emphasized for the public sector where sources of external funding are spread thinly among many pressing health priorities, and where sources of know-how are becoming less freely available.

A study by McKinsey (2002), commissioned by GAVI and the World Bank, compared the choice of sourcing GAVI-programs with vaccines produced by multinational firms to those produced by DCVMs. The study findings recommended that GAVI source its procurement with readily available vaccines and technologies supplied by multinationals. An important assumption was that vaccines produced by emerging manufacturers would require a time trade off, because it would take time for these suppliers to access technology and establish supplies, including waiting for patent expiry on vaccines. The study also reported the lengthy time and high costs related to technology transfers of even simple conjugate vaccine technology, involving four to five years of technology transfer plus an additional five years to scale up to required capacity and obtain expensive raw materials and limited price advantages in developing countries.

2.6. Viability of vaccine production

Milstien, Batson, and Meaney (1997) published a landmark study on the viability of local vaccine production. Based on a series of country assessments, they analysed characteristics of viable or successful producers, and established a systematic method to evaluate the potential viability of producers in providing a reliable supply of existing and new vaccines. This study provided a structured way to analyse vaccine producers by identifying seven critical elements for viability, each defined by several factors (Table 2.2). Further, the findings refuted two popular assumptions: 1) that a lack of funds for state-of-the-art facilities is the primary barrier to viable vaccine production in developing countries, and 2) a large captive population is needed for viability. This study concluded that the most important factors for viable vaccine production were national wealth, or total GNP, and a commitment to invest in local vaccine production on the part of the government.

Table 2.2. Vaccine viability characteristics

	Viability elements	Indicator
1.	**Economic/scale**	• Number of children (population ~50 million) • Number of vaccines > 2
2.	**Good Manufacturing Process (GMP) / consistency of production**	• Percentage of lots failed <5% • Consistent number of lots per year • Consistent number of doses per lot • Maintenance programme and budget • Planned, significant capital expenditure (CAPEX) per year • QA budget and programme
3.	**New technology**	• Process development budget, programme • Research budget and programme • Realistic plan to meet national needs • Added new technology in last 5 years
4.	**Historical performance/quality**	• Supply sufficient for national demand • Proven scale up in last 5 years
5.	**Credibility of quality**	• Customer has choice • National Regulatory Authority (NRA) with six functions • NRA independent, with authority
6.	**Management structure**	• Detailed 3 year economic plan • Price covers full cost-per-dose • Research on future demand • Human resource training plan • Appropriate ratio skilled/unskilled staff
7.	**Legal status-autonomy**	• Control to set salaries • Control to hire and fire as necessary • Control over revenues, budgets • Political stability (number of Health Ministers within last 5 years)

Source: Excerpt from Milstien et al. (1997)

The role of DCVMs has evolved over past 30 years. The focus has now shifted from developing countries acquiring the ability to manufacture a sustainable and sufficient supply of assured quality vaccines (W. Muraskin, 1998) to including viable vaccine producers in developing countries as partners in securing the global supply of vaccines.

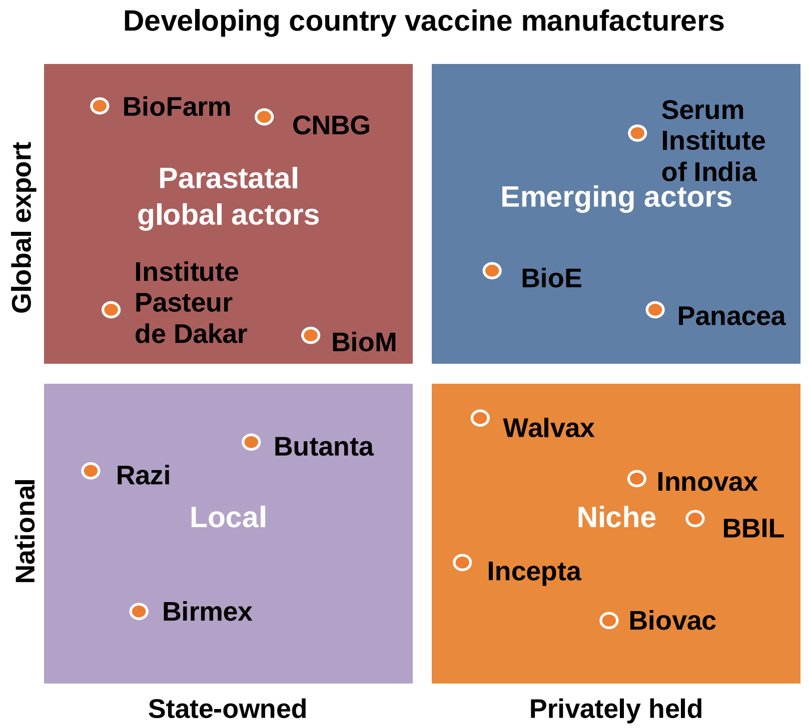

Figure 2.9. The diversity of developing country manufacturers.
The graph does not exhaust the list of developing country vaccine manufacturers. Adapted from Program for Appropriate Technology in Health (PATH)'s presentation to WHO, 2016

The chart in Figure 2.9 shows the span of current local vaccine manufacturers across ownership and markets served[24,25]. At the present time, the question is no longer whether developing country manufacturers are able to produce sustainable and sufficient supply of high quality vaccines, because DCVMs are already major suppliers of vaccines. In recent decades, natural selection has driven inefficient suppliers out of the market. The question now is how to ensure, and assess, the viability of vaccine production in developing countries, and to determine whether the viability factors assessed previously are still relevant at the present time. Such an assessment will be conducted in Chapter 4, where the seven viability factors presented in the paper by Milstein and colleagues were assessed amongst several additional factors, in terms of their impact on revenue sizes and percent market share.

[24] The chart has been adapted to include only manufacturers that are not based in high income countries
[25] Using World Bank income bracket of GNI/capita below US$12,736. The complete list of the World Bank country classification is available in Table 2.1.

The global vaccine market witnessed a sharp contraction in the number of vaccine suppliers during the 1980s – 1990s due to pressures of liability and unattractive profits (Danzon & Pereira, 2011). However, the global vaccine market size has grown more rapidly than before (Figure 2.10), and the numbers of manufacturers and vaccine types that have achieved the World Health Organization's (WHO) prequalification (PQ) status have also increased. (Figure 2.11).

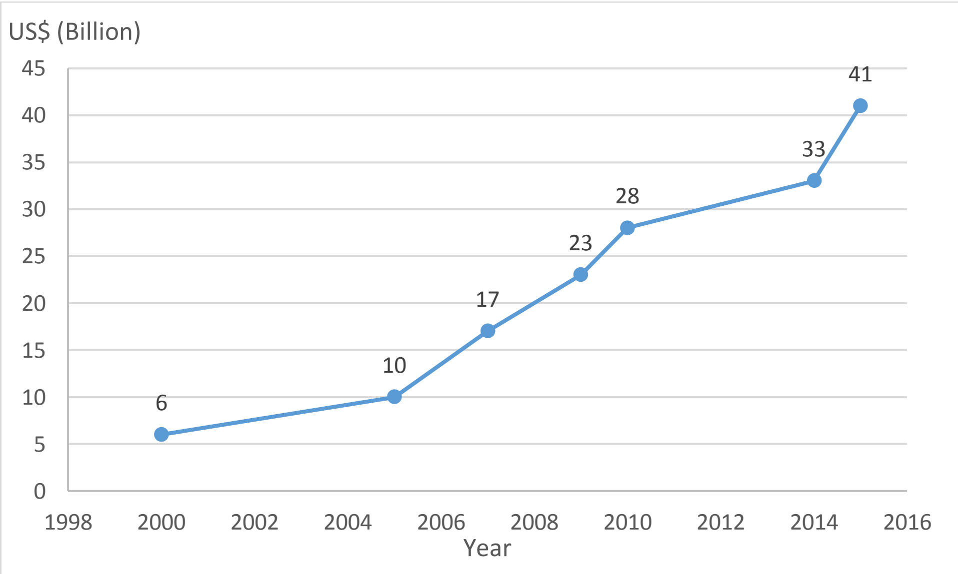

Figure 2.10. Global vaccine market (2000 – 2015).
Data derived from Batson (2014), Kaddar (2013) and (Statistista, 2016)

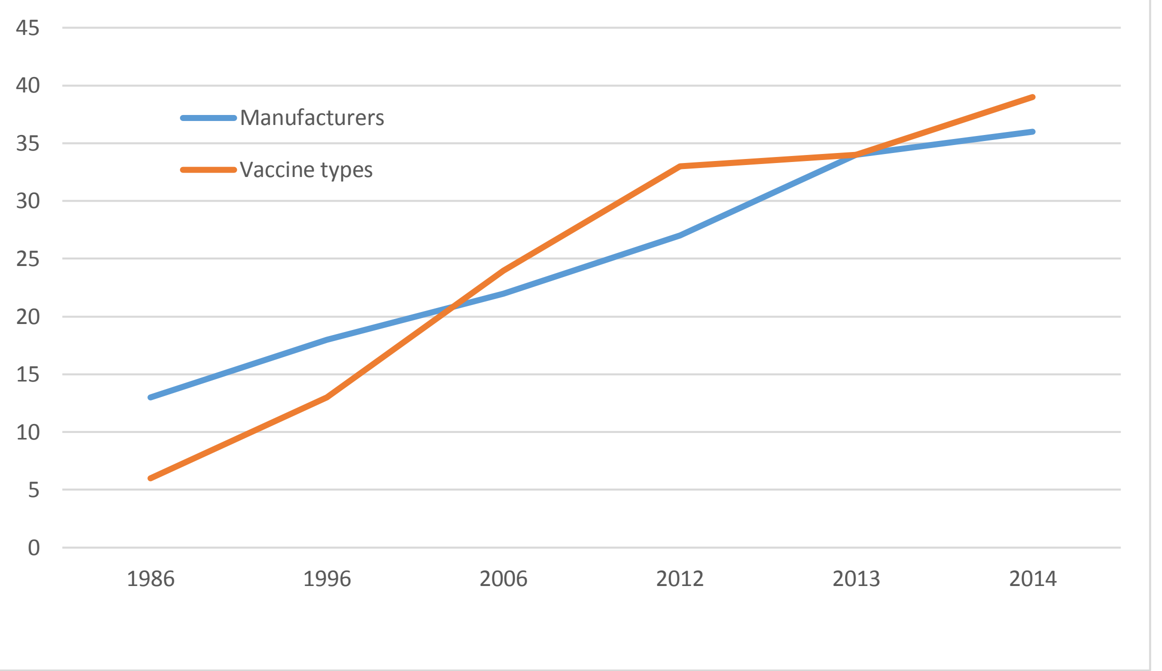

Figure 2.11. Global production of prequalified vaccines (1986 – 2012)*.* Data from WHO prequalified vaccine list. https://extranet.who.int/gavi/PQ_Web/Default.aspx. Accessed 11/03/2016

This increase in numbers of vaccines achieving prequalification status is an important development in global vaccine supply, because it not only indicates the number of vaccines available for public markets globally but also those of assured quality. From a manufacturer's perspective, meeting the requirements of the PQ system provides access to the large vaccine market that is managed via bulk procurement by UN agencies such as the United Nations Children's Fund (UNICEF), WHO and the Pan American Health Organization (PAHO)[26] (Figure 2.12).

[26] PAHO is WHO's regional office in the Americas, and has established a procurement system using a Revolving Fund, operating since 1979 years now.

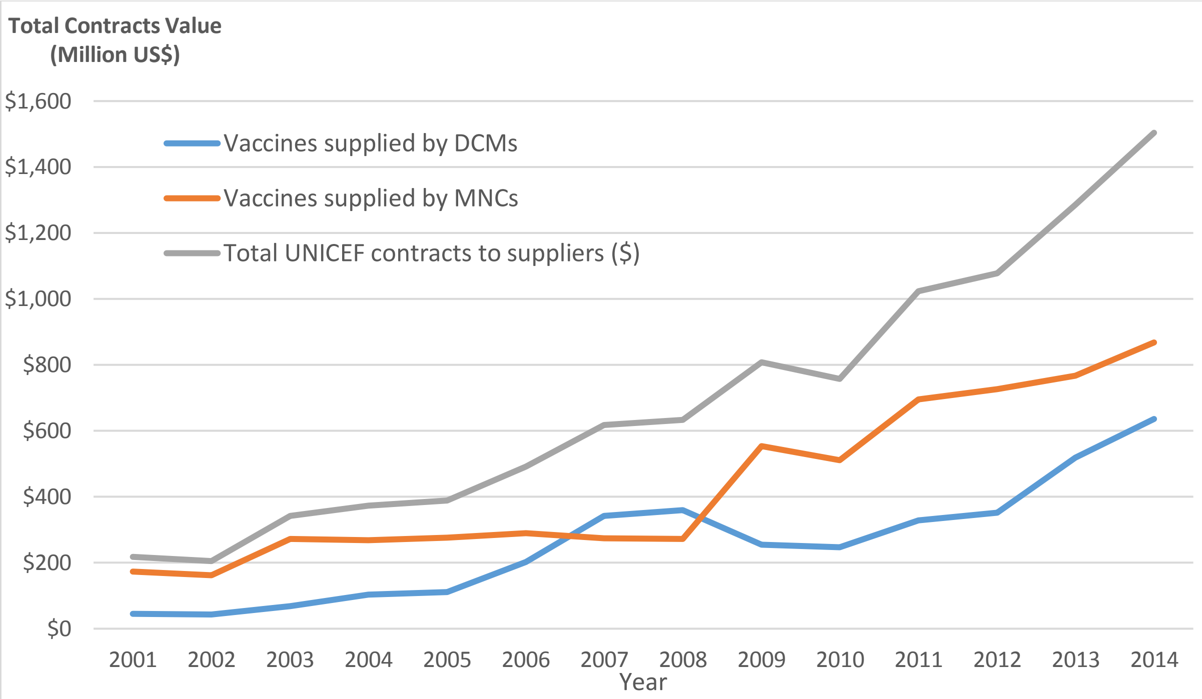

Figure 2.12. Trend of supply to UNICEF vaccine markets. Contract value to developing country manufacturers (DCMs) may include those awarded to countries such as South Korea which is no longer a developing country. UNICEF Supply Division data, 2015. Accessed 16/10/2016

A recent study by de los Angeles Cortes, Cardoso, Fitzgerald, and DiFabio (2012) noted the global vaccine market to be growing at a rate of 16.52% per annum, and highlighted that not all vaccine manufacturers operate on a level playing field, or are able to produce successful products. Their study finds that the challenges manufacturers face in timely production of efficacious products often stem from the biological nature of vaccines. Vaccine production requires more care to ensure stability and safety than other pharmaceutical products. The same rigour also applies to non-originating vaccines[27].

[27] The term non-originating is used in this thesis to differentiate between 'originating vaccines' that were developed by research-based manufacturers and vaccines produced by non-research based manufacturers through technology transfer mechanisms.

2.7. Vaccine production costs

Different from other pharmaceutical products such as drugs, where generic or me-too products exist based mainly on bioequivalence[28], a 'generic vaccine' technically does not exist (WHO, 2011a). This is because vaccines are complex biological products (as opposed to simple small molecule products which typify drugs). As a result, the actual process employed to produce a vaccine can have a significant effect on vaccine efficacy. By contrast, with drugs, different processes can be employed and yet still result in the same drug product. Therefore, vaccines produced through technology transfer processes, even when the originating vaccine's patents have expired, are still required to undergo a clinical trial process or at a minimum, bridging studies where applicable[29], whenever production is done in a new location or facility. Therefore the figures produced in estimating production costs of pharmaceutical products cannot be generalised to vaccine products, though some of the basic principles can be adopted.

A number of published studies have proposed the mean estimates of R&D costs for pharmaceutical drugs, and highlight that variations exist across therapeutic areas, firm sizes and compound origins (DiMasi, Hansen, & Grabowski, 2003; Mestre-Ferrandiz, Sussex, & Towse, 2012; Pronker, Weenen, Commandeur, Osterhaus, & Claassen, 2011). A study commissioned by the GAVI reviewed vaccine production costs, using multinational producers as a benchmark, suggested that similar variations also apply to vaccine production (Mercer Managment Consulting, 2002).

In its 2015 industrial report, the pharmaceutical industry provided an estimate of US$2.6 billion as the average cost to develop a drug[30]. This was reported to be more

[28] the property where two products with identical active ingredients or two different dosage forms of the same product possess similar bioavailability and produce the same effect at the site of physiological activity.
[29] Bridging studies are often conducted for vaccine production via technology transfers where the vaccine is needed in time-pressing and public health objective, such as in pandemic situations.
[30] This estimate includes the cost of failures and is said for the period between 2000s and early 2010s.

than double the cost estimated for the previous decade, which was in turn double the cost for two decades prior (PhRMA, 2015). Waye, Jacobs, and Schryvers (2013) in a systematic review provided a range of US$800 million to US$1.8 billion as the cost of drug development. Their review however suggested that "a similar statistic for vaccines is yet to be estimated, and it is unclear whether the cost of vaccines is similar to drug development".

Studies on vaccine production costs by DCVMs are mostly presented as costs-per-dose, whilst studies on vaccine production by multinational companies usually focus on the capitalised fixed costs or R&D costs in total. Presenting an aggregate estimate of capital costs and/or R&D costs is important in that it provides evidence regarding the necessity of high prices of newer vaccines (in particular the large difference between marginal production costs and vaccine prices) for manufacturers to recoup their R&D investments as well as to sustain and motivate innovation in vaccine research.

Though an industry-wide estimate may not yet exist specifically for vaccines, a number of studies have estimated the cost of producing vaccines at an individual product level. One of the earliest was the report by Mahoney (1990), who presented an estimate of producing a plasma-derived hepatitis B vaccine with an assumed production of four million doses. His estimates for the year 1989 showed the cost-per-dose ranged from $20 to around $0.10 as the production volume increased from small quantities to 20 million doses per year. This study highlighted the effect of increasing the scale of production on reducing costs-per-dose. Another study by Mahoney et al. (2012) analysed the cost of producing a tetravalent dengue vaccine in Brazil and suggested that it would not exceed US$ 0.20 per dose in 10 dose vials and US$ 0.70 per dose in single dose vials when producing 60 million doses annually.

In 2014, Chit et al. (2014) reviewed the production costs of a seasonal influenza vaccine and estimated that taking the vaccine from preclinical development in 2011 to licensure in 2022 would cost $337–570 M Canadian dollars[31]. A more recent study by Herlihy, Hutubessy, and Jit (2016), which included a review of the producer surplus of the human papillomavirus (HPV) vaccine, provides an estimate of the development cost of the HPV vaccine of US$2.9billion. This was a much larger estimate than a previous study of rotavirus vaccines by Light, Andrus, and Warburton (2009), who estimated a cost of around $317–$974 million. However the latter study did not include failure rates, which is an important element in calculating the full cost of producing a successful vaccine product (Levin, 1983; Struck, 1996). Producer surplus is an economic concept that measures the difference between the amount a producer receives and the minimum payment it is willing to accept. This difference represents the benefit that the producer receives for the good or service it sells in the market.

Further, a source of economic advantage for a producer can be obtained through economies of scale and economies of scope (Galambos & Sewell, 1997). Economies of scale occur when a manufacturer's average costs lowers as a result of increasing its production scale of a single product type. In the case of producing vaccines, despite having such high fixed costs, an economies of scale can be achieved by increasing its batch size (GAVI, 2002). Economies of scope on the other hand, is obtained when average costs lower by producing more types of products (Lipsey, Ragan, & Courant, 1997). For example, adding a new vaccine production line to an existing one may reduce the total average costs due to shared costs of administrative overheads for each vaccine, compared to the average cost of each vaccine being produced separately. Henderson and Cockburn (1996) observed the relationship between research productivity in the pharmaceutical with a firm's size and discovered that larger firms were more productive by sustaining economies of scale and in particular due to economies of scope through diversifying its portfolios. Good coordination of growing

[31] At the time of the study the Canadian dollar was close to parity with the US dollar.

portfolios however is an important aspect in order to avoid diseconomies of scale (Mankiw, 2014).

In addition to the published literature, a GAVI commissioned study by Mercer Management Consulting (2002) suggested that vaccine production costs vary significantly, ranging between $0.05 to $3-$4 per dose. The report suggested six factors that are main drivers of variation to these costs, among which are presentation, scale of production, method of vaccine inputs, location of production, size of vaccine batches, and vaccine production characteristics. Vaccine production characteristics include the amount of time, labour intensity and testing regimen required to produce a given vaccine. In addition to these, vaccine manufacturing costs also depend on whether production is set up on a brownfield or greenfield production site. Brownfield production uses facilities built on pre-existing structures, usually involving a lower setup cost, depending on the level of refurbishment required and any complications associated with it. By contrast, greenfield production sites are built using completely new facilities.

Among the published literature, only the studies by Mahoney (1990) and Mahoney et al. (2012) estimated the costs of production by DCVMs. In light of the tendency of developing countries to prioritise local production of vaccines, particularly when considering new vaccine introduction (see sub-section 2.3), it is important for such countries to evaluate the costs associated with establishing new vaccine manufacturing facilities. An analysis of cost structures for DCVMs is presented in Chapter 3.

2.8. Vaccine prices

Vaccine prices can influence a government's decision to introduce a vaccine into their national immunisation programs. Prices of new vaccines, which are typically higher than traditional EPI vaccines (Hinman, 1999), are often quoted as a major impediment to vaccine uptake, particularly in developing countries (Milstien, Munira, & McKinney, 2003). However, vaccine prices often signal to manufacturers the potential revenue and profit that they would be able to generate should they choose to produce the vaccine locally. Therefore, the market price of a vaccine may influence a government's decision to either source the vaccine locally or import it from external sources.

Multiple studies have analysed the role of prices in influencing the demand and supply of vaccines (Arnould & DeBrock, 1996; Batson et al., 2003; Lee & McGlone, 2010; Milstien & Candries, 2000). Arnould and DeBrock (1996) suggested a number of ways that prices help indicate vaccine production viability. One is that the structure and movement of prices may reflect the "underlying behaviour of the industry and [can help] identify the extent and nature of market failure". They suggest that increases in vaccine prices may indicate market imperfections or even monopolistic behaviour.

In producing vaccines, scale plays a very important role in vaccine viability (Milstien & Candries, 2000). Vaccine manufacturers must make investment decisions on their size of production well in advance, often without certainty regarding revenue and quantities demanded. These decisions influence the prices of vaccines, particularly as a result of assumed production sizes and risks. Furthermore, competition has also been suggested to influence price (Milstien & Candries, 2000; Muraskin, 1995; Srinivas, 2006). A study by Jadhav, Datla, Kreeftenberg, and Hendriks (2008) provided some examples of how declining prices have occurred as a result of competition from DCVMs entering the market. An example given was the Diphtheria-Tetanus-Pertussis-Hepatitis B combination vaccines, where prices dropped by 40% due to competition. By contrast, prices of Haemophilus-influenza type b (Hib) vaccines did not decline even after 5 years of GAVI support. The latter was believed to be a result of a near monopoly market for the Hib vaccine.

Though the prices of vaccines tend to be strongly influenced by market forces, prices in domestic markets for local producers are influenced by additional factors. In her book chapter, Batson et al. (2003) highlighted findings from a number of field assessments of local vaccine producers conducted by WHO on behalf of the Children's Vaccine Initiative (CVI). Based on these assessments, she reported that "vaccine prices were often set by the government and in many cases did not cover the full costs of the manufacturer, making it difficult for these entities to maintain the facilities, train staff, or invest in new vaccine research and development or production." These requirements may affect the viability of local manufacturers.

2.8.1. The Vaccine Product, Price and Procurement (V3P) project

Another barrier to vaccine affordability is the presence of asymmetric information[32]. A WHO study by Results for Development (R4D) identified that a key barrier in vaccine procurement and pricing is a lack of access to information regarding vaccine products and prices from vaccine manufacturers and their procuring countries. In response to this, WHO developed a Vaccine Product, Price and Procurement (V3P) project in 2011. V3P's objective was to improve transparency of public sector vaccine prices by creating a shared platform where procuring countries provide information regarding prices, products and procurement information on vaccines that they have purchased from manufacturers. The V3P database compiled information from procuring countries as well as from PAHO and UNICEF. As of 20 November 2016, the database included 1394 transactions and corresponding prices of 55 vaccine products that were produced by 43 different vaccine manufacturers. These were located in one low income, 18 upper middle-income, 18 lower middle-income and 19 high income countries and included procurements over 11 years (2005 – 2015). The data included 9 transactions by a low income country, 398 transactions by a lower middle-income country, 423 transactions

[32] Also known as information failure, asymmetric information occurs when one party has more information than the other. This often provides more power towards the one with more information.

by an upper middle-income country and 564 transactions by a high-income country. The average price of vaccines reported by the V3P participating countries was $3.67, while the average prices for each vaccine reported to the V3P are shown in Table 2.3. The full database, as well as documents relating to vaccine pricing, are available on the WHO website: http://www.who.int/immunization/v3p. The project is expected to help countries make fully informed decisions when negotiating with vaccine manufacturers.

The V3P dataset captures a subset of all vaccine transactions along with their prices and procurement terms and conditions, based on data reported by participating countries. To increase the validity of the data provided, WHO provides countries with a two-year period to report any necessary changes to the data they have provided.

Table 2.3. Summary of vaccine prices-per-dose sold by vaccine manufacturers to V3P-participating countries.

Vaccine	Weighted average price per dose (US$)	Minimum price per dose (US$)	Maximum price per dose (US$)	Number of observations
BCG	0.27	0.03	15.08	121
bOPV1,3	0.16	0.13	0.33	9
Cholera	0.47	0.47	0.47	1
Diphteria	0.05	0.05	0.05	1
DT (ped)	0.55	0.01	14.47	38
DTaP	5.66	2.65	30.97	15
DTaP-HepB-Hib-IPV	30.56	12.25	59.15	31
DTaP-Hib	19.07	16.46	41.67	4
DTaP-Hib-IPV	10.79	7.98	44.49	40
DTaP-IPV	9.60	6.19	34.36	33
DT-IPV	8.09	8.09	8.09	1
DTP	0.15	0.01	3.14	46
DTP-HepB	3.20	3.20	3.20	1
DTP-HepB-Hib	2.09	1.19	5.10	69
DTP-Hib	1.27	1.24	2.80	2
HepA (adult)	18.61	15.36	34.26	12
HepA (pediatric)	7.07	6.65	20.55	5
HepA-HepB	41.22	37.72	45.12	2
HepB (adult)	1.76	0.17	66.34	40
HepB (pediatric)	0.86	0.16	11.41	103
Hib	5.43	0.78	19.90	28
HPV	22.96	5.00	103.49	41
Influenza (seasonal - Adult)	4.13	1.12	12.73	49

Influenza (seasonal - Ped)	1.95	1.95	5.46	4
IPV	3.32	0.00	42.18	43
JE_Inactd	0.59	0.50	1.50	2
JE_LiveAtd	5.77	0.42	27.27	7
Measles	0.35	0.14	5.98	37
MenA,C,Y,W-135 (conjugate)	36.11	14.21	41.99	5
MenA,C,Y,W-135 (polysaccharide)	7.73	4.65	42.72	7
MenA+C	9.29	9.29	9.29	1
MenB	78.09	73.94	88.46	2
MenC	17.30	8.98	82.19	19
MMR	4.35	0.50	15.34	101
MMRV	28.83	26.07	31.19	2
mOPV3	0.23	0.22	1.31	2
MR	0.73	0.52	1.73	20
Mumps	0.71	0.71	0.71	1
PCV	18.30	3.30	72.89	90
Pneumo ps	12.26	7.52	21.23	20
Rabies	5.30	2.86	101.91	15
Rota	3.79	2.06	61.00	39
Rubella	0.43	0.43	8.29	4
TBE (adult)	3.95	2.93	17.86	5
TBE (pediatric)	15.55	14.10	16.86	2
Td (Adult)	2.43	0.00	26.51	74
Tdap (booster)	12.38	4.21	24.04	25
Tdap-IPV (booster)	8.82	8.72	22.97	6
Td-IPV	13.58	12.54	15.01	3
tOPV	0.17	0.01	7.67	77
TT	0.15	0.00	7.65	55
Typhoid	1.16	0.49	17.51	9
Varicella	18.77	16.52	50.46	11
YF	1.61	0.59	82.92	14

Source: Data based on vaccine prices reported to WHO (2005 – 2015), based on transactions between V3P-participating countries and manufacturers from industrialised and developing countries. N = 1394. Last accessed 20/11/2016

Though procuring vaccines at very low prices may be desirable for countries, it is also noted that prices need to be at a level that still encourages innovation and production of vaccines (Lieu, McGuire, & Hinman, 2005). The ability of vaccine manufacturers to recoup their investments and gain enough profit will help ensure the vaccines market retains and sustains adequate, viable suppliers. This in turn may help secure the global supply of vaccines.

This thesis focuses on the prices that DCVMs set for their vaccines. An analysis of the determining factors of these prices is presented in Chapter 5.

2.9. Conclusions

DCVMs play and important role in ensuring that the aims of immunisation programs in developing countries continue to be achieved. Building capacity for new vaccine production in developing countries is crucial to secure global supply of vaccines. Gaps in the existing literature regarding local vaccine production include: quantification of industry-wide production costs of vaccines manufactured in developing countries; quantification of the factors contributing to the viability of vaccine production by these manufacturers in the public health market; and the quantification of procurement factors' influences on vaccine prices offered by DCVMs. These gaps are analysed in Chapters 3–5 of the thesis.

2.10. Appendices

Appendix 2.1. World Bank country classifications

Year:	*2005*	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Low income (L)	<= 875	<= 905	<= 935	<= 975	<= 995	<= 1,005	<= 1,025	<= 1,035	<= 1,045	<= 1,045	<= 1,025
Lower middle income (LM)	876-3,465	906-3,595	936-3,705	976-3,855	996-3,945	1,006-3,975	1,026-4,035	1,036-4,085	1,046-4,125	1,046-4,125	1,026-4,035
Upper middle income (UM)	3,466-10,725	3,596-11,115	3,706-11,455	3,856-11,905	3,946-12,195	3,976-12,275	4,036-12,475	4,086-12,615	4,126-12,745	4,126-12,735	4,036-12,475
High income (H)	> 10,725	> 11,115	> 11,455	> 11,905	> 12,195	> 12,275	> 12,475	> 12,615	> 12,745	> 12,735	> 12,475
Afghanistan	L	L	L	L	L	L	L	L	L	L	L
Albania	LM	LM	LM	LM	UM	UM	LM	UM	UM	UM	UM
Algeria	LM	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM
American Samoa	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Andorra	H	H	H	H	H	H	H	H	H	H	H
Angola	LM	LM	LM	LM	LM	LM	UM	UM	UM	UM	UM
Antigua and Barbuda	H	H	H	H	UM	UM	UM	H	H	H	H
Argentina	UM	UM	UM	UM	UM	UM	UM	UM	UM	H	UM
Armenia	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Aruba	H	H	H	H	H	H	H	H	H	H	H
Australia	H	H	H	H	H	H	H	H	H	H	H
Austria	H	H	H	H	H	H	H	H	H	H	H
Azerbaijan	LM	LM	LM	LM	UM	UM	UM	UM	UM	UM	UM
Bahamas, The	H	H	H	H	H	H	H	H	H	H	H
Bahrain	H	H	H	H	H	H	H	H	H	H	H
Bangladesh	L	L	L	L	L	L	L	L	L	LM	LM
Barbados	UM	H	H	H	H	H	H	H	H	H	H
Belarus	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Belgium	H	H	H	H	H	H	H	H	H	H	H

Belize	*UM*	*UM*	*UM*	*LM*	*LM*	*LM*	*LM*	*UM*	*UM*	*UM*	*UM*
Benin	L	L	L	L	L	L	L	L	L	L	L
Bermuda	H	H	H	H	H	H	H	H	H	H	H
Bhutan	L	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Bolivia	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Bosnia and Herzegovina	LM	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM
Botswana	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Brazil	LM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
British Virgin Islands	..	..	..	..	..	..	..	..	..	..	H
Brunei Darussalam	H	H	H	H	H	H	H	H	H	H	H
Bulgaria	LM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Burkina Faso	L	L	L	L	L	L	L	L	L	L	L
Burundi	L	L	L	L	L	L	L	L	L	L	L
Cabo Verde	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Cambodia	L	L	L	L	L	L	L	L	L	L	LM
Cameroon	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Canada	H	H	H	H	H	H	H	H	H	H	H
Cayman Islands	H	H	H	H	H	H	H	H	H	H	H
Central African Republic	L	L	L	L	L	L	L	L	L	L	L
Chad	L	L	L	L	L	L	L	L	L	L	L
Channel Islands	H	H	H	H	H	H	H	H	H	H	H
Chile	UM	UM	UM	UM	UM	UM	UM	H	H	H	H
China	LM	LM	LM	LM	LM	UM	UM	UM	UM	UM	UM
Colombia	LM	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM
Comoros	L	L	L	L	L	L	L	L	L	L	L
Congo, Dem. Rep.	L	L	L	L	L	L	L	L	L	L	L
Congo, Rep.	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Costa Rica	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM

Côte d'Ivoire	*L*	*L*	*L*	*LM*	*LM*	*LM*	*LM*	*LM*	*LM*	*LM*	*LM*
Croatia	UM	UM	UM	H	H	H	H	H	H	H	H
Cuba	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Curaçao	..	..	..	..	..	H	H	H	H	H	H
Cyprus	H	H	H	H	H	H	H	H	H	H	H
Czech Republic	UM	H	H	H	H	H	H	H	H	H	H
Denmark	H	H	H	H	H	H	H	H	H	H	H
Djibouti	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Dominica	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Dominican Republic	LM	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM
Ecuador	LM	LM	LM	LM	LM	UM	UM	UM	UM	UM	UM
Egypt, Arab Rep.	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
El Salvador	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Equatorial Guinea	UM	UM	H	H	H	H	H	H	H	H	UM
Eritrea	L	L	L	L	L	L	L	L	L	L	L
Estonia	UM	H	H	H	H	H	H	H	H	H	H
Ethiopia	L	L	L	L	L	L	L	L	L	L	L
Faeroe Islands	H	H	H	H	H	H	H	H	H	H	H
Fiji	LM	LM	UM	UM	UM	LM	LM	UM	UM	UM	UM
Finland	H	H	H	H	H	H	H	H	H	H	H
France	H	H	H	H	H	H	H	H	H	H	H
French Polynesia	H	H	H	H	H	H	H	H	H	H	H
Gabon	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Gambia, The	L	L	L	L	L	L	L	L	L	L	L
Georgia	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	UM
Germany	H	H	H	H	H	H	H	H	H	H	H
Ghana	L	L	L	L	L	LM	LM	LM	LM	LM	LM
Gibraltar	..	..	..	..	H	H	..	..	..	..	H

Greece	*H*	*H*	*H*	*H*	*H*	*H*	*H*	*H*	*H*	*H*	*H*
Greenland	H	H	H	H	H	H	H	H	H	H	H
Grenada	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Guam	H	H	H	H	H	H	H	H	H	H	H
Guatemala	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Guinea	L	L	L	L	L	L	L	L	L	L	L
Guinea-Bissau	L	L	L	L	L	L	L	L	L	L	L
Guyana	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	UM
Haiti	L	L	L	L	L	L	L	L	L	L	L
Honduras	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Hong Kong SAR, China	H	H	H	H	H	H	H	H	H	H	H
Hungary	UM	UM	H	H	H	H	H	UM	UM	H	H
Iceland	H	H	H	H	H	H	H	H	H	H	H
India	L	L	LM	LM	LM	LM	LM	LM	LM	LM	LM
Indonesia	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Iran, Islamic Rep.	LM	LM	LM	LM	UM	UM	UM	UM	UM	UM	UM
Iraq	LM	LM	LM	LM	LM	LM	LM	UM	UM	UM	UM
Ireland	H	H	H	H	H	H	H	H	H	H	H
Isle of Man	H	H	H	H	H	H	H	H	H	H	H
Israel	H	H	H	H	H	H	H	H	H	H	H
Italy	H	H	H	H	H	H	H	H	H	H	H
Jamaica	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Japan	H	H	H	H	H	H	H	H	H	H	H
Jordan	LM	LM	LM	LM	LM	UM	UM	UM	UM	UM	UM
Kazakhstan	LM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Kenya	L	L	L	L	L	L	L	L	L	LM	LM
Kiribati	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Korea, Dem. Rep.	L	L	L	L	L	L	L	L	L	L	L
Korea, Rep.	H	H	H	H	H	H	H	H	H	H	H
Kosovo	..	..	..	LM	LM	LM	LM	LM	LM	LM	LM
Kuwait	H	H	H	H	H	H	H	H	H	H	H
Kyrgyz Republic	L	L	L	L	L	L	L	L	LM	LM	LM

Lao PDR	*L*	*L*	*L*	*L*	*L*	*LM*	*LM*	*LM*	*LM*	*LM*	*LM*
Latvia	UM	UM	UM	UM	H	UM	UM	H	H	H	H
Lebanon	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Lesotho	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Liberia	L	L	L	L	L	L	L	L	L	L	L
Libya	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Liechtenstein	H	H	H	H	H	H	H	H	H	H	H
Lithuania	UM	UM	UM	UM	UM	UM	UM	H	H	H	H
Luxembourg	H	H	H	H	H	H	H	H	H	H	H
Macao SAR, China	H	H	H	H	H	H	H	H	H	H	H
Macedonia, FYR	LM	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM
Madagascar	L	L	L	L	L	L	L	L	L	L	L
Malawi	L	L	L	L	L	L	L	L	L	L	L
Malaysia	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Maldives	LM	LM	LM	LM	LM	UM	UM	UM	UM	UM	UM
Mali	L	L	L	L	L	L	L	L	L	L	L
Malta	H	H	H	H	H	H	H	H	H	H	H
Marshall Islands	LM	LM	LM	LM	LM	LM	LM	UM	UM	UM	UM
Mauritania	L	L	L	L	L	LM	L	LM	LM	LM	LM
Mauritius	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Mexico	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Micronesia, Fed. Sts.	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Moldova	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Monaco	H	H	H	H	H	H	H	H	H	H	H
Mongolia	L	L	LM	LM	LM	LM	LM	LM	LM	UM	LM
Montenegro	..	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Morocco	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Mozambique	L	L	L	L	L	L	L	L	L	L	L
Myanmar	L	L	L	L	L	L	L	L	L	LM	LM
Namibia	LM	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM
Nauru	..	..	..	..	..	..	..	..	..	..	H
Nepal	L	L	L	L	L	L	L	L	L	L	L

Netherlands	*H*	*H*	*H*	*H*	*H*	*H*	*H*	*H*	*H*	*H*	*H*
New Caledonia	H	H	H	H	H	H	H	H	H	H	H
New Zealand	H	H	H	H	H	H	H	H	H	H	H
Nicaragua	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Niger	L	L	L	L	L	L	L	L	L	L	L
Nigeria	L	L	L	LM	LM	LM	LM	LM	LM	LM	LM
Northern Mariana Islands	UM	UM	H	H	H	H	H	H	H	H	H
Norway	H	H	H	H	H	H	H	H	H	H	H
Oman	UM	UM	H	H	H	H	H	H	H	H	H
Pakistan	L	L	L	LM	LM	LM	LM	LM	LM	LM	LM
Palau	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Panama	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Papua New Guinea	L	L	L	LM	LM	LM	LM	LM	LM	LM	LM
Paraguay	LM	LM	LM	LM	LM	LM	LM	LM	LM	UM	UM
Peru	LM	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM
Philippines	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Poland	UM	UM	UM	UM	H	H	H	H	H	H	H
Portugal	H	H	H	H	H	H	H	H	H	H	H
Puerto Rico	H	H	H	H	H	H	H	H	H	H	H
Qatar	H	H	H	H	H	H	H	H	H	H	H
Romania	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Russian Federation	UM	UM	UM	UM	UM	UM	UM	H	H	H	UM
Rwanda	L	L	L	L	L	L	L	L	L	L	L
Samoa	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
San Marino	H	H	H	H	H	H	H	H	H	H	H
São Tomé and Principe	L	L	L	LM	LM	LM	LM	LM	LM	LM	LM
Saudi Arabia	H	H	H	H	H	H	H	H	H	H	H
Senegal	L	L	L	L	LM	LM	LM	LM	LM	LM	L
Serbia	..	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Seychelles	UM	UM	UM	UM	UM	UM	UM	UM	UM	H	H
Sierra Leone	L	L	L	L	L	L	L	L	L	L	L
Singapore	H	H	H	H	H	H	H	H	H	H	H

Sint Maarten (Dutch part)	..	..	..	..	..	*H*	*H*	*H*	*H*	*H*	*H*
Slovak Republic	UM	UM	H	H	H	H	H	H	H	H	H
Slovenia	H	H	H	H	H	H	H	H	H	H	H
Solomon Islands	L	L	L	LM	L	LM	LM	LM	LM	LM	LM
Somalia	L	L	L	L	L	L	L	L	L	L	L
South Africa	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
South Sudan	..	..	..	..	..	..	LM	L	LM	L	L
Spain	H	H	H	H	H	H	H	H	H	H	H
Sri Lanka	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
St. Kitts and Nevis	UM	UM	UM	UM	UM	UM	H	H	H	H	H
St. Lucia	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
St. Martin (French part)	..	..	..	..	..	H	H	H	H	H	H
St. Vincent & the Grenadines	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Sudan	L	L	LM	LM	LM	LM	LM	LM	LM	LM	LM
Suriname	LM	LM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Swaziland	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Sweden	H	H	H	H	H	H	H	H	H	H	H
Switzerland	H	H	H	H	H	H	H	H	H	H	H
Syrian Arab Republic	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Taiwan, China	H	H	H	H	H	H	H	H	H	H	H
Tajikistan	L	L	L	L	L	L	L	L	L	LM	LM
Tanzania	L	L	L	L	L	L	L	L	L	L	L
Thailand	LM	LM	LM	LM	LM	UM	UM	UM	UM	UM	UM
Timor-Leste	L	L	LM	LM	LM	LM	LM	LM	LM	LM	LM
Togo	L	L	L	L	L	L	L	L	L	L	L
Tonga	LM	LM	LM	LM	LM	LM	LM	UM	UM	UM	LM
Trinidad and Tobago	UM	H	H	H	H	H	H	H	H	H	H
Tunisia	LM	LM	LM	LM	LM	UM	UM	UM	UM	UM	LM
Turkey	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM	UM
Turkmenistan	LM	LM	LM	LM	LM	LM	UM	UM	UM	UM	UM
Turks and Caicos Islands	..	..	..	..	H	H	H	H	H	H	H

Tuvalu	*..*	*..*	*..*	*..*	*LM*	*LM*	*UM*	*UM*	*UM*	*UM*	*UM*
Uganda	L	L	L	L	L	L	L	L	L	L	L
Ukraine	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
United Arab Emirates	H	H	H	H	H	H	H	H	H	H	H
United Kingdom	H	H	H	H	H	H	H	H	H	H	H
United States	H	H	H	H	H	H	H	H	H	H	H
Uruguay	UM	UM	UM	UM	UM	UM	UM	H	H	H	H
Uzbekistan	L	L	L	L	LM	LM	LM	LM	LM	LM	LM
Vanuatu	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Venezuela, RB	UM	UM	UM	UM	UM	UM	UM	UM	UM	H	UM
Vietnam	L	L	L	L	LM	LM	LM	LM	LM	LM	LM
Virgin Islands (U.S.)	H	H	H	H	H	H	H	H	H	H	H
West Bank and Gaza	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM	LM
Yemen, Rep.	L	L	L	L	LM	LM	LM	LM	LM	LM	LM
Zambia	L	L	L	L	L	LM	LM	LM	LM	LM	LM
Zimbabwe	L	L	L	L	L	L	L	L	L	L	L

Note: GNI per capita in US$ (Atlas methodology). Changes in classification indicated in light green. Presentation is limited to years relevant to thesis: 2005 – 2015. **Source:** World Bank historical country classification, 2016

Chapter 3 The cost structure of establishing new vaccine manufacturing facilities in developing countries

3.1. Introduction

As outlined in the previous chapter, a review of the literature found that research on individual vaccine production costs is limited and that published studies that have quantified and characterised industry-wide vaccine production costs in developing countries are still lacking. (Mahoney, 1990; Mahoney et al., 2012; Oliver Wyman, 2007; Pronker et al., 2011). An assessment of cost structure and cost behaviour is important to understand whether developing countries can produce and offer vaccines at an affordable price. It is also important information to justify whether such investments are sustainable. This is especially necessary because local vaccine production often involves public funds in developing countries, where budgets are particularly constrained, and vaccine production competes with numerous other investment priorities. Therefore, a careful analysis is required on whether local vaccine production is suitable for each country that expresses interest.

Local production is known to be an important consideration for governments when seeking access to new vaccines (Clemens, 2003; Hendriks, Liang, & Zeng, 2010; Munira & Fritzen, 2007; W. Muraskin, 1996; Woodle, 2000). A study commissioned by the World Health Organization (WHO) and the CVI [33] surveyed local vaccine manufacturers to understand their motivations. They discovered that the primary motivations are based on political and strategic objectives, and that economic inefficiencies alone may unlikely result in a decision to cease production (Blanc & Brewer, 1999). The need to secure sufficient supply of vaccines is critical to ensure the

[33] Now defunct

success of immunisation programs. However such investments must meet certain measures of cost efficiency in order to be justified.

In general, establishing vaccine production in a country comprises of different step. Firstly is the establishment of a facility and acquisition of equipment, followed by upstream processes involving pre-clinical and clinical trials at the start of a new production; these components are called the Clinical Development stage. This process depends on whether the vaccine technology used is novel or reinvented from originating/existing products. Once completed, there are two manufacturing phases - bulk vaccine production and filling processes, which are known as the Bioprocess Development stage. An assay development stage is done afterwards where different testing are conducted, including tests for purity, stability and potency (Figure 3.1).

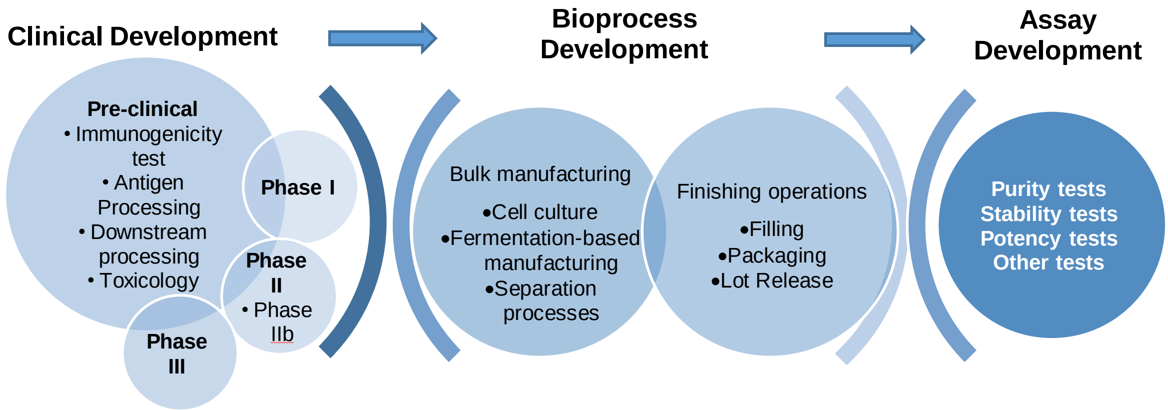

Figure 3.1. Process of vaccine development. Adapted from various sources; including Plotkin, Orenstein, and Offit (2013), H. L. Levine (2010); and Technology Transfer Initiative, WHO. Note: In some instances, vaccine manufacturers establish bulk manufacturing construction prior to Phase III clinical trials but after Phase I and Phase II clinical trials show promising results.

Many countries have approached the WHO indicating their interest in establishing new vaccine facilities. There is a common perception within the public sector that local production of health products will ensure a country's self-sufficiency, less dependency on foreign currency and means of enhancing capacity in the science and technology sector. An earlier study by the CVI however found that these perceptions are often unfounded (Milstien, 1999). For example, in cases where raw materials are imported, capital expenditures may be higher due to high interest rates on loans, and lower-cost facilities and poorer regulatory process may pose challenges in achieving standards of good manufacturing processes (GMP).

For a newly built vaccine production facility to be sustainable, the output and revenue must generate returns that can justify the investment. Investors, either governments or funding agencies, must be able to have a clear plan as to how long subsidies, if any, will be required and at what scale. An understanding of the costs to research and develop a vaccine will help countries estimate the required size of investments involved and evaluate the appropriateness of the prices achieved for vaccines produced.

Lang and Wood (1999) argue that vaccine costs-per-dose is a primary driver in predicting the adoption of new EPI vaccines, and assessments should be made at each stage from research to production and delivery of vaccines to identify whether the potential cost-per-dose ensures production is competitive in the current market. Milstien and Batson (1998) discussed a joint WHO/UNICEF commissioned report by Mercer Management Consulting in 1993, which presented an economic model of vaccine production highlighting that the number of doses produced by a vaccine manufacturer was inversely related to the cost-per-dose.

Only two studies, by the same group of authors, have quantified cost-per-dose of vaccines produced in a developing country (Mahoney, 1990; Mahoney et al., 2012). These papers evaluated 1) the cost of producing an existing plasma-derived hepatitis B vaccine by an unidentified manufacturer (Mahoney, 1990) and 2) a candidate vaccine which is the live attenuated dengue vaccines developed by Instituto Butantan, Sao Paulo, Brazil (Mahoney et al, 2012). In the first study, a hypothetical 50-million population country was assumed with the production done in two distinct facilities, one for producing the bulk antigen without adjuventing, and the other for the adjuventing process, sterile filling, and vaccine packaging. The results of the first study found that the vaccine can be sold at US$0.50 per dose packed in10-dose vials, if about 4 million doses per year were procured, with a condition that about 8% of total production is sold in the private sector for a profit. The study also identified the need for an initial capital investment of around US$3.7 million (1990 prices). The study also found that if the model was extended to the quantity of 10 to 20 million doses per year, the vaccine can be sold for less than US$0.10 per dose, similar to other EPI vaccines. The study concluded that the hepatitis B vaccine would be viable when large-scale procurement is undertaken by governments and international donor agencies.

The second paper assess a candidate tetravalent vaccine which was in the later stages of development. The economic analysis used a standard industrial methodology, applying accepted accounting practices, originally developed at the US National Institutes of Health (National Institute of Allergy and Infectious Diseases). The direct costs of materials, direct costs of personnel and labor, indirect costs, and depreciation were all determined, and assumed a production of 60 million doses per year. The study was not aimed at identifying the price of the final licensed vaccine, and concluded that the vaccine could be made available at a price affordable to governments in developing countries.

This chapter adopts a similar approach to assessing cost drivers as these two studies, but for a larger number of countries and vaccine types. The aims of this chapter were firstly, to calculate the costs-per-dose of establishing local vaccine production in developing countries based on data provided by existing vaccine producers; and secondly, quantify the variability of these costs across different driving factors, namely production scale and scope, as well as vaccine technology and formulation types. The findings will allow non-producing developing countries to inform their plans to establish new vaccine manufacturing facilities, by estimating the cost required to establish a new vaccine facility and to bring a vaccine to market.

This chapter is organised as follows: the production cost data used in the analysis are described in section 3.2, followed by the results of the cost structures, patterns and comparison to vaccine market prices in both developing and industrialised country markets in section 3.3. A secondary analysis on the economic benefits of fill-finish mechanisms in comparison to procuring finished products is also presented in section 3.3, followed by a discussion, study limitations and conclusions in section 3.4.

3.2. Methods

Cost production data, as in any industry, are of a sensitive nature and are proprietary information. This is especially the case in the vaccines industry, where competition is high because the number of companies in the industry is limited and the entry and exit barriers are high. Given the commercial sensitivity of the data from manufacturers, this study uses a questionnaire for data collection rather than accessing actual cost data. The data were collected based on self-reporting of cost figures in the form of ranges, where the range options were based on existing assumptions in the discipline (Friede, 2013; Mahoney, 1990; Mahoney et al., 2012) The questionnaire was sent to ten manufacturers, in which nine manufacturers provided data and of these, eight were DCVMs. The questionnaire included questions 11-15 to identify manufacturers in case this information was accidently missed during the colelction. The answers for these questions however were not reported to maintain the respondents' annonymousity.

3.2.1. Data collection

The questionnaire was developed under close supervision of two senior vaccine experts in WHO, based on the existing literature and industrial practice regarding vaccine cost estimations (Friede, 2013; Mahoney, 1990; Mahoney et al., 2012). An early draft of the questionnaire was reviewed in consultation with eight experts in vaccine production and costing (Table 3.1). This involved three rounds of pretesting before the final version was created.

Table 3.1. List of experts consulted on questionnaire development

Expert 1	Senior vaccine economist, former WHO staff
Expert 2	Vaccine economist, former WHO staff
Expert 3	Senior pharmaceutical industry expert, UNIDO
Expert 4	Pharmaceutical industry expert, UNIDO consultant
Expert 5	Vaccine expert, PATH
Expert 6	Senior vaccine expert, former WHO staff
Expert 7	Senior vaccine expert, WHO staff
Expert 8	Senior vaccine expert, WHO staff

By using hypothetical scenarios of different production scales and scope that respondents are asked to provide their expert judgement on, the questionnaire was designed to ensure comparability of the data collected across different companies. This is important given that different cost accounting methods are used in different companies and different tax policies exist in different countries[34]. The questionnaire is presented in Appendix 3.1.

Ten vaccine producers with senior management positions were contacted by a senior vaccine expert in WHO during an annual meeting of the DCVMN. The data were collected during this meeting to maximise efficiency. The completion of the questionnaire were unsupervised and followed up via face to face and postal method for clarification and confirmation of responses. Nine of the ten respondents provided responses, and eight respondents qualified as a developing country vaccine manufacturer. The respondents were later contacted to clarify the answers provided and to ask for any mission information in their responses to the questionnaire. A presentation showing preliminary results from the questionnaire was made to the respondents in a subsequent DCVMN-related meeting, where respondents along with other DCVMs were present. During the meeting, the respondents were also approached again to clarify any unclear responses from the questionnaire.

[34] Personal communication with Kristopher Howard, vaccine industry expert and UNIDO consultant

Each respondent was asked to consider a specific vaccine product upon which they based their responses and was asked to estimate three types of cost associated with production of that vaccine. The first was fixed costs associated with facility and equipment costs; the second was development costs which are semi-fixed costs; and the third was variable costs related to bulk-dose release and fill-finish costs for a single unit of vaccine produced.

Fixed costs

Economics theory defines fixed costs as indirect costs or overheads that are spent at the onset of production and are not dependent on the level of goods or services produced (Solberg, 1982). The respondents were asked to indicate, based on their experiences with fixed costs, estimates for three different hypothetical scenarios of production of scale and scope, assuming greenfield production, where building facilities are set up on completely new infrastructure. These scenarios were:

Scenario A: A production scale of 20 million doses per year, producing 1 vaccine.

Scenario B: A similar set up as in Scenario A, but producing 5 vaccines instead of 1. This scenario allowed assessment of shared costs from producing more vaccines in a single facility.

Scenario C: A much larger production scale of 100 million doses per year, for the same number of vaccines as Scenario B (5 vaccines). This allowed estimation of the potential cost savings of a much larger production scale than in scenario B.

In estimating fixed costs, manufacturers were asked to provide figures that included buildings, equipment, quality control (QC) laboratories, utilities, administration and offices. The scenarios above are only applied to fixed cost estimations[35].

In addition to the three greenfield scenarios, an additional **Scenario D** was presented to respondents in which estimates were generated. This scenario assumes brownfield production, where facilities are built on pre-owned and existing infrastructure. In this scenario, the production scale was for 100 million doses of one additional vaccine. This scenario did not provide a direct comparison with the production scale and scope of the other scenarios, therefore the estimates will be presented independently as a fixed cost figure (Figure 3.2), but not included in the observation of economies of scale and economies of scope.

Semi fixed costs

Semi-fixed costs are defined as costs that contain components of both fixed and variable costs (Solberg, 1982). Fixed costs are costs that are spent irrespective of the level of output, while variable costs increase proportionally to production levels. Semi-fixed costs in vaccine production are costs that are not dependent on the number of vaccine vials produced but are spent each time a new vaccine type is manufactured in the facility. R&D costs would fall under this category. DCVMs however, do not typically expend R&D costs to the level of novel vaccines, where very large sums of money are spent on preclinical studies. In the context of local vaccine production in developing countries, semi fixed costs are usually spent on validation batches and/or technical transfer costs.

The R&D costs required in local vaccine production depend on whether the vaccine is an originating or non-originating product, with the latter being more common for

[35] The fixed cost estimations under each Scenario assumptions is reflected in the resulting annualised capital costs and total average costs-per-dose.

developing country manufacturers. R&D costs in non-originating vaccines are based on the costs of validation batches, whereas for novel vaccines, the costs would include preclinical and clinical trials. In the case of vaccines produced through technology transfer arrangements, R&D costs would also depend on the stage in which the technology transfer arrangement was conducted. Technology transfer vaccines provided at a more ready or advanced stage may not require all three clinical trials and have lower failure rates but may incur higher transactional fees given the lower risk of the product.[36]

For this expense, respondents were asked to provide estimates for the R&D cost of bringing a vaccine product to market. This includes costs on personnel, pre-clinical and Phase I, II, III clinical trials and supplies. Respondents were also asked to estimate the average failure rates associated with such a development. These failure rates are important to economically estimate the contribution of attrition costs to the full cost of production.

Variable costs

Within the context of vaccine production, variable costs are expenditures related to downstream processes, including: fill and finishing of each vaccine batch produced (Appendix 3.1). For this component, respondents were asked to provide two different variable costs, relevant to downstream processes. The first question asked for the cost of goods required for vaccine manufacturing, estimated per bulk dose released. These costs only included running costs such as labour, materials and maintenance, with no account of R&D, buildings or equipment. In the second question, respondents were asked to provide estimates of the costs of filling. These were comprised of costs of vials or syringes, stoppers, labels, QC, and release.

[36] Personal communication with biotechnological expert, Ines Atmosukarto.

Given the variability of vaccine formulation presentations, respondents were also asked to identify costs based on four common vaccine presentations, these are: multi-dose vial (in this case a 10-vial dose), single-dose vials, pre-filled syringes and a lyophilised (or freeze dried) dose.

Economic benefit of fill-finish mechanisms versus procuring finished vaccines

Respondents were asked to estimate, based on their experiences, the economic benefit of procuring antigens as bulk doses in comparison to procuring finished vaccines for both traditional and modern vaccines. This economic benefit was estimated by the differences reported between the two procurement methods, by different vaccine technologies (traditional and modern vaccines) and production scale (1-5 million doses and 10–20 million doses)[37] (see question number 10 in Appendix 3.1).

Comparison to vaccine market prices

To assess how the estimated costs generated in this analysis would perform in both developing country and industrialised country markets, a comparison was made with market prices of vaccines in both markets. Vaccine market price data were obtained from a WHO database for the Vaccine Product, Price and Procurement (V3P) project[38]. These data, reported by countries, included prices of vaccines procured by low, middle and high income countries over 11 years (2005 – 2015). For the purpose of this analysis, the market price data used were for 2014. The data for 2014 included prices for 48 vaccine types, produced by 31 vaccine manufactures, procured and reported by 41 different countries. A separate analysis on vaccine prices is presented in Chapter 5.

[37] An example was provided to the responded as follows: if procuring finished vaccine costs $10 for a vial but fill-finish vaccine costs $4 ($3 for bulk purchase + $1 for filling) the benefit would be 60%.
[38] Data as of 15 August 2016

To have a comparable analysis, the price data from the V3P database were aggregated by similar cost drivers applied to the questionnaire data. These were: vaccine formulation presentations (i.e.: multi-dose, single-dose, prefilled syringe and lyophilised) and vaccine technology types (i.e.: all, bacterial, viral, combination, recombinant and conjugate vaccines). The vaccine price data included additional estimates for vaccines using lyophilised with pre-filled formulations, which will be presented though not compared to the cost data, which did not include information for this vaccine type. A price index from the V3P data was constructed and compared to the cost index, across comparable cost drivers.

Given that manufacturers face two different vaccine markets: those of industrialised and developing countries; the comparison was presented for both markets separately.

3.2.2. Analysis

The assumptions used in the analysis were adopted from studies by Mercer Management Consulting (2002), Mercer Management Consulting (2006), Mahoney (1990), and Mahoney et al. (2012). The analysis in this chapter however differed from these studies in that it included opportunity costs, by incorporating the cost of failure rates and an annualisation factor (Levin, 1983; Pronker et al., 2011). Opportunity costs were included to ensure that the total economic costs of production were accounted for and represented in the vaccine costs-per-dose estimations. This annualisation factor(a), takes into account the depreciation and interest rate on the remaining or undepreciated value, for which the following factors need to be quantified: the replacement cost and lifespan of the capital, and the rate of interest that is foregone by investing in vaccine production rather than any other alternative investment (Levin, 1983). Life year assumptions were applied to each fixed and semi-fixed cost component: buildings, equipment and validation batches. These assumptions were adopted from Mahoney et al. (2012) as follows: buildings and equipment were assumed to have 25 and 10 year lifespans respectively. For semi-fixed costs of validation batch production, the analysis used the life-year applied to equipment (10 years) with the assumption that validation batches are required when a new piece of equipment and/or facility is used.

To calculate the cost-per-dose, all three components were added as follows: fixed costs and semi-fixed costs both annualised and averaged over total doses produced, together with variable costs, also as an average cost-per-dose. The analysis did not differentiate between bulk doses produced in-house and those that were imported. The currency of analysis was US dollars. Where a different currency was provided in the questionnaire response, an exchange rate at the time of data collection was used[39].

From the estimates obtained, three main comparisons were conducted:

- To establish the effect of increases in production scale on cost-per-dose, scenarios B and C were compared, where production increased from 20 million doses to 100 million doses annually, with five vaccines produced in each facility. This comparison was labelled as (*A1*).
- To establish the effect of an increase in production scope on cost-per-dose, scenarios A and B were compared, where production scale was the same but the scope, or number of vaccine types produced, increased. This comparison was labelled as (*B1*).
- A comparison between the production scale effect to that of the production scope effect was conducted (*A1* versus *B1*).

Annualised fixed cost-per-dose

The annualised fixed cost-per-dose was calculated by adopting the following formula (Butler, 1990; Levin, 1983):

$$\boldsymbol{C_a = (V - R)_a} \qquad \textbf{Equation 3.1}$$

[39] The exchange rate was based on an online currency converter service (http://www.xe.com/).

where C_a is the annualised capital cost of equipment, obtained by multiplying the acquisition cost of the equipment *V*, after deducting its estimated residual value *R*, by an annualisation factor *a*.

Further, the annualisation factor was calculated as follows:

$$\boldsymbol{a} = \frac{\boldsymbol{r}(\mathbf{1}+\boldsymbol{r})^{\boldsymbol{n}}}{(\mathbf{1}+\boldsymbol{r})^{\boldsymbol{n}}-\mathbf{1}}$$ **Equation 3.2**

where *r* is the annual interest rate and *n* is the life of the equipment (in years) and the residual value *R* is assumed to be zero. Using standard industry practices[40], the interest rates for buildings was 10%, while for equipment it was 5%. The reference for life years of buildings and equipment used by Mahoney et al. (2012) was adopted and fixed costs were assumed to be made up of two-thirds of facility costs and one-third of equipment costs. These were then divided by the total number of doses produced in each production setting.

<u>Annualised capital costs</u>

Annualised capital costs consist of annualised fixed costs-per-dose[41] and annualised semi-fixed costs-per-dose (Mahoney, 1990). Each of these components was calculated using the assumptions mentioned earlier.

<u>Variable costs</u>

For the variable costs of the bulk-dose released and fill-finish processes, estimates were taken from the different questionnaire responses and followed up with respondents to clarify and complete the dataset. Following the study by Mahoney (1990), factory overheads were calculated as 15% of the total of direct materials and inputs, plus direct manpower and labour; while administrative overheads were

[40] Reference to (classified) Hexavalent vaccine proposals to WHO from manufacturers
[41] Termed “depreciation” in Mahoney (1990).

assumed to be 5% of that same total. The variable costs were presented as variable costs-per-dose.

Total average cost-per-dose

The total average cost was obtained by the summation of the fixed cost-per-dose, semi-fixed cost-per-dose and variable cost-per-dose, for each vaccine observed, as described below (Equation 3.3)

Fixed costs per dose	*a*	
Semi-fixed costs per dose	*b* +	
Capital costs per dose	*a+b*	
Variable costs per dose	*c* +	
Total average costs per dose	***(a+b)+c***	**Equation 3.3**

As in Mahoney (1990), the estimates were summarised as follows:

- *Raw Materials & Direct Labour*, equalled the fill and finish costs;
- *Assay Costs*, equalled the bulk-dose release costs;
- *Indirect costs*, equalled 15% of the total of the two costs above as factory overhead, plus 5% of the same total for administrative overheads;
- *Depreciation*, which was the annualised capital cost-per-dose; and
- *Total cost-per-dose*, the sum of all of the above.

Further, to analyse the cost behaviour of vaccines, an index was constructed using the total average cost-per-dose as the index base (1.00). All other costs-per-dose were compared against this figure, to display metrics of the cost drivers relative to the overall average (Oliver Wyman, 2007).

To address the uncertainty in the data and assumptions used in the analysis, a sensitivity analysis was conducted on the cost-range of the fixed cost responses, range of success rates responses, as well as the assumptions used for the annualisation factor.

3.3. Results

3.3.1. Cost structures

<u>Fixed costs</u>

On average, fixed costs based on the 12 observed vaccines were respectively US$ 47.5 million, US$ 80 million and US$ 147.1 million for Scenarios A, B and C, respectively. Further, the average estimate provided for Scenario D was US$ 18 million. (Figure 3.2).

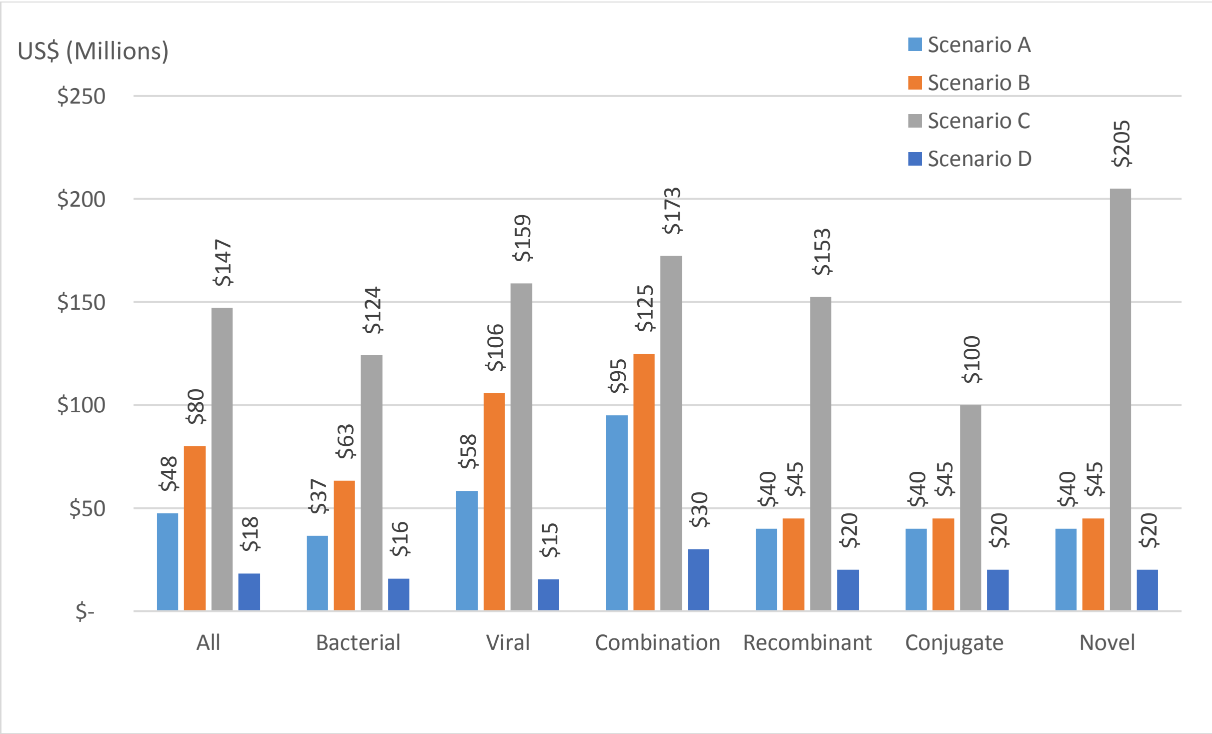

Figure 3.2. Calculations of fixed costs for vaccine facilities in developing countries, based on four hypothetical scenarios. *<u>Scenario A</u>*: 20 million annual doses – 1 vaccine (Greenfield); *<u>Scenario B</u>*: 20 million annual doses – 5 vaccines (Greenfield); *<u>Scenario C</u>*: 100 million annual doses – 5 vaccines (Greenfield); *<u>Scenario D</u>*: 100 million annual doses – 1 vaccine (Brownfield)

Theoretically, fixed costs are generally not influenced by the number or volume of outputs produced. However, all of the responses indicated that as production scale and production scope increased, fixed costs in vaccine production have a step-costs pattern, where higher fixed costs are required when the current production surpasses a certain threshold.

Semi-fixed costs

R&D costs in bringing a vaccine to market were estimated to be an average of $16.9 million, with vaccine type-specific estimates of between $7.5 million (combination vaccines) and $80 million (novel vaccines). One respondent provided an estimated figure ranging between US$ 500 million to US$ 1 billion, however as this was assumed to be taken from the existing literature (DiMasi et al., 2003; Pronker et al., 2011), rather than being an empirical observation, this estimate was excluded from the analysis.

The respondents estimated the success rates to be an average of 75%, ranging from 55% (novel vaccines) to 98% (combination vaccines). This was inversely correlated with the R&D costs reported above. The novel vaccines included in this chapter analysis, which showed the lowest success rates, were produced under technology-transfer arrangements. These are shown in Figure 3.3.

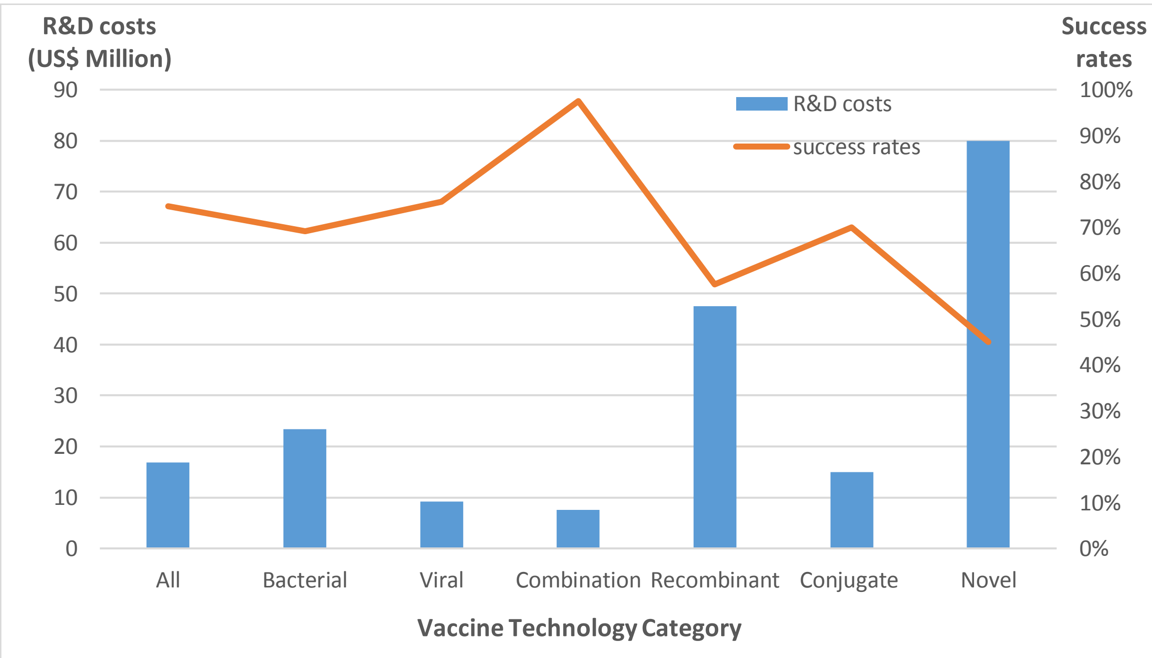

Figure 3.3. Estimations of R&D costs and success rate of vaccine production in developing countries. Estimations are based on eight DCVM responses.

Annualised capital costs

The annualised capital costs (Figure 3.4) were on average US$ 0.37, US$ 0.11 and US$ 0.040 per dose across scenarios A, B and C, respectively. Capital costs-per-dose were found to be lower as production scale and scope increased.

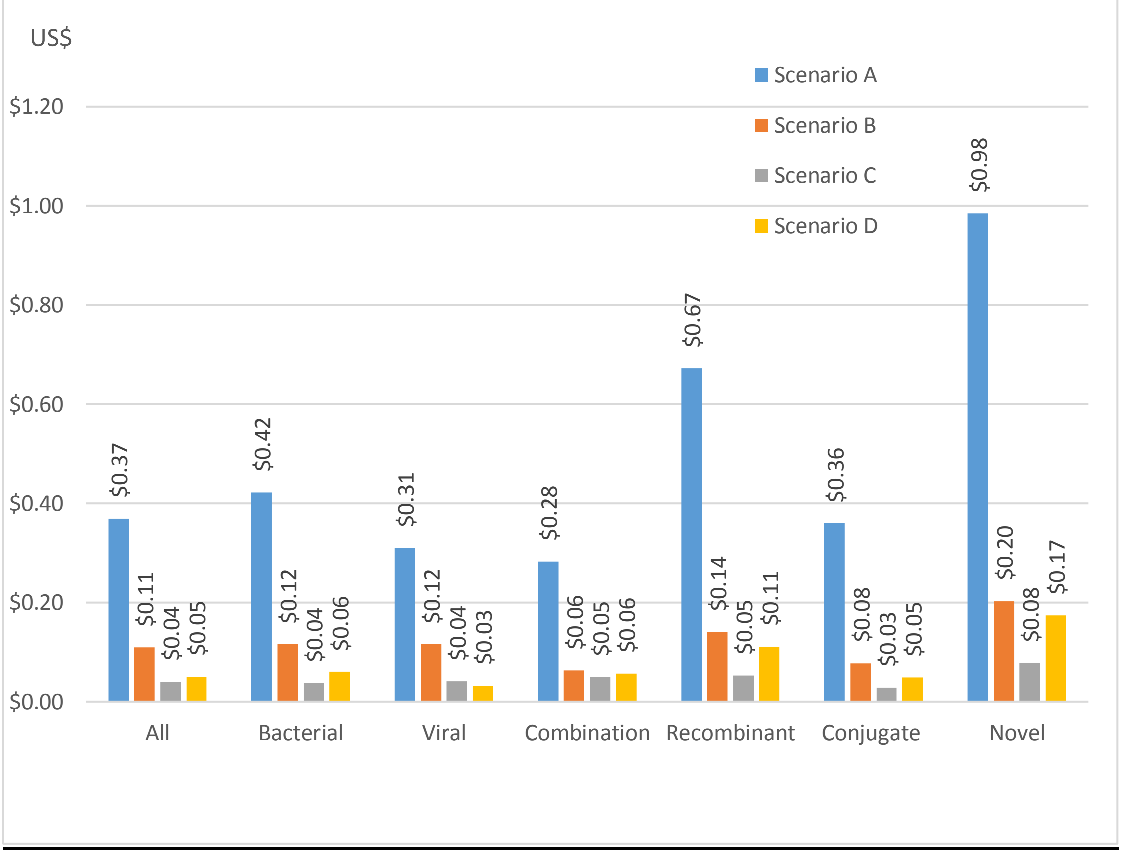

Figure 3.4. Estimations of annualised capital cost-per-dose for vaccine produced in developing countries. Based on information provided by eight DCVMs on 12 vaccine examples. Figures are based on four hypothetical scenarios. *Scenario A*: 20 million annual doses – 1 vaccine (Greenfield); *Scenario B*: 20 million annual doses – 5 vaccines (Greenfield); *Scenario C*: 100 million annual doses – 5 vaccines (Greenfield); *Scenario D*: 100 million annual doses – 1 vaccine (Brownfield).

Variable costs

The average variable cost-per-dose were US$ 1.77 for a one million dose production, and US$ 1.74 and US$ 1.15 respectively for 20 million and 100 million dose productions (Figure 3.5).

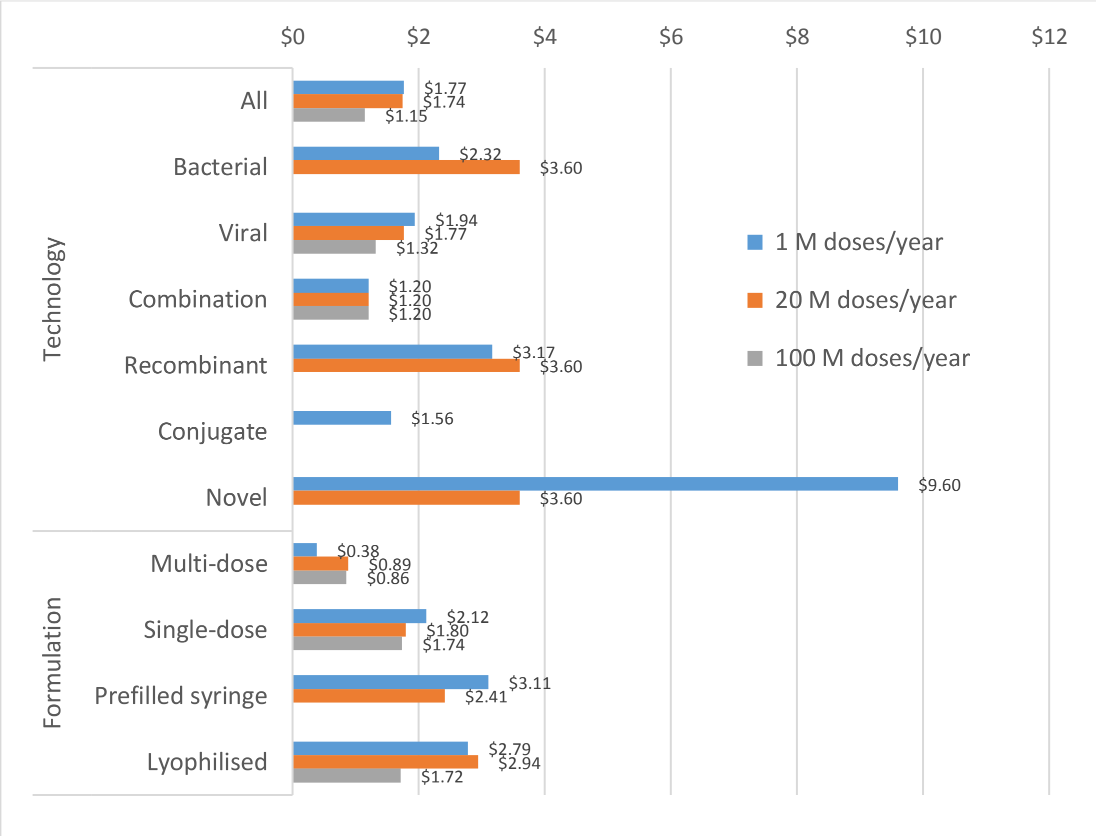

Figure 3.5. Estimations of variable costs of vaccine production in developing countries. Information based on 12 vaccine examples provided by eight DCVMs.

Average costs-per-dose

The overall average costs-per-dose were found to be US$ 2.3 (Scenario A), US$ 2.02 (Scenario B) and US$ 1.82 (Scenario C). The costs lowered as production scale and scope increased (from Scenario A – C). This was also consistent across both observed cost drivers: vaccine technology types and formulation presentation (Table 3.2 and Figure 3.6).

Table 3.2. Estimations of average cost-per-dose for vaccines produced in developing countries, with standard deviations.

	Categories	Scenario A (SD)	Scenario B (SD)	Scenario C (SD)
Technology	All	$ 2.30 (0.91)	$ 2.02 (0.86)	$ 1.82 (0.78)
	Bacterial	$ 2.32 (0.97)	$ 2.02 (0.87)	$ 1.82 (0.77)
	Viral	$ 2.26 (0.83)	$ 2.02 (0.85)	$ 1.83 (0.80)
	Recombinant	$ 2.56 (1.16)	$ 2.18 (0.99)	$ 1.72 (0.63)
	Conjugate	$ 2.06 (0.63)	$ 1.77 (0.63)	$ 1.72 (0.63)

	Novel	$ 4.58 -	$ 3.80 -	
Formulation	Multi-dose	$ 1.26 (0.38)	$ 0.99 (0.38)	$ 0.92 (0.39)
	Single-dose	$ 2.24 (0.36)	$ 1.97 (0.36)	$ 1.90 (0.36)
	Pre-filled syringe	$ 2.59 (1.07)	$ 2.26 (0.89)	$ 1.93 (0.74)
	Lyophilised	$ 3.04 (0.36)	$ 2.81 (0.38)	$ 2.54 (0.52)

Note: Data based on 12 vaccine examples provided by eight DCVMs. Estimations based on three hypothetical scenarios. <u>*Scenario A*</u>: 20 million annual doses – 1 vaccine; <u>*Scenario B*</u>: 20 million annual doses – 5 vaccines; <u>*Scenario C*</u>: 100 million annual doses – 5 vaccines.

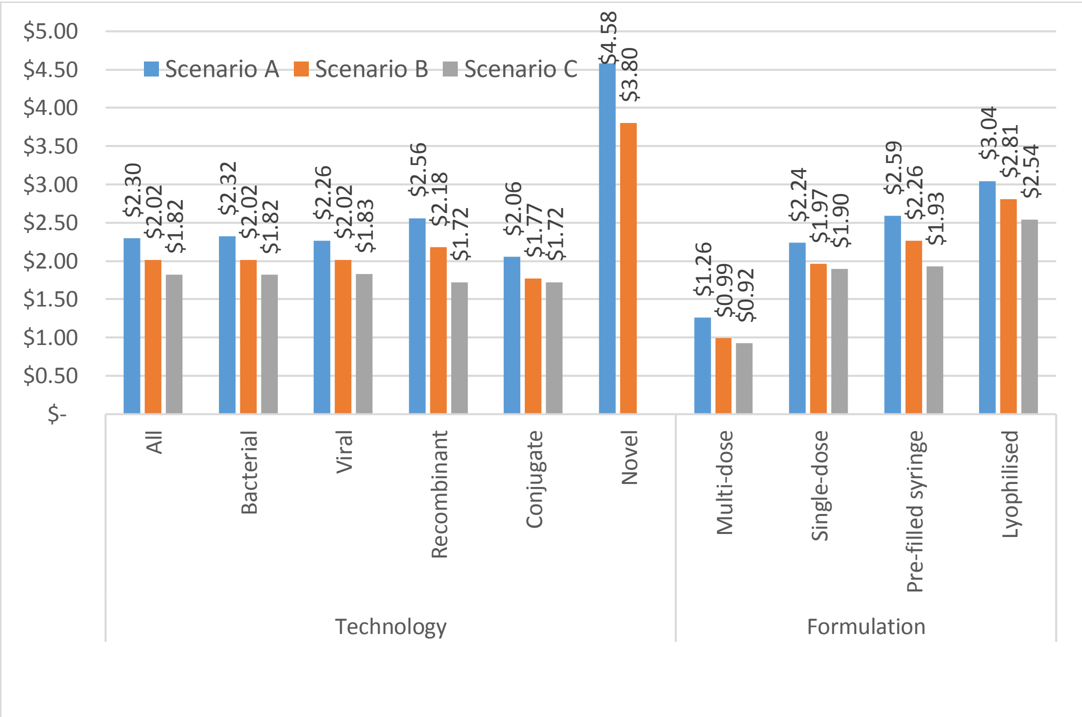

Figure 3.6. Estimations of average cost-per-dose for vaccines produced in developing countries. Data based on 12 vaccine examples provided by eight DCVMs. Estimations based on three hypothetical scenarios. <u>*Scenario A*</u>: 20 million annual doses – 1 vaccine; <u>*Scenario B*</u>: 20 million annual doses – 5 vaccines; <u>*Scenario C*</u>: 100 million annual doses – 5 vaccines.

3.3.2. Cost patterns

In comparing production scenarios A, B and C (Figure 3.6), two observations can be made; first, that average costs-per-dose were lower as production scale and production scope increased. This was consistent across all vaccine technology categories. Second, across vaccine formulations, the average cost-per-dose increased (in ascending order): from multi-dose to single-dose, pre-filled syringe and lyophilised vaccine formulation. The cost index also showed similar results for formulation types, while for technology types, production was most costly for novel and recombinant vaccines, whereas technologies such as viral, and conjugate vaccines were less costly (Table 3.3).

Table 3.3. Cost index of vaccine production in developing countries, based on three hypothetical scenarios

Cost drivers	Categories	Scenario A	Scenario B	Scenario C
Technology	All	1.00	1.00	1.00
	Bacterial	1.01	1.00	1.00
	Viral	0.99	1.00	1.00
	Recombinant	1.12	1.08	0.95
	Conjugate	0.90	0.88	0.95
	Novel	2.00	1.89	0.00
Formulation	Multi-dose	0.55	0.49	0.51
	Single-dose	0.98	0.97	1.04
	Pre-filled syringe	1.13	1.12	1.06
	Lyophilised	1.33	1.39	1.39

Note: Average cost-per-dose was used as the base index (1.00) and values shown are multiples of the base index.

Economies of scale

Economies of scale (*A1*) occur when the cost-per-dose decreases as the volume size (production scale) increases. This was observed in the study by comparing Scenario B to Scenario C. The results show that the economies of scale for all vaccine types was an average of 9.5%, meaning that increasing the production scale from Scenario B to C (from 20 million doses to 100 million doses) will reduce the cost-per-dose of the vaccine by 9.5% (Figure 3.7). The economies of scale, across vaccine technology types, were highest in recombinant vaccines (20.9%) and lowest in conjugate vaccines (2.8%). The economies of scale for novel vaccines were not observable because responses for novel vaccines in Scenario C were not available. Across vaccine formulations, the highest economies of scale were found in pre-filled syringe vaccines (14.7%) and lowest in single-dose vaccines (3.3%).

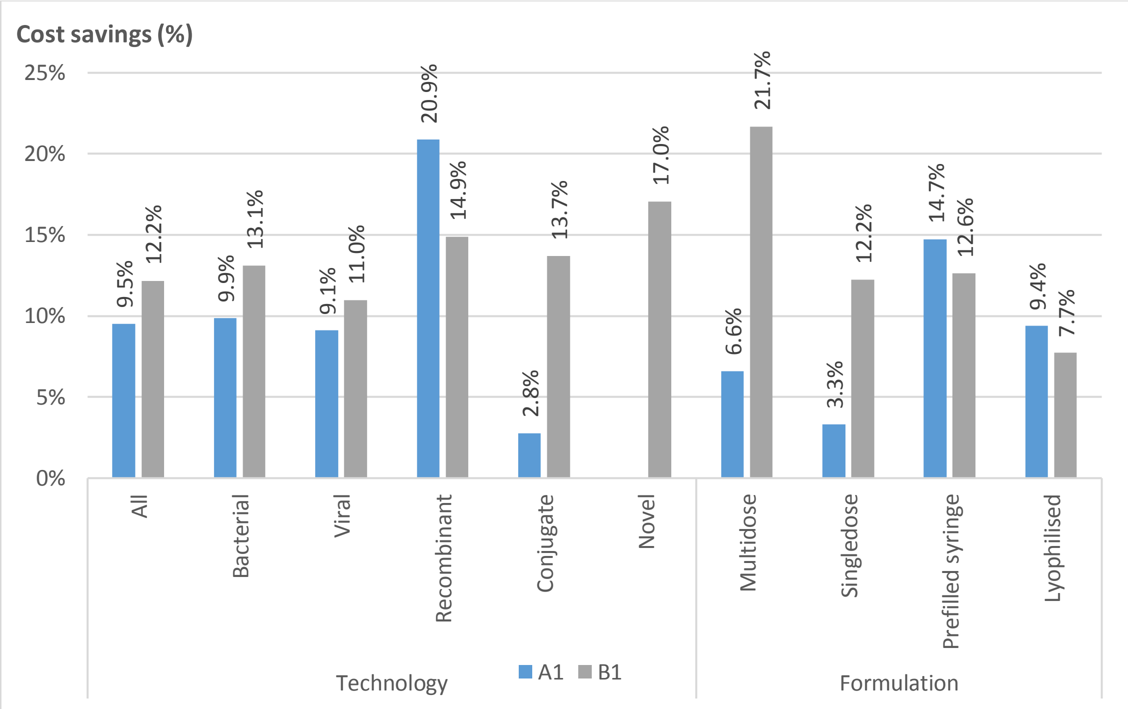

Figure 3.7. Estimations of economies of scale and economies of scope for costs-per-dose of vaccines produced in developing countries. *A1*: Economies of scale; *B1*: Economies of scope. Data based on three hypothetical scenarios. *Scenario A*: 20 million annual doses – 1 vaccine; *Scenario B*: 20 million annual doses – 5 vaccines; *Scenario C*: 100 million annual doses – 5 vaccines.

Economies of scope

Economies of scope (*B1*) occur when cost-per-dose lowers due to multi-product manufacturing, and was observed by comparing Scenarios A and B. Figure 3.7 shows that economies of scope were present in general and across all cost drivers at an average of 12.2%. Among vaccine technology types, economies of scope were highest in recombinant vaccines (14.9%) and lowest in viral vaccines (11.1%). For vaccine formulations, the economies of scope were highest in multi-dose vaccines (21.7%) and lowest in lyophilised vaccines (7.7%).

Comparing economies of scale to economies of scope (*A1* vs *B1*)

A comparison between economies of scale and economies of scope show that though the economies of scale and economies of scope for costs-per-doses were both positive across all vaccines observed; on average, the economies of scope were higher than the economies of scale (12.2% versus 9.5%). Further, the economies of scope had a smaller range (7.7% to 21.7%) than economies of scale (2.8% to 20.9%). With the exception of recombinant vaccines and prefilled syringe vaccines, the economies of scope were higher than economies of scale for the different vaccine technology types and formulation presentations (Figure 3.7).

3.3.3. Market price comparisons

Comparison in industrialised-country markets

Figure 3.8 shows the comparison between costs-per-dose in Scenarios A, B and C and the price-per-dose of vaccines, within the industrialised-country market. The costs-per-dose estimated from the analysis was much lower than the vaccine price-per-doses reported being procured in industrialised vaccine markets. This suggests a producer surplus can be gained in this market (Herlihy et al., 2016).

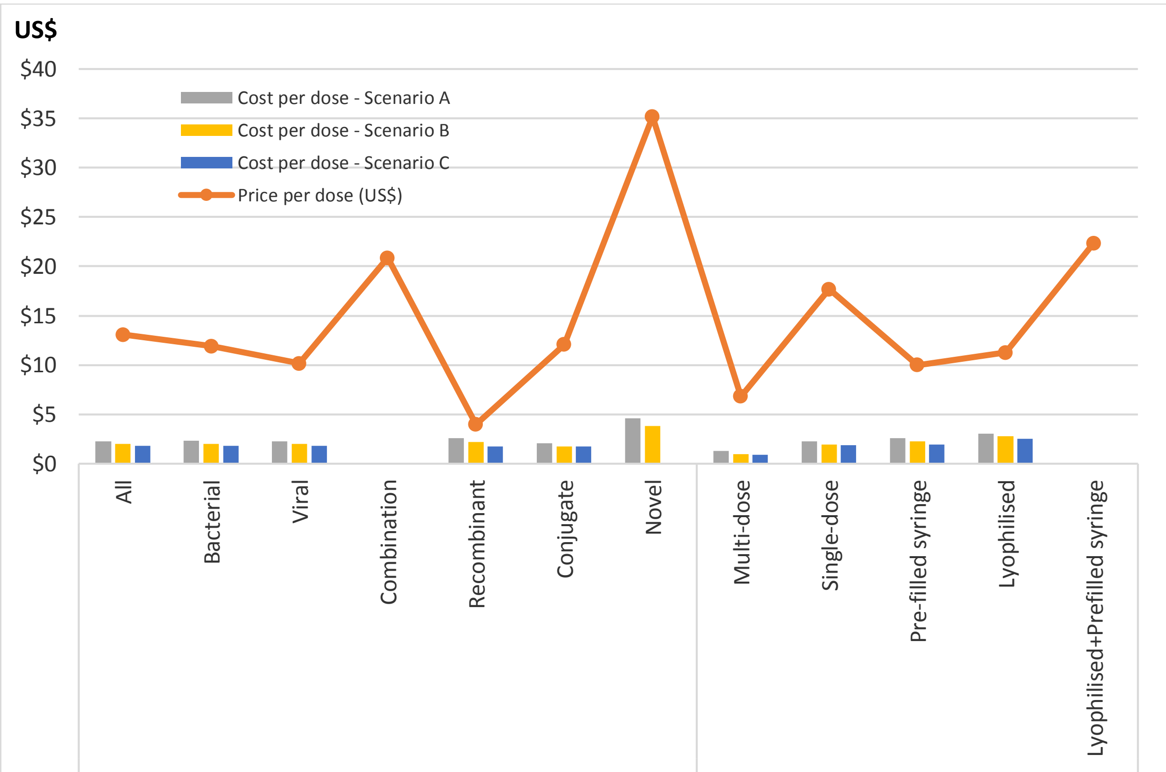

Figure 3.8. A comparison of estimated developing country vaccines' costs-per-dose based on hypothetical Scenarios A, B and C to prices-per-dose paid by industrialised countries. Costs based on scenarios: _Scenario A_: 20 million annual doses – 1 vaccine; _Scenario B_: 20 million annual doses – 5 vaccines; _Scenario C_: 100 million annual doses – 5 vaccines; Price data for industrialised countries from V3P database, WHO (2014).

Figure 3.9 shows that the pattern of the costs-per-dose index was similar to that of the price-per-dose index in industrialised-country markets, with the exception of pre-filled syringes, lyophilised vaccines and recombinant vaccines. Cost-per-dose data were not available for combination vaccine types nor lyophilised with pre-filled syringe vaccines formulations, therefore a comparison to the price index could not be made.

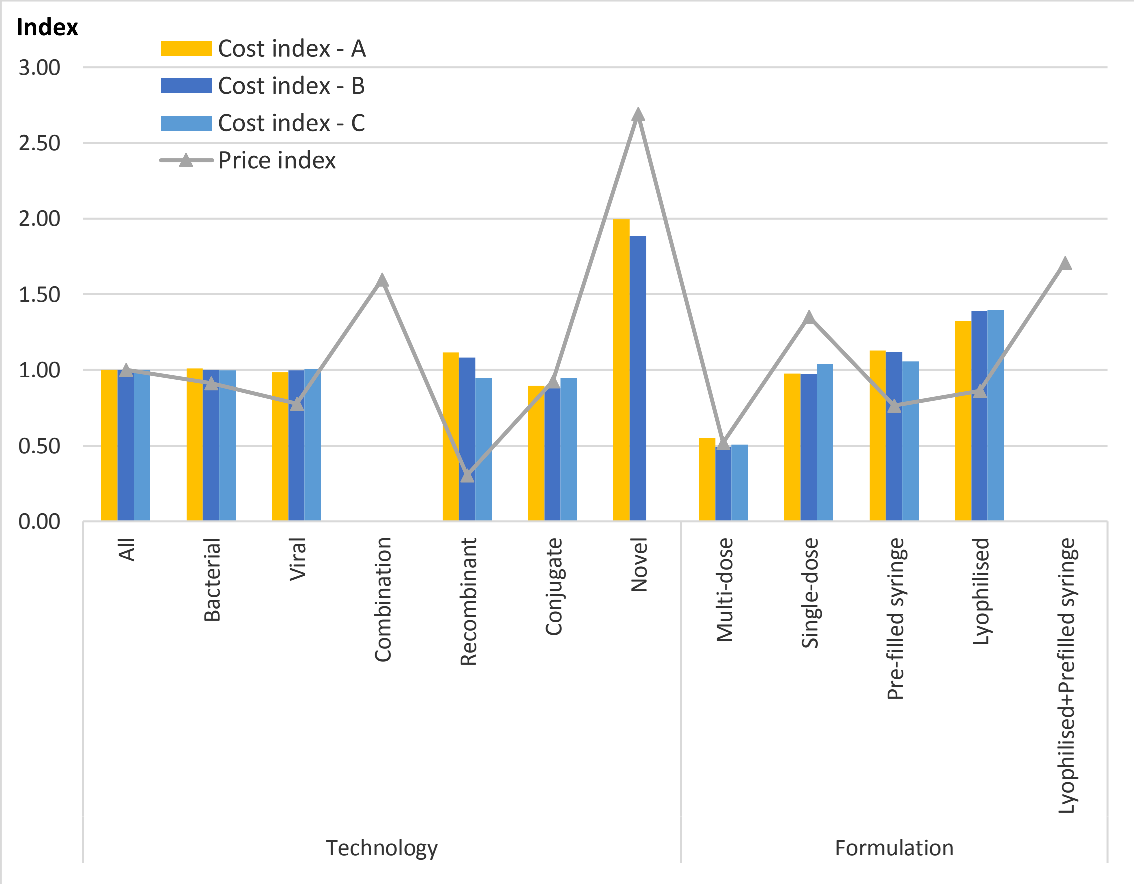

Figure 3.9. A comparison of estimated developing country vaccines' cost index based on hypothetical Scenarios A, B and C to price index for industrialised country vaccine markets. Costs based on scenarios: _*Scenario A*_: 20 million annual doses – 1 vaccine; _*Scenario B*_: 20 million annual doses – 5 vaccines; _*Scenario C*_: 100 million annual doses – 5 vaccines; Price data for industrialised countries from V3P database, WHO (2014). Index base (1.00) for cost and price indexes used average of all vaccines.

Comparison in developing-country markets

A similar comparison was made for the developing-country markets. Figure 3.10 shows that the overall average costs-per-dose was relatively lower than the vaccine prices-per-dose in developing-country markets. Vaccine categories where the reported prices were lower than the estimated costs were recombinant vaccines, multi-dose vaccines and (only slightly) lyophilised vaccines.

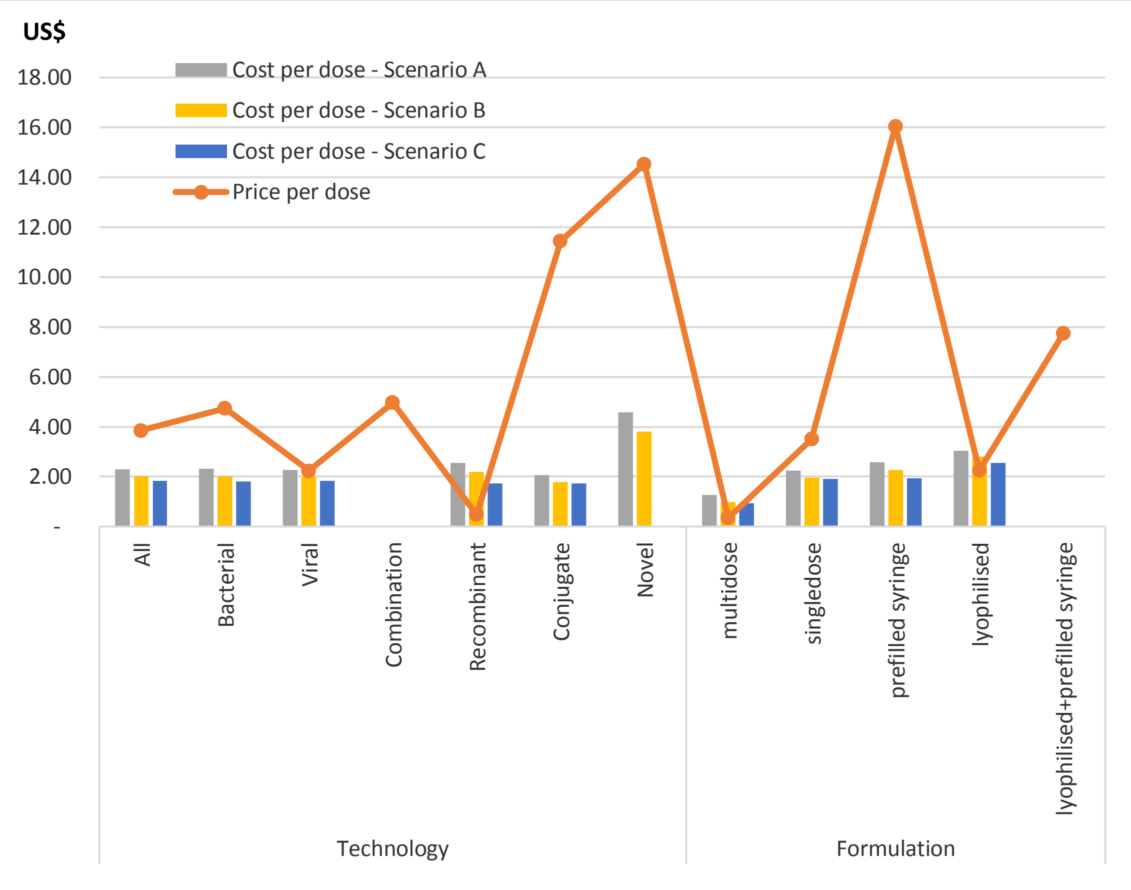

Figure 3.10. A comparison of estimated developing country vaccines' costs-per-dose based on hypothetical Scenarios A, B and C to prices-per-dose paid by developing countries. Costs based on scenarios: _Scenario A_: 20 million annual doses – 1 vaccine; _Scenario B_: 20 million annual doses – 5 vaccines; _Scenario C_: 100 million annual doses – 5 vaccines; Price data for developing countries from V3P database, WHO (2014).

Figure 3.11 shows the pattern of the costs-per-dose index to be similar to the price-per-dose index in developing-country markets. The only differences were in recombinant vaccines and pre-filled syringes and lyophilised vaccine presentation types. There were also no comparable cost index estimates for the price index of combination vaccines and lyophilised with pre-filled syringe vaccines.

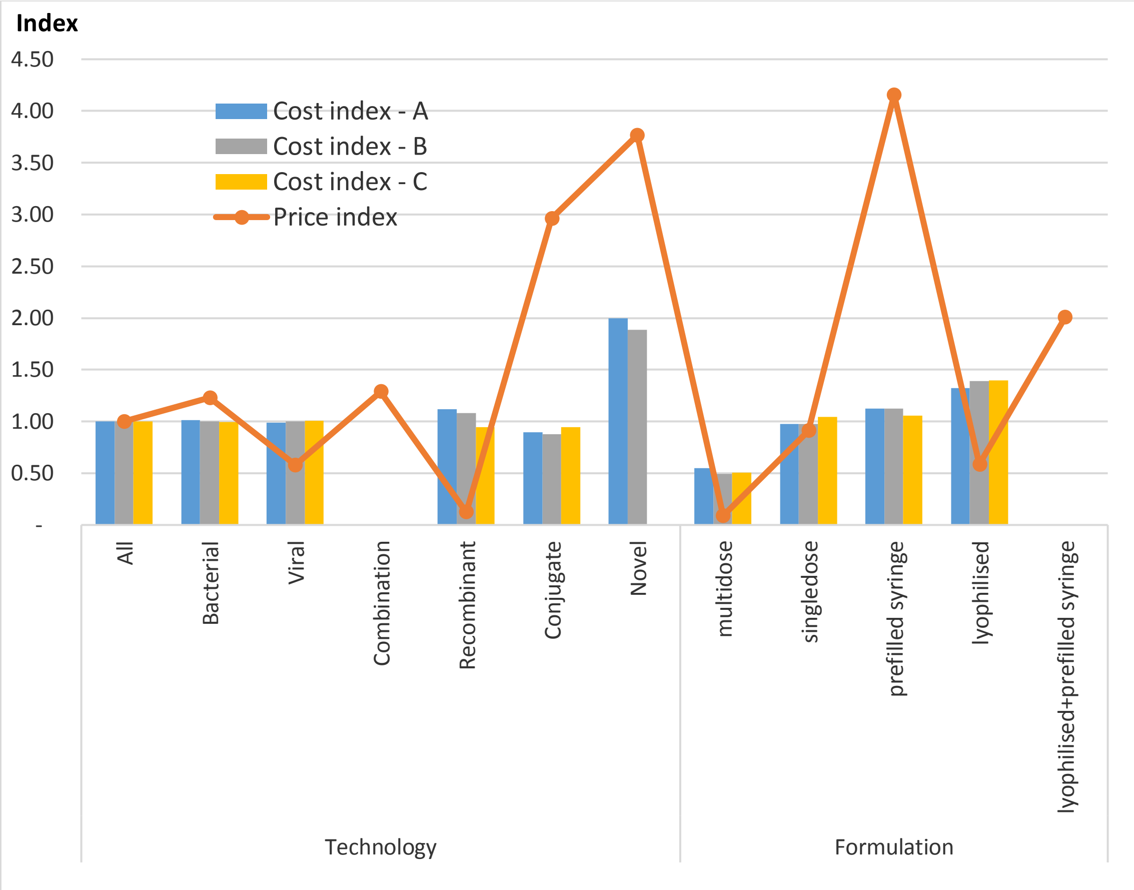

Figure 3.11. A comparison of estimated developing country vaccines' cost index based on hypothetical Scenarios A, B and C to price index paid by developing countries. Costs based on scenarios: _Scenario A_: 20 million annual doses – 1 vaccine; _Scenario B_: 20 million annual doses – 5 vaccines; _Scenario C_: 100 million annual doses – 5 vaccines; Price data for industrialised countries from V3P database, WHO (2014). Index base (1.00) for cost and price indexes used average of all vaccines.

3.3.4. Economic benefit of fill finish mechanisms versus procuring finished vaccines

Six of the eight respondents provided estimates of the economic benefits of vaccines procured as a finished product as opposed to establishing a fill and finish mechanism for bulk material, as shown in Figure 3.12. Overall, the economic benefit was reported to be higher when vaccines are procured as antigen and filled locally, for high volume procurement and in modern vaccines.

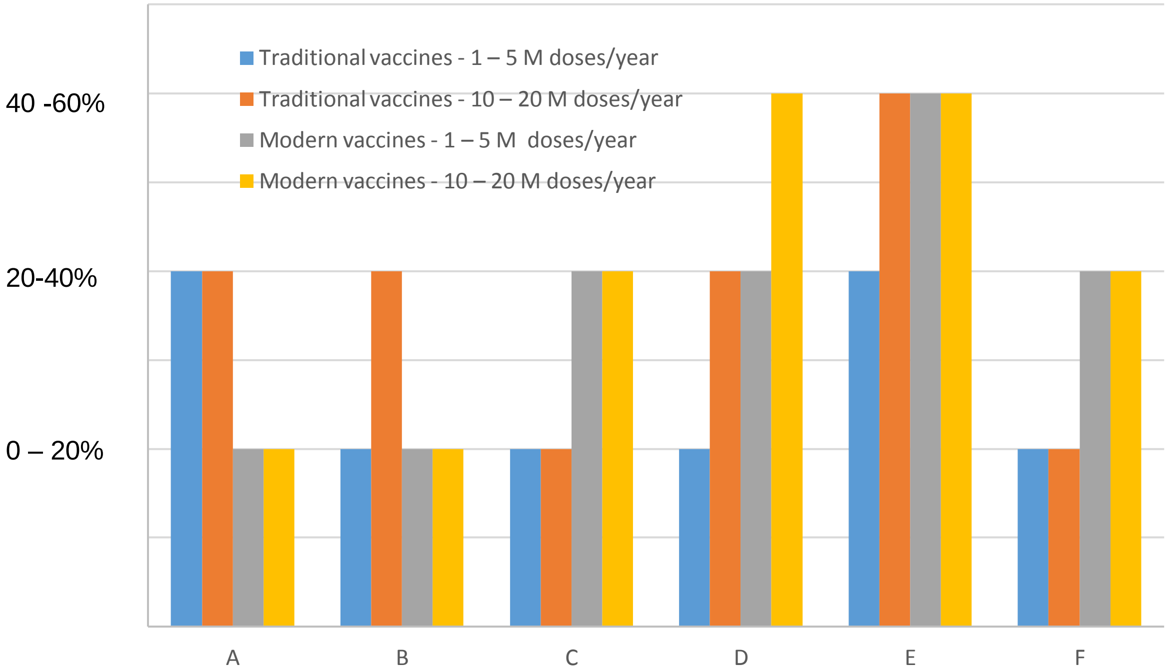

Figure 3.12**. Estimated economic benefit of procuring antigens and filling compared to procuring finished vaccines.** Data based on six DCVMs, e.g: if procuring finished vaccine costs $10 for a vial but fill-finish vaccine costs $4 ($3 for bulk purchase + $1 for filling) the benefit would be 60%.

3.3.5. Sensitivity analyses

Using the lower bound of the fixed cost ranges provided by the respondents, the results showed a similar pattern of step fixed costs, yet the difference was that fixed cost estimates for recombinant, conjugate and novel vaccine technologies were considerably lower in Scenario B where the production scope increased from one vaccine to five vaccines. Yet the annualised capital cost which is made of fixed costs and semi fixed costs per dose, lowered as the production scale and scope increased maintained a similar patter to the original analysis. Similarly for total average costs-per-dose, there were no differences. The results from using the upper bound did not present any significant difference in regards to the cost structures. The comparison between costs and market prices in developing country markets also showed a similar pattern to the original analysis. Using the lower bound for success rates also did not show any significant difference in cost structures. Economies of scale and economies of scope were found in all the sensitivity analyses conducted. Lowering the discount rates (5% for building and 1% for both equipment and validation batches) and life years (10 years for building and 5 years for both equipment and validation batches) did not show any significant differences to the original analysis.

3.4. Discussion

The study found that the overall average cost-per-dose of establishing new vaccine facilities in developing countries were reported to be highest for Scenario A, followed by Scenarios B and C respectively, indicating both economies of scale and scope. The estimated costs-per-dose across all cost drivers ranged between US$ 0.92 (Scenario C for multi-dose vaccines) and US$ 4.40 (Scenario A for novel vaccines). These estimates are in agreement with the costs suggested in the report by Mercer Management Consulting (2002), which used a multinational manufacturer as its benchmark and found costs ranging between $0.05 to $3-$4 per dose. The study also showed that the estimated cost-per-dose by formulation types followed the pattern typically found in industrial practices[42], that is the average cost-per-dose increased (in ascending order) from multi-dose to single-dose, pre-filled syringe and lyophilised vaccine formulation.

Under the three hypothetical scenarios, costs-per-dose of vaccines produced by developing countries were on average 47% lower than vaccine prices in developing-country markets and 84% lower than prices in industrialized country markets. This suggests that a producer surplus may be attainable for both markets, in which the difference will allow for profit that can support sustainable production.

Comparing the potential price-cost margin for specific vaccine types, the result show that DCVMs have the potential to obtain producer surpluses in vaccine technology types such as bacterial and conjugate vaccines for the developing-country markets, and conjugate and novel vaccines for industrialised markets. The potential producer

[42] Personal communication, vaccine production expert Jan Hendriks.

surplus in developing country markets can be obtained for pre-filled syringe vaccines. As for industrialised country markets, the potential for producer surplus would be in multi-dose and single-dose vaccines.

A comparison of the cost index and price index for industrialised vaccine markets showed a similar pattern between the two, with the exception of pre-filled syringes, lyophilised vaccine formulations and recombinant vaccine types. For developing-country markets, the pattern was similar, with the exception of recombinant vaccine types and formulations with pre-filled syringes and lyophilised vaccines.

A general observation of the fixed costs was that there are an economies of scale and economies of scope in the vaccine costs-per-dose across the different scenarios examined. However, the fixed costs required across these different scenarios suggest a pattern of step fixed costs in establishing new vaccine manufacturing facilities in developing countries. These step fixed costs occur whereby, upon passing a certain production threshold[43], a higher fixed costs is required, mainly due to the equipment capacity used for manufacturing vaccines in these different settings. The presence of this step cost feature emphasises the importance of demand forecasting for vaccine manufacturers. Uncertainties exist in demand forecasting, particularly in developing countries as well as in the case of pandemics, which poses a great problem for manufacturers. This step cost feature however also implies that the cost estimates generated in this Chapter may not be applicable to production scale and scope settings that are different from the ones used in the analysis.

Economies of scale and economies of scope were found to exist across vaccine production scenarios. The lowest economies of scale were found in the conjugate vaccine category while the highest were in recombinant vaccines. By formulation

[43] i.e.: from single to multiple vaccine facilities, or production scales of 20 million doses to 100 million doses, or the combination of these.

category, the lowest economies of scale were found in single-dose vaccines and the highest in pre-filled syringes. Economies of scope however, were lowest in bacterial vaccines and highest in recombinant vaccines. By formulation category, the lowest economies of scope were in lyophilised vaccines and highest in multi-dose vial vaccines. These findings suggest that despite the high fixed-cost requirements in establishing new vaccine manufacturing facilities (Sloan, 2012), setting a production scale at 20 million annual doses and above as well as establishing a multiproduct facility can reduce the final costs-per-dose.

Though results from this study suggested that local vaccine production, which involves mainly the production of pre-existing vaccines, would have fixed costs that are lower than those of manufacturing pipeline vaccines, large scale and scope of production are still required in order to maintain costs-per-dose at a level close to the marginal costs.

Vaccine facilities of these scenario sizes however may not be attainable or sustainable for many countries, including those wanting to invest in local vaccine production. This is especially true given that vaccine manufacturers would normally need to first secure and sustain their domestic market before expanding into export markets, where competition and regulatory requirements are more challenging[44].

The failure rates of developing country manufacturers were an average of approximately 25% (range 3% – 55%). This range was significantly lower than what was found by Pronker et al. (2011) who found a wide variety of figures across different studies, ranging from 7% to 78%. Their study however covered originating vaccines or new chemical entities where success rates are notoriously low (Struck, 1996).

This is not entirely surprising given that vaccines produced by developing country manufacturers are mostly developed through technology transfer arrangements that

[44] Personal communication with vaccine industry expert in WHO, Martin Friede

have passed some if not all of the development and preclinical steps. Additionally, the R&D costs in developing countries were found to be much lower and to have higher success rates than those of drug products and vaccines produced by multinational companies. This is also not surprising given that the R&D required in vaccine production by developing countries is usually done in a technology transfer context. Given that several (or all) clinical trial phases might be required, the success rates for novel vaccine production would be much lower and certainly more costly than for other vaccine types (Pronker et al., 2011; Struck, 1996).

The cost estimations under Scenarios A, B and C compared to the V3P price data suggest that our estimates were lower than prices reported in industrialised country vaccines markets. Given the divergence market phenomenon[45], whereby vaccine demand is increasingly divergent between different geographical regions and income levels, manufacturers in developing countries that are interested in supplying to the vaccines markets in industrialised-countries may encounter a different set of epidemiological demands and needs than current clientele in developing country markets (Jarrett, 2008; Pauly & Cleff, 1996).

This chapter used the 2014 data from the V3P database as an indication of market prices of vaccines. The figures show that the vaccine prices in industrialised and developing country markets are structured differently across the different vaccine technology types. Prices for some technology categories between these two markets, relative to their respective overall average price, are either different (i.e.: higher in industrialised markets but lower in developing country markets) or are in the same direction yet more pronounced. The most notable differences would be in the categories of bacterial vaccines (higher than the average in developing countries yet lower than the average in industrialised countries) and combination vaccines (higher

[45] Please refer to Chapter 2, section 2.3

than average in both markets but more pronounced in the industrialised market). For formulation types, differences are pronounced for single-dose vaccines (close to overall average in developing country markets and more than double in the industrialised market), prefilled syringes (significantly higher than average in developing country markets, yet not in industrialised markets) and lyophilised with prefilled syringe vaccines (opposite to that found in prefilled syringe vaccines). These differences may affect the cost – price comparison between the two markets, therefore the comparisons are treated separately. Also important to note is that these vaccine prices are likely to include subsides available through market access initiatives by agencies such as GAVI. However, the prices that developing country vaccine manufacturers must compete against in the market are those that are reported in the V3P database. Further, to assess the affordability of vaccines produced by developing countries would require a budget impact analysis which assess the affordability of a certain product or treatment while taking into account the resources and budget constraints in context.

With regards to the difference in cost for brownfield and greenfield production, the fixed costs for brownfield facilities (Scenario D) were as low as US$ 18 million compared to scenarios using greenfield facilities (US$ 48 million, US$ 80 million and US$147 million for Scenarios A, B and C respectively) (Figure 3.2). However there was no direct comparison for the production scale and scope in the scenario for brownfield (scenario D) to the other scenarios using greenfield production (Scenarios A, B and C), without making some assumptions about the applicability of the findings from the other scenarios to the brownfield scenario. Such comparisons could form the basis of future research.

With regards to the economic benefits observed by local vaccine manufacturers between the options of procuring finished vaccines and procuring antigens to then be filled locally, the results suggest that the economic benefit of the latter is higher for new/modern vaccines and for vaccines procured in larger volumes (10 – 20 million annual doses compared to 1 – 5 million doses). These results confirm the findings by Mestre-Ferrandiz et al. (2012) that type (viral, bacterial or combination vaccine), and technology (new or traditional) are driving factors in the cost of vaccine production.

The findings in this study also complement those of Mercer Management Consulting (2002), Mahoney (1990) and Mahoney et al. (2012), who highlighted that capital expenditure constitutes a large proportion of the cost; and that the size of capital expenditure plays a big role in determining the cost-per-dose. Cost-per-dose is highly volume sensitive and becomes lower when more vaccines are produced in one facility. However, this study has also found that at production sizes as large as 20 million and 100 million doses annually, the cost-per-dose becomes largely driven by variable costs. This is further supported by the findings in the sensitivity analyses where using the upper bound of the fixed cost range did not present any significant difference in regards to the average cost-per-dose, suggesting the determining role of variable costs at production scales above 20 million annual doses.

3.4.1. Limitations

A number of constraints were faced in generating the data, which are largely a result of the sensitivity of commercial cost data. Ideally direct observation would be made, where disaggregate cost estimations are generated based on each respondents' actual vaccine production scale and scope. However, such an approach may not easily generate a large number of respondents or case studies. Further, given the structural differences in cost accounting methods across companies and countries, cost estimates may not necessarily be comparable across different countries or manufacturers.

In relation to the data sensitivity mentioned above, the cost-analysis mostly relied on information provided by the respondents, which may be subject to selection bias.

Efforts to minimise this risk was made as much as possible, by randomly selecting the respondents, yet the options were limited to those attending the DCVMN meeting where the data collection process was conducted. In order to maximise the opportunity of attracting respondents, the questionnaire was designed to be as easy as possible for respondents to answer, therefore multiple-choice answers were provided, where possible. The figures in the multiple-choice however were based on existing literature and industrial practice of vaccine cost estimations (Friede, 2013; Mahoney, 1990; Mahoney et al., 2012) and were consulted to eight vaccine experts (Table 3.1).

Another potential selection bias may arise from the small number of experts interviewed in the questionnaire. Though the number may be limited, these experts however were all well experienced vaccine experts with long standing international exposure, with many years of experience working with vaccine manufacturers, including those in developing countries. Their judgement and feedback therefore, can be assumed to be fair and representative of the practical knowledge regarding developing country vaccine manufacturers.

Further, some improvements can be made to the questionnaire. Among the questions posed to respondents, two questions were noted as ambiguous. These are: question 4, which asks about the cost of brownfield production for an additional one vaccine that is produced once a five vaccine production is running; and question seven which asks for information on the R&D costs of five vaccines. Though Scenario D is presented in the results, a comparison could have been made if Scenario D had the same production scale and scope to the baseline greenfield scenarios (Scenarios A, B or C).

Finally, though economies of scale is generally calculated by analysing the change in average costs-per-dose, the dataset does not support the identification of the point at which scale efficiency is likely to be achieved. Comparing marginal costs for different output levels with average cost estimates from the same data set would have allowed the diagnosis of economies or diseconomies of scale.

3.4.2. Conclusions

At an annual production of 20 million doses of one vaccine, increasing the scale and scope of production will result in a lower cost-per-dose. Cost-per-dose, though mainly driven by fixed costs, becomes driven by variable costs at production scales over 20 million doses. This is an advance on the current literature because other vaccine cost studies have focused mainly on the contributions of fixed costs. Under the three hypothetical scenarios used to analyse and compare respondents, costs-per-dose of vaccines produced by developing countries were on average 47% lower than vaccine prices in developing country markets and 84% lower than prices in industrialized country markets. In developing country markets, local producers would gain most producer surplus in bacterial, and conjugate technology type vaccines and in pre-filled syringe formulations. With regards to industrialised country markets, these manufacturers have the potential to gain higher producer surplus when producing conjugate and novel technology vaccines as well as in multi-dose single-dose vaccine formulations. For local vaccine producers to access industrialised country markets however, they must consider changes to their current portfolio and production processes, including additional public health needs to cater for, and required upgrades to their existing manufacturing processes, to comply with regulatory requirements in industrialised countries.

In conclusion, local producers can produce vaccines that are economically viable in both developing country and industrialised country markets and also gain producer surpluses in these markets, when production is made at a scale that is over 20 million annual doses. For this, manufacturers should ideally have facilities that produce multiple vaccines.

3.5. Appendices

Appendix 3.1 Questionnaire on the cost structure of vaccine production in developing countries

CONFIDENTIAL

World Health Organization

WHO Project to determine economic feasibility of new vaccine manufacturing facilities

Questionnaire for Emerging Market Manufacturers

Introduction

The landscape of the vaccines market has dramatically evolved over the past 20 years. The vaccines industry has tripled in value over the last decade, with more than 120 new products in the development pipeline with 60 of these of importance for developing countries. Vaccines are now considered to be an engine for the pharmaceutical industry, with the prospect of new business models expected to emerge. Emerging manufacturers are now venturing from its national markets into the global market, making up half of UNICEF and WHO's global procurement volumes and 30% of value. The literature however is lacking a reliable assessment of what the **costs of making a vaccine are and therefore the economic benefit or risk to a country intending to make its own vaccines**. Any decision to establish vaccine manufacturing should be based on economic viability, however data on which to evaluate such business models is lacking. We hope therefore through this study to generate such data.

Project Purpose. The purpose of this study is to conduct an analysis of the **cost of vaccine manufacturing**. We would like to understand the costs required in producing and ensuring the supply of these vaccines. Ideally we would like to separate between fixed costs (costs that do not increase with number of doses produced) and variable costs (costs that are directly related to number of doses produced).
In order to increase our understanding, we'd like to ask you to fill in the interview questionnaire hereunder. The results of this study will be used to guide public health advocates in supporting developing countries to increase access to new and underused vaccines, particularly those in middle income countries.

Data Confidentiality. All information included in study output and findings will be aggregated with data from other companies such that individual manufacturers cannot be directly or indirectly identified. All information you provide to us will be held under strict confidentiality. The team accessing company-specific data is limited to these individuals: Liza Munira (intern at WHO, PhD student at the Australian National University), Jan Hendriks (WHO), Martin Friede (WHO). None of the individuals have any interests in the companies being interviewed. If you have specific questions about how the information you provide will be used, we would be happy to discuss them in any further correspondence.

Thank you in advance for your cooperation.

For further information, please contact:

Liza Munira <muniras@who.int>
Jan Hendriks <hendriksj@who.int>

Technology Transfer Initiative (TTi)
Public Health Innovation and Intellectual Property (PHI)
Department of Essential Medicines and Health Products (EMP)
World Health Organization
Avenue Appia 20, 1211 Geneva, Switzerland

Position:	☐ CEO, Executive VP ☐ Director, __________	☐ CFO ☐ VP, _________	☐ Other: _________

Questions 1 – 7 relate to API (Active Pharmaceutical Ingredients), i.e: local antigen production

1. **How much do you need to build a completely new vaccine manufacturing facility – for <u>20 million doses</u> of 1 vaccine* (building, equipment, QC labs, utilities, administration and offices)**

   ☐ US$ 10 – 30 M ☐ US$ 30 – 50 M ☐ Around US$ 60 M ☐ US$ 60 – 100 M ☐ US$ 100 – 200 M

   Other (please specify): __________________

   ** assume any EPI vaccine (eg: HiB, HepB, Rota, etc)*

2. **If this facility was built to produce 5 different vaccines* at a production capacity of <u>20 million doses/year</u>, the cost would be:**

   ☐ US$ 10 – 80 M ☐ US$ 80 – 120 M ☐ US$ 120 - 160 M ☐ US$ 160 – 250 M ☐ US$ 250 – 500 M

   Other (please specify): __________________

   Comments: __________________

   ** please indicate whether it is bacterial or viral.*

3. **If this facility was built to make <u>not 20 million, but 100 million doses</u>, the cost would be:**

   ☐ US$ 10 – 80 M ☐ US$ 80 – 120 M ☐ US$ 120 - 160 M ☐ US$ 160 – 250 M ☐ US$ 250 – 500 M

   Other (please specify): __________________

4. **Once such a facility (5 vaccines) is up and running – how much does it cost to add a new building and equipment for 1 vaccine:**

   ☐ US$ 5 – 10 M ☐ US$ 10 – 30 M ☐ US$ 30 - 50 M ☐ US$ 50 – 80 M ☐ US$ 80 – 100 M

   Other (please specify): __________________

   Comments: __________________

R&D Costs (if applicable)

5. **The R&D cost of bringing a product to market, which includes all staff costs, pre-clinical + Phase I, II, III + material, supply, etc. for <u>only 1 vaccine</u> would be:**

   ☐ US$ 5 – 10 M ☐ US$ 10 – 20 M ☐ US$ 20 - 40 M ☐ US$ 40 – 80 M ☐ US$ 80 – 150 M

   Other (please specify): __________________

   **assume it is a 'generic' version of an existing EPI vaccine for which Ph III efficacy studies are required (eg: Rota, Pneumo, HPV, etc)*

   ***assume development in-house, no tech transfer*

6. **The average failure/success rate (please specify) of such a development would be:**

   ☐ 50 – 60% ☐ 60 – 80% ☐ 80 – 95% ☐ 95 – 100%

   Other (please specify): __________________

7. The above R&D costs in question 5 is for 1 vaccine. How does the cost compare if you have 5 vaccines:

☐ Much less (< 50%) ☐ A bit less (< 25%) ☐ Same ☐ A bit more (>20%) ☐ Much more (> 40%)

Other (please specify):__________________

8. The cost of goods of manufacturing per bulk-dose released (Only: running costs, i.e.: labour, materials, running and maintenance; with no account of R&D, building or equipment)

Please fill in according to your experience (as applicable):

	Capacity of Facility			*Comments/Observations*
	1 M doses/year	20 M doses/year	100 M doses/year	
Influenza				
DTP				
HepB				
Polysacharide-conjugated Hib				
A live viral vaccine (eg. Measles/rota)				
Other:				

9. The cost of filling*:

	Capacity of Facility			*Comments/Observations*
	1 M doses/year	20 M doses/year	100 M doses/year	
1 dose vial				
10 dose vial				
Pre-filled syringes				
1 dose lyophilized				

**vial (syringes), stopper, label, QC, release*

The following question is about fill – finish

10. What is the economic benefit of procuring antigens and filling it compared to procuring finished vaccines (please tick ☑ in the following table as applicable):

e.g: if procuring finished vaccine costs $10 for a vial but fill-finish vaccine costs $4 ($3 for bulk purchase + $1 for filling) the benefit would be 60%

Traditional Vaccine	Procurement of 1 – 5 M doses/year (e.g.: DTP 10 dose vial)	☐ 0 – 20%	☐ 20 – 40%	☐ 40 – 60%
	Procurement of 10 – 20 M doses/year (e.g.: DTP 10 dose vial)	☐ 0 – 20%	☐ 20 – 40%	☐ 40 – 60%
New Vaccines	Procurement of 1 – 5 M doses/year (e.g.: PCV 1 dose vial)	☐ 0 – 20%	☐ 20 – 40%	☐ 40 – 60%
	Procurement of 10 – 20 M doses/year (e.g.: PCV 1 dose vial)	☐ 0 – 20%	☐ 20 – 40%	☐ 40 – 60%

General Questions about your company/institute

11. Have you ever applied for WHO – prequalification : ☐ Yes ☐ No

12. Have you ever received prequalification status for your products : ☐ Yes ☐ No

13. Will you apply for prequalification in the next 5 years? : ☐ Yes ☐ No

14. Quantitative information

Number of vaccines (API produced in house) : ☐ 1 ☐ 2 – 5 ☐ > 5

Number of fill – finish : ☐ 1 ☐ 2 – 5 ☐ > 5

Number of vaccines in 5 years (API) : ☐ 1 ☐ 2 – 5 ☐ > 5

Number of fill – finish in 5 years (API) : ☐ 1 ☐ 2 – 5 ☐ > 5

15. Total number of doses/year – all vaccines :

☐ < 1M ☐ 1 – 5 M ☐ 5 – 20 M ☐ 20 -100 M ☐ > 100 M

a. Domestic market (%) : ______________

b. Export market (%) : ______________

Thank you.

Chapter 4 A multilevel modelling analysis of viability factors for vaccine production in developing countries

4.1. Introduction

Vaccinations and immunisation programs are known for being highly cost-effective public health interventions, with the need to maintain and secure the global supply of vaccines being high on the public health agenda. However, technological developments and changes in standards have constantly posed challenges to vaccine manufacturers globally (Danzon & Pereira, 2011), making it necessary for manufacturers to find ways to cope with these changes and remain viable. The term viability, commonly used in the financial or corporate sector, is indicative rather than specific. Viability is best described as survivability, or the ability of an entity to perform its objective/task. Commercial viability can be defined as a company's ability to generate sufficient income for its operations and to cope with changes in the long run, and is closely linked to financial performance and position (ATO, 2013). Viability was introduced into the local vaccine production context by a series of studies based on country assessments conducted by the CVI in the early 1990s.

Within a similar context, that is for pharmaceutical companies, a commissioned study by the British Government's Department for International Development (DFID) states that financial viability of pharmaceutical companies is dependent on percent market share and prices of raw materials (Guimier, Lee, & Grupper, 2004). In a more general context, Buzzell, Gale, and Sultan (1975) studied 57 companies and suggested that there is a close link between percent market share and returns on investment, identifying percent market share as the main determinant of business profitability.

The global vaccines market has dramatically evolved over the past 30 years. The vaccines industry has often been considered the 'poor cousin' of the pharmaceutical industry with only 2-3% market share of the whole pharmaceutical industry. However, this share has tripled in value over the last decade, from US$5 billion in 2000 to almost US$24 billion in 2013, with even higher numbers projected in the next 10 years (Kaddar, 2013). Further, there are over 120 new products in the vaccine development pipeline, and half of these are important to the developing world. Vaccines are now considered to be an engine for the pharmaceutical industry, with an anticipation of new business models expected to emerge (Kaddar, 2013).

An industry report on the global vaccine market outlook (Research & Markets, 2014) compared the pharmaceutical industry (excluding vaccines) and the vaccines industry and suggested that pharmaceuticals are facing declining prospects due to lower rates of research and productivity, whereas vaccines have been highly profitable as a result of advances in genomics and manufacturing technologies and from the increasing demand in emerging economies.

Emerging manufacturers that mainly originated as an arm of Pasteur institutes in their respective developing countries, and are known to be the main suppliers of traditional vaccines, are now transitioning from being 'suppliers of local markets' to 'suppliers of global markets' (Jadhav, Datla, Kreeftenberg, & Hendriks, 2008). Figure 4.1 shows the proportion of vaccine doses supplied by both industrialised and developing countries, and indicates that in the last few decades a growing proportion of the global vaccine market represented by UNICEF and PAHO has been sourced from emerging manufacturers. Figures 4.2 and 4.3 which illustrate the proportion of vaccines supplied by manufacturing country type, show that emerging country manufacturers make up nearly two-thirds of UNICEF and PAHO procurement volumes in 2014 and about 40% of its total value.

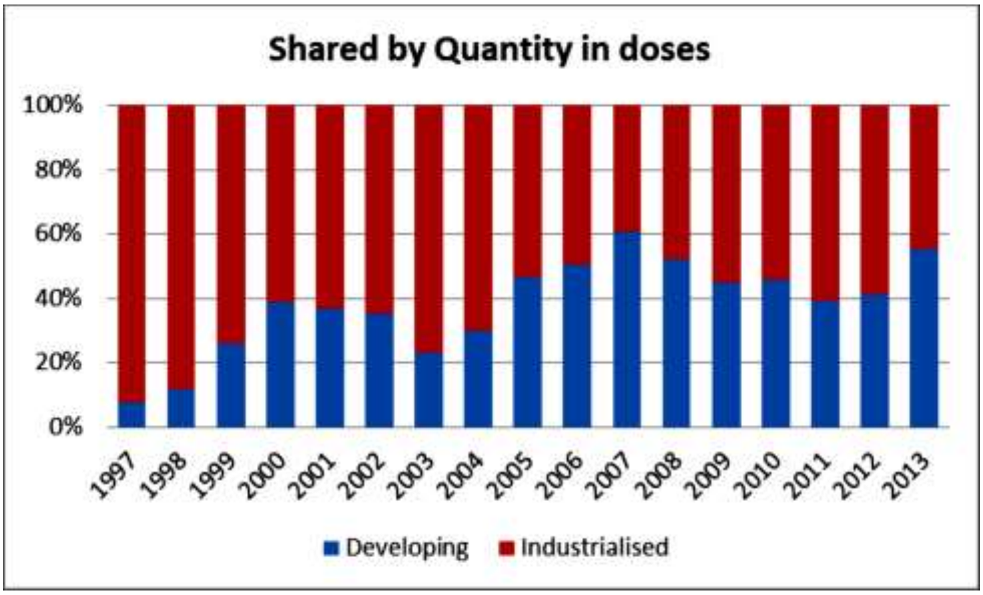

Figure 4.1 Quantity share of UNICEF vaccine supply by manufacturing country type. Reproduced from UNICEF (2014).

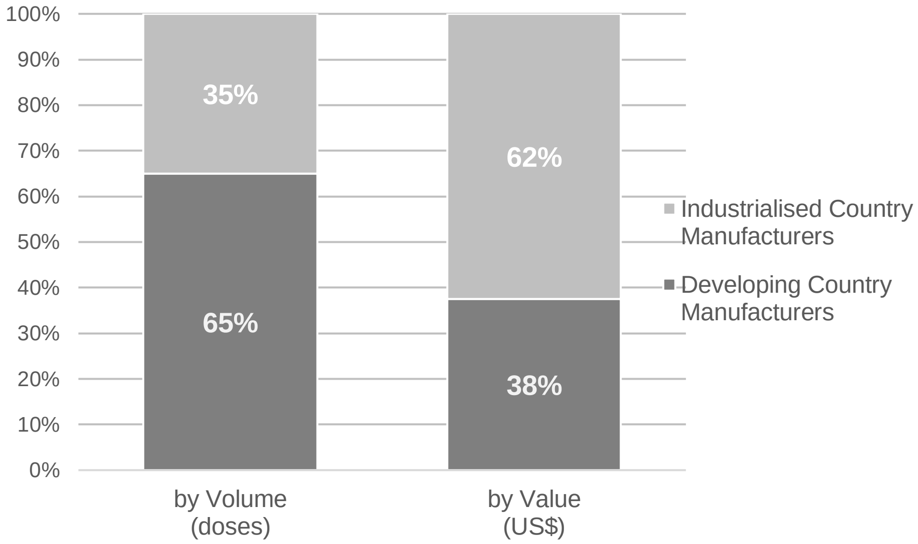

Figure 4.2. Source of vaccines supplied to UNICEF & PAHO (2014). Calculated based on country reporting to WHO/UNICEF's Joint Reporting Form.

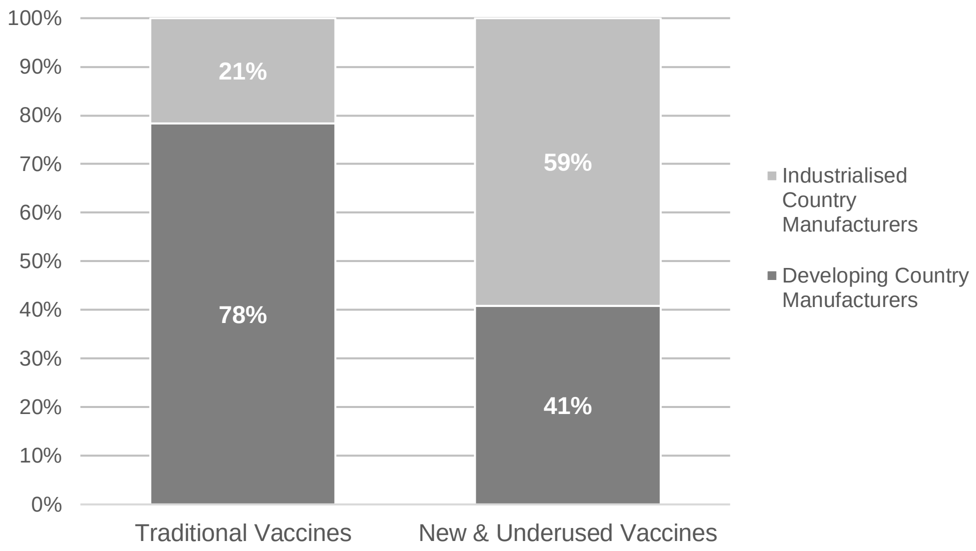

Figure 4.3. Volume of vaccines supplied to UNICEF & PAHO by vaccine and manufacturing country type (2014). Calculated based on country reporting to WHO/UNICEF's Joint Reporting Form

The majority of the human population and disease burden can be found in developing countries, and 16 of the 33 countries worldwide that manufacture vaccines are developing countries (Figure 4.4). However, the greatest share of vaccine manufacturing revenue is generated by multinational companies in industrialised country markets (Kaddar, 2013; WHO, UNICEF, & World Bank, 2009). This poses considerable challenges for vaccine producers in developing countries to remain viable.

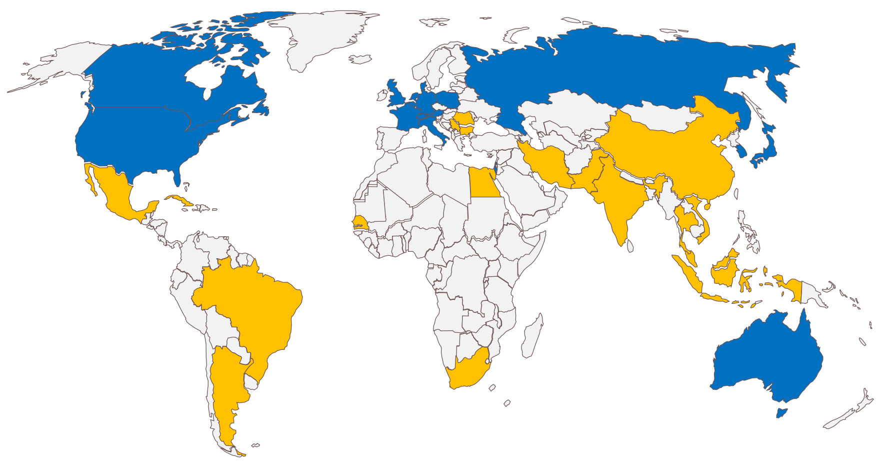

Figure 4.4 Vaccine production worldwide (2013). Note: Vaccine production as reported by WHO member countries and defined by Douglas and Samant (2013). All vaccine producing countries in colour. Vaccine production in low and middle income countries in yellow (16 countries: Argentina, Brazil, Bulgaria, China, Cuba, Egypt, India, Indonesia, Iran, Mexico, Pakistan, Senegal Serbia, Thailand, Tunisia, Vietnam).

Industrial organization theories state that the decision to locally produce is generally taken when the price of purchasing a good is higher than the cost to manufacture it or when one is not able to rely on existing suppliers (Belleflamme & Peitz, 2010). However, this decision assumes that local producers possess the required skills and infrastructure to meet their needs and standards. Many developing country authorities consider local vaccine production as a panacea that will enable vaccine self-sufficiency, and provide a foundation to develop and further advance their national science and research base (Milstien et al., 1997).

A limited number of studies have reviewed the viability of vaccine production. These include studies conducted by the UN agency for Industrial Development (UNIDO), which assessed the cost and benefit of local manufacturing of vaccines (UNIDO, 1986), as well as a more recent study by the WHO (WHO, 2011a). Some of these studies have also identified determinant factors, such as Rautiainen (2001), who identified several internal and external factors[46] that are critical in determining success of the biopharmaceutical industry. Internal factors included human resources, products, networking and company climate, whereas external factors included agglomeration of firms[47] infrastructure and national polices. A series of country assessments conducted by WHO in 1992 as part of a Task Force on Situation Analysis of the Children's Vaccine Initiative reported that the quality, cost and reliability of vaccine producers, which at the time existed in over 55 countries, ranged from the very good to very poor (Milstien, 1999) (Milstien et al., 1997). Seven critical elements were identified by these authors as viable characteristics of successful vaccine producers: economies of scale[48], consistency of production, access to new technologies, historical performance to meet demand and scale up production, credibility of quality, management structure and legal

[46] Rautiainen (2001) suggests that internal factors are those affected by the company itself; while external factors are defined as those not influenced by company activities and often depend on the company's location.
[47] Geographic concentration of interconnected firms
[48] In this chapter, this element is further divided into economies of scale and economies of scope.

status. These seven elements were used as the basis for evaluation of DCVM viability in this Chapter.

This chapter aims to identify and quantify the effect of factors determining the viability of production by DCVMs. This chapter does not aim to grade the viability of individual producers or vaccines. Five outcomes were investigated that included revenue sizes and percent market shares for global markets, and specifically for domestic and export markets given the trend of DCVMs expanding into vaccine export markets. These outcomes were used as proxies for viability. The goal was to provide evidence for developing countries and public health advocates to develop policies and strategies that can further ensure the quality and supply of global vaccines.

This chapter is organised as follows: the description of the variables used in the analysis and the econometric methods are presented in section 4.2. Section 4.3 presents the results of the regression model of determinants of vaccine producer viability in developing countries, followed by a discussion, summary, study limitations and conclusions in section 4.3.

4.2. Methods

4.2.1. Data management and inclusion and exclusion criteria

The data for the variables used in this chapter were collected from various sources, including the WHO, World Bank and the Vaccine Information Management System (VIMS) database from John Hopkins Bloomberg School of Public Health.

A dataset was compiled with identifiers for country, vaccine type, and year. The compilation used the Joint Reporting Form (JRF) data as an anchor, where each manufacturer’s vaccine sales were listed by procuring country. Once relevant indicators were joined to the matching procuring and producing country, the data were collapsed by manufacturer, vaccine product and year. Some indicators were created to allow for specific calculations, such as an identifier of transaction frequency per manufacturer vaccine product and how many of these procurements were conducted through bulk-procurement mechanisms. The total number of vaccine doses procured globally was identified for each vaccine type, and was used to calculate each vaccine manufacturer's revenue size and percent market share.

Inclusion and exclusion criteria were adopted in selecting observations for the regression. The inclusion criteria were vaccine doses procured from local vaccine manufacturers owned by developing countries[49]. Production by industrialised country manufacturers acquired by a developing country[50] were also included in the analysis. The exclusion criteria were vaccines that did not have corresponding vaccine price information from the Vaccine Product, Price and Procurement (V3P) database. This resulted in exclusion of five data points of a total 323 observations. For data where procurement was reported as being from multiple sources, volumes procured were divided equally amongst the reported manufacturers. This was to avoid selection bias from excluding data on potential competition in domestic vaccine sources. Developing country manufacturers identified as subsidiaries of multinational companies were considered as multinational manufacturers in this analysis and were excluded. Production under joint ventures between local producers and foreign or multinational companies was not excluded.

The analysis focused on five aspects of viability: revenue sizes from global, domestic and export markets (the latter two being subsets of the former), along with percent market shares for global and export markets. Percent market share for domestic markets was not included in the analysis, because the percent market shares found in

[49] Developing countries based on classification by the World Bank. For countries where over the three years of observation have experienced changes in their country classification, only the vaccines produced during the years in which they are classified as either low and or middle income countries are included.
[50] This includes Bilthoven, a Netherlands vaccine manufacturer, acquired by Serum Institute of India in 2012

the domestic markets were consistently above 95% (shown in Table 4.5.). Data on revenue sizes and percent market shares used in this chapter were calculated based on data from the JRF database and V3P database. The data were based on sales of DCVM vaccine products to immunisation programs globally between 2012 – 2014.

The JRF is a key tool and includes the most comprehensive data for immunisation that WHO member countries complete on an annual basis. The JRF mechanism has collected data from WHO member countries on its immunization financing indicators since 1998, to measure health system performances and trends. The indicators collected through the JRF tries to capture the expenditure on routine immunization programs, vaccine procurement, and government financing and planning for procurement of vaccines and injection supplies.

The data on percent market share were calculated by dividing the revenue of each vaccine sold by manufacturers by the total revenue for each respective vaccine. The revenue was calculated by multiplying the number of doses of each vaccine sold by manufacturers, by its estimated vaccine price. The vaccine prices were estimated based on data from WHO's V3P database. The vaccine price reference used from the V3P database used a weighted average price that was summarised by vaccine type, procurement method and income level of procuring country. The official UNICEF/PAHO price list could not be used as reference, because the V3P database shows that vaccine prices procured through UNICEF and PAHO tend to differ in its transactions.

Markets shares were determined in two ways: 1) for global market shares, the denominator was the total revenue of the respective vaccine's sales globally, 2) for export markets, the denominator was the total vaccine export revenue. Global market share indicates a product's profitability, while export market share measures the degree of importance of a country within the total export market. A country may lose export market share not only from declining exports but also if its exports are not growing at the same rate as world exports, causing its relative position at the global level to deteriorate (Eurostat, 2013).

In estimating revenue sizes and percent market shares, the dataset was structured by vaccine type, manufacturer and originating country. Though most of the data collected through the JRF questionnaire were available on the WHO and UNICEF websites, specific information on vaccine procurement and its sources were not available to the public. For the purpose of this chapter, data on vaccine source were obtained for the years 2012, 2013 and 2014.

Three sensitivity analyses were performed: the first one excluded vaccine procurement data that were reported as having multiple producers; the second sensitivity analysis categorised the vaccine technology types by two groups: traditional and modern (binary: 0, 1) instead of the original four groups: pre-GAVI, Phase I, Phase II and Phase III GAVI vaccines (category: 0,1,2,3); while the third sensitivity analysis was for each vaccines' target market, where instead of using the number of doses administered, the immunization programs' target doses were used instead.

4.2.2. Explanatory variables

There were seven characteristics of viable producers identified by Milstien et al. (1997). This chapter uses these characteristics to define domains for the explanatory variables, as follows:

1. Economies of scale and scope
    a. Birth cohort/surviving infants

       In the case of national immunisation programs, which mainly target children, the number of surviving infants, referred to as birth cohort, drives the number of vaccines needed by countries. A larger birth cohort size would work positively for vaccine sales in two ways. First is that if a captive market is possible, then the larger the birth cohort, the larger the number of potential sales. Secondly, a larger domestic sales base would assist manufacturers to establish sustainability in the lead up to accessing the global market. This will be identified as economies of scale. The number of surviving infants (per 1000 live births) was calculated as follows:

$$\boldsymbol{SInf_{i,t}} = \boldsymbol{Pop_{i,t}} * \boldsymbol{CBR_{i,t}} * (\mathbf{1} - \boldsymbol{IMR_{i,t}}) \qquad \textbf{Equation 4.1}$$

Where:

$SInf_{i,t}$: Number of surviving infants

$Pop_{i,t}$: Total population

$CBR_{i,t}$: Crude birth rates

$IMR_{i,t}$: Infant mortality rates

b. Number of vaccine products produced by a single manufacturer (nominal).

This variable identifies the number of different vaccine products that the manufacturer produces. The data were obtained from the DCVMN Directory (2014) and each of the manufacturers' company websites. Different vaccines are identified by antigens and technology used. For the purpose of this research, similar vaccines with different presentation types were not considered to be different products. This variable will be able to address the question of whether a larger portfolio dictates a larger revenue. Though Milstien et al. (1997) identified this variable as economies of scale, this chapter will further specify this variable as economies of scope, where multiple products may lower costs-per-dose from a number of shared costs and not necessarily by the scale of production.

2. Consistency of Production/Annual capital expenditure

c. Consistent number of doses per year.

Milstien et al. (1997) highlighted the importance of having consistent and reliable supply of vaccines. The indicators used in their study were production-process specific, such as number of failed lots, consistency of lots and doses per lot per year. Given the unavailability of such data for this thesis, this chapter instead measures the consistency of production by measuring the number of years that each vaccine was sold within the three years. Vaccines with sales missing in 2012 or 2013 were further assessed as to whether they were in fact new products launched in either 2013 or 2014. For such newly launched products, the codes were adjusted to identify as 'consistent production'.

3. New technology

    d. Vaccine technology type produced.

    This variable captures the manufacturer's ability to access new technology. Vaccines were categorised by traditional and modern vaccines based on WHO and GAVI's classification of vaccine priorities and market-shaping strategies for developing countries[51]. The first category, traditional vaccines, are those introduced through the initial EPI program, prior to GAVI's establishment. These vaccines include diphtheria, tetanus, wholecellular pertussis (wP), rabies, influenza, smallpox, measles, OPV and BCG vaccines. The next categories are for modern vaccines, also known as new and underused vaccines (NUVs). These modern vaccines are further divided by GAVI's phases of support to developing countries. The second category, which was based on GAVI's Phase I, included vaccines for hepatitis B, acellular pertussis (aP), yellow fever, haemophilus type B (Hib) and pentavalent vaccine. The third category based on GAVI's Phase II included HPV, rotavirus, and pneumococcal vaccines. The fourth category based on GAVI's Phase III included meningitis A, measles rubella (MR), IPV, cholera and Japanese encephalitis vaccines. Influenza vaccines however were reclassified into category 3 because the technology transfer to DCMs was only facilitated in 2007. The categorical variable was structured as follows: 0 for pre-GAVI vaccines, 1 for Phase I vaccines, 2 for

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[51] Phase I (2000-06), Phase II (2007-10), Phase III (2011-15) and Phase IV (2016-20), please refer to: http://www.gavi.org/about/strategy/

Phase II vaccines and 3 for Phase III vaccines. Though GAVI has a Phase IV, there weren't any vaccines in the dataset that were part of Phase IV. The order of these categories indicates access to more advanced technology.

Whilst it has been suggested that vaccines are categorised by year of development (Plotkin et al., 2013), vaccine technologies accessible to developing countries are not necessarily chronologically ordered with the time in which they were developed. Developing countries often lag far behind the curve of vaccine adoption in developed country markets (Vandersmissen, 2001). Figure 4.3 shows that traditional EPI vaccines were supplied mainly by DCVMs (78%), but a much smaller proportion of the NUVI vaccines supply was from DCVMs (41%).

4. Historical performance/quality

   e. Supply sufficiency for global demand. (%)

   Vaccine sufficiency is defined as the ability to provide a sustainable supply of high-quality vaccines to meet demand. (Towse, Keuffel, Kettler, & Ridley, 2012) suggested that sufficient demand determines whether or not a vaccine is deemed viable. In this chapter supply sufficiency was derived in two steps. First was the identification of the target market (defined below), and secondly by whether vaccine sales fulfilled the total need of immunisation programs (classified as a binary variable, 1 = fulfilled and 0 = did not fulfil the total need).

In their paper, Milstien et al. (1997) analysed supply sufficiency from a national perspective, however this chapter takes the perspective of sufficiency in meeting global demand. Sufficient supply for global demand is measured by comparing the number of vaccine doses sold relative to the targeted market. This was done by measuring the targeted market of each vaccine, obtained by multiplying the program cohort size[52] in

[52] Program cohort size refers to the number of people receiving the vaccine. In cases where the immunisation program coverage is lower than the total number of people within the target coverage, the program cohort size will reflect those receiving the vaccine only, as reported by countries to WHO.

each procuring country by the number of doses required in each country's immunisation schedule. The total number of doses sold for each vaccine was measured as a proportion of this targeted market. Not only was this variable indicative of the sufficiency of supply, it may also have provided an indication of each manufactures' percent market share for the vaccines it produced.

Some vaccines are known to have significantly high wastage rates and so some vaccines are procured in much larger doses than required by the birth cohort size. These were subsequently reclassified to reflect a 100 percent sufficiency.

Vaccine target market

The size of the target market is a measure of the potential market for a given vaccine. Most vaccines in the dataset were paediatric vaccines procured for national immunisation programmes. Two factors are known to determine the potential size of the paediatric vaccines market, these are: annual birth cohort and the number of vaccines administered to a child (Institute of Medicine, 1993). Though the Institute of Medicine (1993) defined the annual birth cohort by live births per year, this definition was refined in the current chapter to be numbers of surviving infants, who are the members of the birth cohort specifically receiving the vaccine. Surviving infants are used as indicators in the WHO – UNICEF Joint Reporting form for the target group receiving early-life vaccines such as BCG or first dose of DPT vaccine. This chapter calculated the market for each vaccine as the product of the total number of surviving infants and the number of doses required in the procuring countries' immunisation schedule. This can be observed in Equation 4.2 below.

$$\boldsymbol{vxmarket_{i,t} = sinfant_{i,t} * dosefreq_{i,t}} \qquad \textbf{Equation 4.2}$$

Where:

$vxmarket$: potential market for $obs_{i,t}$

$sinfant_{i,t}$: number of surviving infants in vaccine manufacturer's country

$dosefreq_{i,t}$: number of vaccine doses required for $ob_{i,t}$ in procuring country

$obs_{i,t}$: unit of observation, i.e. the vaccine product produced by developing country manufacturer

For vaccines that had not been introduced universally in a country's immunisation schedule at the time of the study, either being phased in, targeted for risk groups, or regional areas or where the above calculation was not applicable, the target market was assumed to be based on the number of vaccine doses procured in a given year.

Two versions of this variable were calculated, the first using target doses and the second using doses administered. The latter takes into consideration countries where immunisation coverages were low for certain vaccines.

5. Credibility of quality/ regulatory infrastructure

   f. Fully functional National Regulatory Authority (NRA) (binary: 0, 1).

   To ensure the quality of vaccines procured through UN agencies on behalf of member countries, WHO established six main functions for which national regulatory authorities are assessed. Producing countries must fulfil all six of these functions to be allowed to export vaccines to other countries, while procuring countries must fulfil a minimum of four functions (Table 4.1**).**

Table 4.1. NRA functions depending on source of vaccines

Vaccine-specific NRA functions needed	Areas of activity by NRA (or WHO) depending on source of vaccines		
	Vaccine procured by United Nations agency	Vaccine procured by NRA	Vaccine manufactured in country
FUNCTION 1 Marketing authorization and licensing activities	✓	✓	✓
FUNCTION 2 AEFI surveillance	✓	✓	✓

<table>
<tr><th rowspan="2">Vaccine-specific NRA functions needed</th><th colspan="3">Areas of activity by NRA (or WHO) depending on source of vaccines</th></tr>
<tr><th>Vaccine procured by United Nations agency</th><th>Vaccine procured by NRA</th><th>Vaccine manufactured in country</th></tr>
<tr><td>FUNCTION 3
NRA lot release</td><td rowspan="4">NRA functions undertaken by WHO on behalf of United Nations agencies or producing countries.</td><td>✓</td><td>✓</td></tr>
<tr><td>FUNCTION 4
Laboratory access</td><td>✓</td><td>✓</td></tr>
<tr><td>FUNCTION 5
Regulatory inspections</td><td rowspan="2">NRA functions undertaken by producing country.</td><td>✓</td></tr>
<tr><td>FUNCTION 6
Oversight of clinical trials</td><td>✓</td></tr>
</table>

Source: http://vaccine-safety-training.org/functions-depending-on-the-source-of-vaccines.html

g. Prequalified vaccine (binary: 0, 1)

The prequalification process for vaccines is an established procedure that WHO conducts as a service to UN procuring agencies such as UNICEF. Prequalification determines that the vaccines procured by UNICEF and GAVI on behalf of countries meet certain standards required. Information regarding each vaccine's prequalification status in each period was requested through WHO for the corresponding years.

6. Type of ownership

h. Public or private (binary: 0, 1)

This variable classifies each vaccine manufacturer by type of ownership vis-a-vis their management structure, whether it is publicly or privately owned. Public manufacturers are associated with management structures that are not as flexible as those in the private sector, particularly in regards to hire and fire-ability of staff, an important element that helps companies maintain efficiency (CVI & WHO, 1999; Mahoney & Maynard, 1999; Milstien et al., 1997). Because the dataset included only three observations that fall under a public-private partnership status, these observations have been reclassified as private, with the assumption that their management structure would be more flexible than a typical public entity.

7. Legal status-autonomy

   i. Political stability/number of Ministers of health in the last five years

   Frequent changes at the health minster level is a potential indicator of health sector stability particularly regarding changes in policies and structures. Instances where ministers stepped down or were replaced and caretakers were appointed, were added to the count because an additional level of change was assumed.

In addition to the characteristics above, this chapter also included additional factors not considered by Milstein and colleagues, which are known to be drivers of vaccine demand. These factors were:

8. Purchasing power (GNI/cap) (US$)

   If the total gross national income represents the size of a country's economy, the GNI per capita provides an indicator of a country's purchasing power. This variable measures the income level of the producing country and investigates how increases in a country' purchasing power would affect its viability in producing vaccines.

9. Proportion of export sales (%)

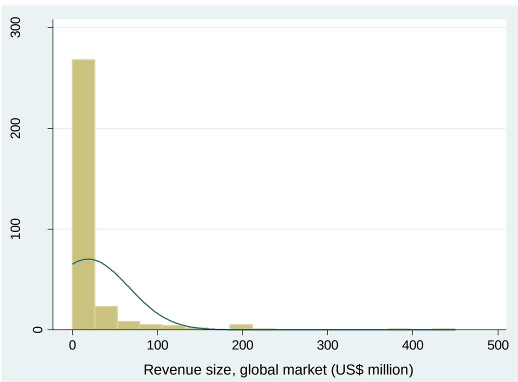
   Most manufacturers differ their vaccine sales destinations, where some have primarily domestic sales, some have a mix of both domestic and export sales, and some have primarily export sales. The proportion of export sales compared to domestic sales will allow a better understanding of the impact on market strategy towards viability factors given the growing tendency of local vaccine producers towards producing for export markets.

4.2.3. Statistical analysis

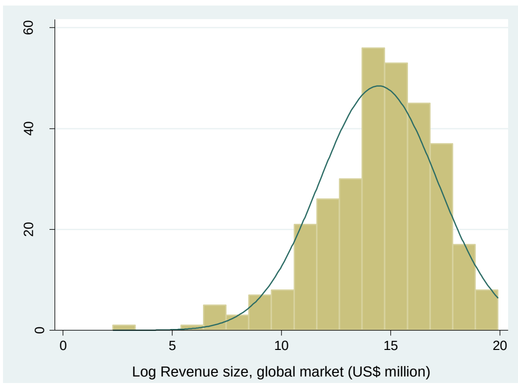
Five outcome variables were identified, and used as proxies of viability. These outcomes were calculated based on sales by vaccine manufacturers to immunisation programs, for each respective vaccine. These outcome variables are:

- Revenue size for global market (Model 1)
- Revenue size for domestic market (Model 2)
- Revenue size for export market (Model 3)
- Percent market share for global market (Model 4)
- Percent market share for export market (Model 5)

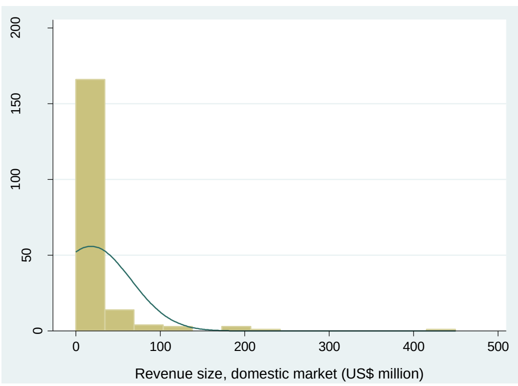
Because the outcome variables were a continuous variables, linear regression was used. All five outcome variables were logarithmically transformed to deal with the skewed data and to ensure that these outcome variables have constant variance, so that the data conformed more closely to a normal distribution (Figure 4.5).



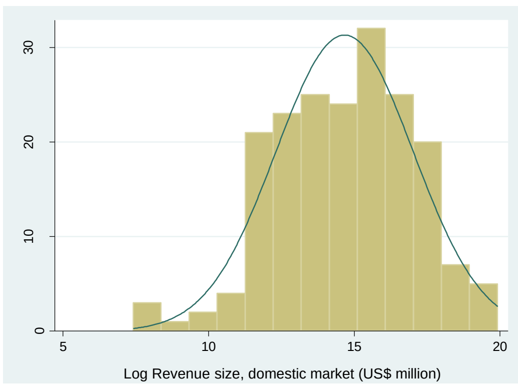
(1a)



(1b)



(2a)



(2b)

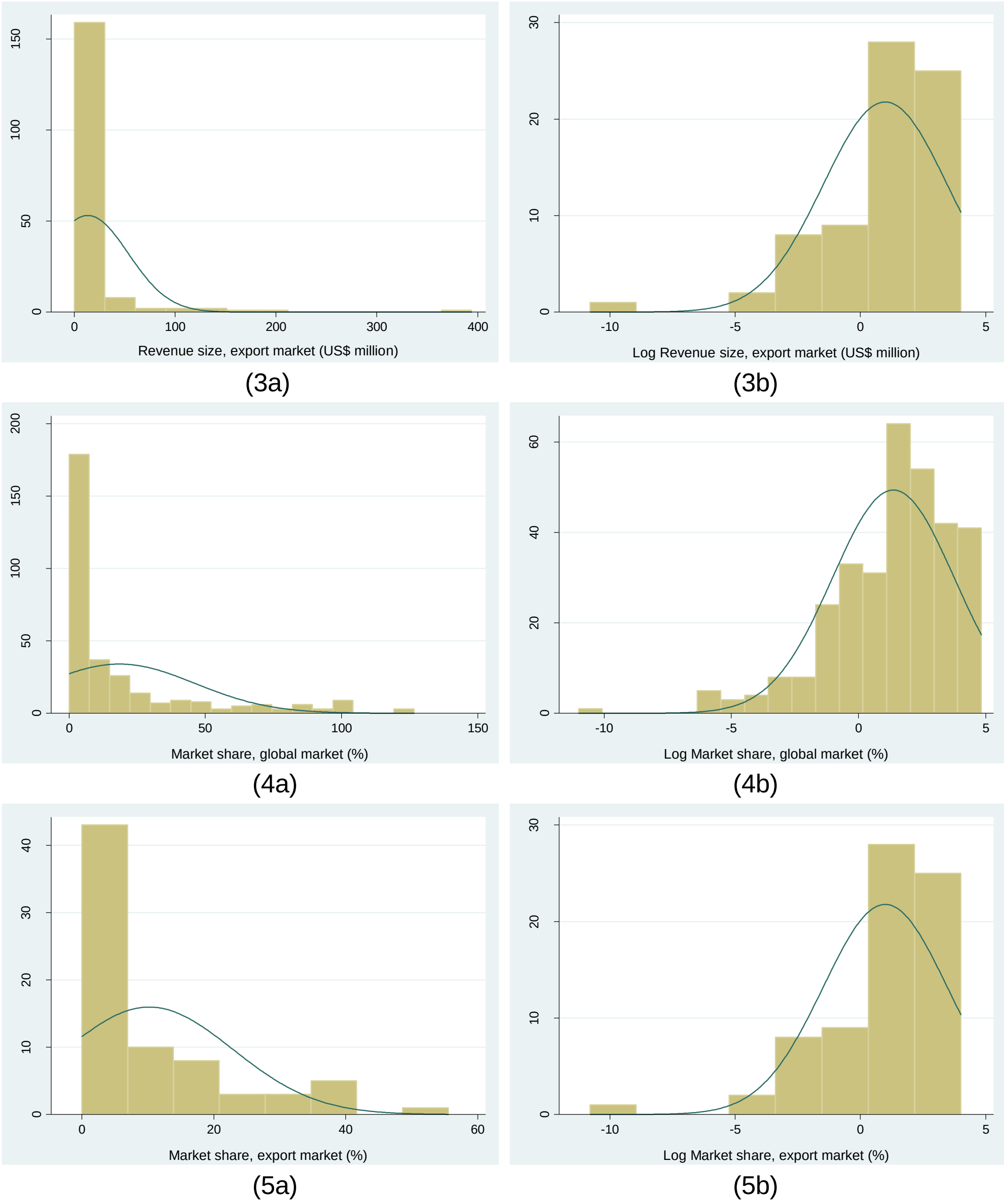


Figure 4.5. Logarithmic transformations of outcome variables for vaccines produced by developing country manufacturers. Note: (1a) revenue size of global market; (1b) revenue size of global market – log transformed; (2a) revenue size of domestic market; (2b) revenue size of domestic market – log transformed; (3a) revenue size of export market; (3b) revenue size of export market – log transformed; (4a) percent market share of global market; (4b) percent market share of global market – log transformed; (5a) percent market share of export market; (5b) percent market share of export market – log transformed

Some explanatory variables varied across different levels (vaccine, manufacturer and country), whilst others varied across both levels and time. Numbers of surviving infants and GNI per capita were log transformed to normalise their skewed distributions (Figure 4.6).

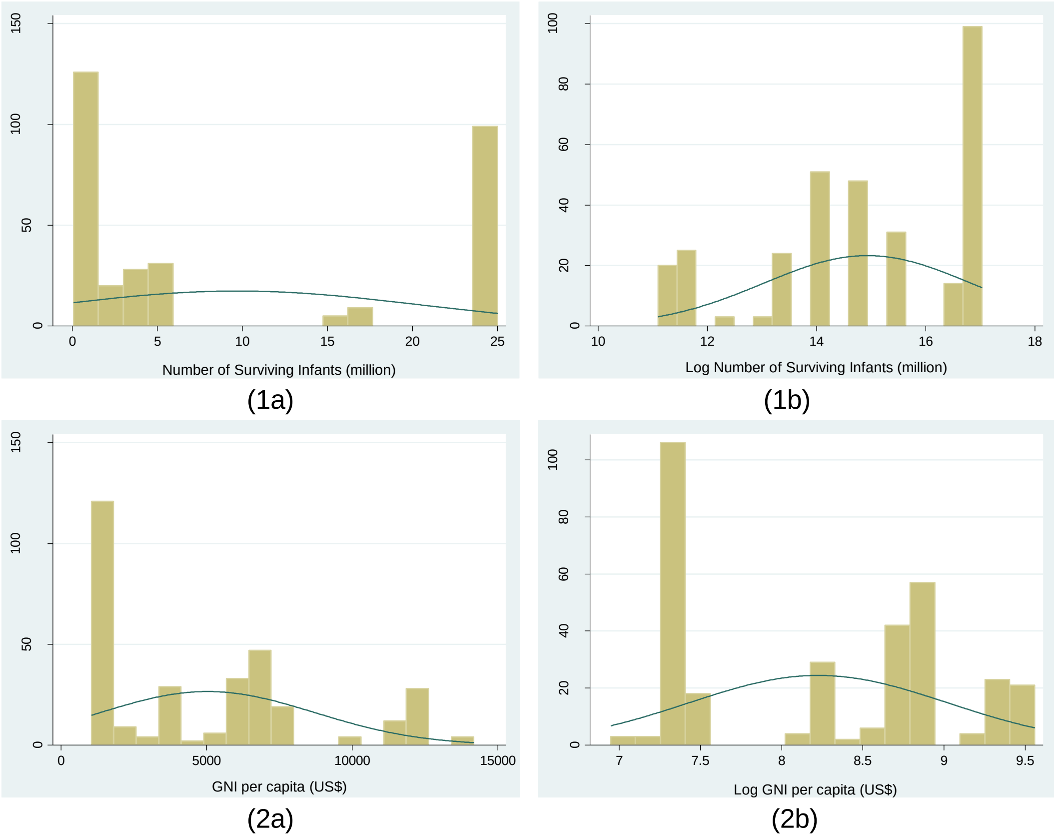


Figure 4.6. Logarithmic transformations of several explanatory variables for vaccines produced by developing country manufacturers. Note: (1a) Surviving infant (million); (1b) Surviving infant – log transformed; (2a) GNI per capita; (2b) GNI per capita – log transformed

Data were imported to STATA 14.0 (Stata Corporation, College Station, Texas) where each observation was linked to its corresponding vaccine type-, manufacturer- and country level explanatory variable. Multicollinearity was investigated using Pearson's correlation coefficients. No pairs of explanatory variables had a Pearson's correlation coefficient >|0.6| (Table 4.2) and therefore no variables were excluded for reasons of multicollinearity. Heteroscedasticity was also tested using Breusch-Pagan / Cook-Weisberg (Table 4.3).

In building the model, a univariable analysis was conducted, where a high significance threshold of P>0.2 was used for subsequent variable selection for multivariable analysis, to avoid potential exclusions of false positives.

Table 4.2. Correlation matrix of explanatory variables associated with revenue sizes and percent market share of vaccines produced by developing country vaccine manufacturers

	Surviving Infants (log)	GNI per capita (log)	Number of vaccines products	Consistent production supply	Vaccine technology	Sufficient supply against demand	NRA	Vaccine PQ status	Manufacture status	Number of MOH, last 5 years	Proportion of export sales
Surviving Infants (log)	1.000										
GNI per capita (log)	- 0.595	1.000									
Number of vaccines products	0.578	- 0.501	1.000								
Consistent production supply	- 0.079	- 0.042	0.082	1.000							
Vaccine technology	0.119	0.078	0.074	- 0.193	1.000						
Sufficient supply against demand	- 0.097	0.213	- 0.098	0.199	0.066	1.000					
NRA	0.362	- 0.008	0.194	0.043	0.176	0.136	1.000				
Vaccine PQ status	0.206	- 0.275	0.379	0.334	- 0.066	- 0.210	0.026	1.000			
Manufacture status	0.565	- 0.522	0.381	- 0.014	0.112	- 0.034	0.196	0.244	1.000		
Number of MOH, last 5 years	- 0.462	0.219	- 0.253	0.056	- 0.257	- 0.039	- 0.336	- 0.011	- 0.210	1.000	
Proportion of export sales	0.278	- 0.349	0.532	0.014	0.041	-0.103	- 0.045	0.322	0.359	-0.066	1.000

Note: None of the correlation estimations exceeded the correlation coefficient threshold of |0.6|, therefore there are no observed multicollinearity in the model

Table 4.3. Breusch-Pagan / Cook-Weisberg test for heteroscedasticity

Ho	*Constant variance*
Variables	logvxrev logsurvinf loggnipercap vxnumb continue vxtech vxsuff vxpq status moh vxtrade
chi2(11)	0.87
Prob > chi2	0.3519

Note: the test statistic has a p-value above 0.05, therefore the null hypothesis of homoscedasticity cannot be rejected.

Multivariable multilevel linear regression models were developed by using a backward stepwise variable selection method, with vaccine type, manufacturer and country level random effects to account for clustering. This was done by using the "stepwise pr(0.2)" command in STATA, where variables were dropped from the models if P>0.2.

Selecting variables for regression analysis involves two contrasting objectives, where the model needs to be as comprehensive and realistic as possible (Darlington, 1968), yet it must include the least numbers of relevant variables (principle of parsimony), because irrelevant variables decrease the precision of the coefficients and predicted values.

Though variables adopted from the paper by Milstien, Batson, and Meaney (1997) provides a general direction as to which explanatory variables should be included into the model, the actual set of explanatory variables used in the regression is determined by the analysis of the data (Conger, 1974). Though multiple variable selection methods exist, the backward stepwise was selected where the model starts with the seven proposed viability characteristic (Milstien et al., 1997), and tests the removal of each variable using a chosen model fit criterion until variables cannot be deleted without a statistically significant loss of fit.

The form of the final models were:

Model 1 (Revenue size for global market):

$$\boldsymbol{Log(LPV_{ijkt}) = \beta_{0jk} + \beta_{1jk}Log(SInf_{kt}) + \beta_2 Log(\frac{GNI}{cap}_{kt}) + \beta_3 VxNumb_{jkt} + \beta_4 Cons_{ijkt} + \beta_5 VxTech_{ijk} + \beta_6 Suff_{ijkt} + \beta_7 Status_{jk} + \beta_8 MOH_{kt} + \beta_9 Trade_{ijkt} + \epsilon_{i,j,k,t}}$$

Equation 4.3

Model 2 (Revenue size for domestic market):

$$\boldsymbol{Log(LPV_{ijkt}) = \beta_{0jk} + \beta_{1jk}Log(SInf_{kt}) + \beta_2 Log(\frac{GNI}{cap}_{kt}) + \beta_3 VxNumb_{jkt} + \beta_4 Cons_{ijkt} + \beta_5 VxTech_{ijk} + \beta_6 Suff_{ijkt} + \beta_7 Status_{jk} + \epsilon_{i,j,k,t}}$$

Equation 4.4

Model 3 (Revenue size for export market):

$$\boldsymbol{Log(LPV_{ijkt}) = \beta_{0jk} + \beta_{1jk}Log(SInf_{kt}) + \beta_2 Log(\frac{GNI}{cap}_{kt}) + \beta_3 Cons_{ijkt} + \beta_4 VxTech_{ijk} + \beta_5 Suff_{ijkt} + \beta_6 VxPQ_{ijkt} + \beta_7 Status_{jk} + \beta_8 MOH_{kt} + \epsilon_{i,j,k,t}}$$

Equation 4.5

Model 4 (Percent market share for global market):

$$\boldsymbol{Log(LPV_{ijkt}) = \beta_{0jk} + \beta_{1jk}Log(SInf_{kt}) + \beta_2 Log(\frac{GNI}{cap}_{kt}) + \beta_3 VxNumb_{jkt} + \beta_4 Cons_{ijkt} + \beta_5 VxTech_{ijk} + \beta_6 Suff_{ijkt} + \beta_7 VxPQ_{ijkt} + \beta_8 Trade_{ijkt} + \epsilon_{i,j,k,t}}$$

Equation 4.6

Model 5 (Percent market share for export market):

$$\boldsymbol{Log(LPV_{ijkt}) = \beta_{0jk} + \beta_{1jk}Log(SInf_{kt}) + \beta_2 Log(\frac{GNI}{cap}_{kt}) + \beta_3 Cons_{ijkt} + \beta_4 VxTech_{ijk} + \beta_5 Suff_{ijkt} + \beta_6 VxPQ_{ijkt} + \beta_7 Status_{jk} + \beta_8 MOH_{kt} + \epsilon_{i,j,k,t}}$$

Equation 4.7

Where:

- $Log(LPV_{ijkt})$, the outcome variable, is revenue size or percent market share (as defined for each model), for vaccine *i*, manufacturer j, country *k* and year *t*;
- $Log(SInf)$, denotes number of surviving infants, in log form;
- $Log(\frac{GNI}{cap})$, denotes gross national income per capita, in log form;
- $VxNumb$, denotes number of vaccines produced by each company;
- $Cons$, denotes consistency of production of each vaccine (coded 0=interrupted supply, 1=consistent supply);
- $VxTech$, denotes vaccine technology level, in categorical form (coded 0=pre-GAVI, 1=GAVI Phase I, 2=GAVI Phase II, 3=GAVI Phase II);
- $Suff$, denotes vaccine sufficiency level;
- NRA, denotes whether the NRA is fully functional in binary form (coded 1=fully functional, 0=not);
- $VxPQ$, denotes prequalification status of vaccines, in binary form (coded 1=prequalified, 0=not prequalified);

- $Status$, denotes firm ownership status, in binary form (coded 0=public, 1=private);
- MOH, denotes number of Ministers of Health over last five years;
- $Market$, denotes proportion of export sales compared to domestic sales.

4.3. Results

4.3.1. Descriptive analysis and correlation analysis

Overall, the dataset had 318 observations that represented 5.13 billion vaccine doses (Table 4.4). The total summed to US$5.83 billion. There were 38 different vaccine types produced by 35 local manufacturers in 16 developing countries.

Table 4.4 Revenue sizes and percent market shares of public vaccine markets supplied by developing country vaccine manufacturers (2012 – 2014).

Country	Vaccine	Manufacturer	Revenue Size, global (US$ million)			Revenue Size, domestic (US$ million)			Revenue Size, export (US$ million)			Percent market share, global (%)			Percent market share, export (%)		
			2012	2013	2014	2012	2013	2014	2012	2013	2014	2012	2013	2014	2012	2013	2014
Argentina	Influenza_Adult	Sinergium	-	11.60	51.58	-	11.60	51.58	-	-	-	-	4.41	21.86	-	-	-
Argentina	Influenza_Pediatric	Sinergium	-	3.44	10.94	-	3.44	10.94	-	-	-	-	11.95	31.72	-	-	-
Mexico	HepB_adult	Probiomed	0.93	-	0.40	0.93	-	0.40	-	-	-	2.25	-	0.89	-	-	-
Mexico	HepB_pediatric	Probiomed	3.27	-	5.18	3.27	-	5.18	-	-	-	4.85	-	6.92	-	-	-
Pakistan	Measles	NIH Pakistan	-	0.11	-	-	0.11	-	-	-	-	-	0.23	-	-	-	-
Pakistan	TT	NIH Pakistan	-	0.02	0.14	-	0.02	0.14	-	-	-	-	0.06	0.44	-	-	-
Senegal	OPV	IP Dakar	-	0.05	-	-	-	-	-	0.05	-	-	0.03	-	-	-	-
Senegal	YF	IP Dakar	-	6.62	1.64	-	-	0.36	-	6.62	1.27	-	9.19	1.96	-	-	1.53
Serbia	BCG	Torlak	-	-	0.03	-	-	-	-	-	0.03	-	-	0.05	-	-	-
Serbia	Td	Torlak	-	-	0.05	-	-	-	-	-	0.05	-	-	0.02	-	-	-
Serbia	TT	Torlak	-	-	0.01	-	-	-	-	-	0.01	-	-	0.03	-	-	-
Serbia	DT	Torlak	-	-	0.01	-	-	-	-	-	0.01	-	-	0.02	-	-	-
Serbia	DTwP	Torlak	-	-	6.0 x 10^-4	-	-	-	-	-	6.0 x 10^-4	-	-	2.2 x 10^-3	-	-	-
Thailand	HepB_pediatric	GPO-Merieux	0.39	0.39	0.62	0.39	0.39	0.62	-	-	-	0.58	0.46	0.83	-	-	-
Thailand	Influenza_Adult	GPO-Merieux	5.68	6.90	6.09	5.68	6.90	6.09	-	-	-	2.53	2.62	2.58	-	-	-
Thailand	OPV	GPO-Merieux	1.48	1.48	1.16	1.48	1.48	1.16	-	-	-	1.05	0.75	0.66	-	-	-
Thailand	JE_Inactd	GPO-Merieux	1.15	1.45	3.00	1.15	1.45	3.00	-	-	-	17.29	27.65	49.34	-	-	-
Thailand	YF	GPO-Merieux	-	-	0.03	-	-	-	-	-	0.03	-	-	0.04	-	-	-
Thailand	MR	Masu	-	-	2.48	-	-	2.48	-	-	-	-	-	10.14	-	-	-
Thailand	Td	Masu	12.15	27.62	24.30	12.15	27.62	24.30	-	-	-	9.57	11.81	12.40	-	-	-
Thailand	DTwPHepB	Masu	7.68	7.68	8.64	7.68	7.68	8.64	-	-	-	6.98	11.73	100.00	-	-	-
Tunisia	BCG	IP Tunis	0.27	0.18	0.30	0.27	0.18	0.30	-	-	-	0.55	0.30	0.57	-	-	-
Vietnam	BCG	IVAC	0.42	0.42	0.42	0.42	0.42	0.42	-	-	-	0.85	0.72	0.81	-	-	-

Country	*Vaccine*	*Manufacturer*	*Revenue Size, global (US$ million)*			*Revenue Size, domestic (US$ million)*			*Revenue Size, export (US$ million)*			*Percent market share, global (%)*			*Percent market share, export (%)*		
			2012	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*
Vietnam	TT	IVAC	0.54	0.63	0.63	0.54	0.63	0.63	-	-	-	2.28	2.12	1.99	-	-	-
Vietnam	DTwP	IVAC	0.36	0.42	0.28	0.36	0.42	0.28	-	-	-	1.69	1.99	1.05	-	-	-
Vietnam	OPV	Polyvac	1.62	1.37	1.33	1.62	1.37	1.33	-	-	-	1.14	0.69	0.76	-	-	-
Vietnam	Measles	Polyvac	1.00	0.96	2.07	1.00	0.96	2.07	-	-	-	1.07	1.98	2.83	-	-	-
Vietnam	HepB_pediatric	Vabiotech	0.46	0.34	0.27	0.46	0.34	0.27	-	-	-	0.68	0.40	0.36	-	-	-
Vietnam	Cholera	Vabiotech	-	0.09	0.09	-	0.09	0.09	-	-	-	-	85.63	95.87	-	-	-
Vietnam	JE_Inactd	Vabiotech	1.25	1.25	2.00	1.25	1.25	2.00	-	-	-	18.86	23.85	32.89	-	-	-
Vietnam	Typhoid	DAVAC	-	0.15	0.15	-	0.15	0.15	-	-	-	-	1.87	2.05	-	-	-
Brazil	Hib	Fiocruz	-	0.18	0.18	-	0.18	0.18	-	-	-	-	3.01	8.44	-	-	-
Brazil	OPV	Fiocruz	4.46	-	5.80	4.00	-	5.80	0.46	-	-	3.14	-	3.30	0.33	-	-
Brazil	IPV	Fiocruz	41.25	56.25	48.75	41.25	56.25	48.75	-	-	-	77.83	86.81	76.53	-	-	-
Brazil	MMR	Fiocruz	94.82	107.75	39.89	94.82	107.75	39.89	-	-	-	40.70	38.07	11.53	-	-	-
Brazil	MMRV	Fiocruz	-	-	73.17	-	-	73.17	-	-	-	-	-	86.80	-	-	-
Brazil	Pneumo_conj	Fiocruz	237.88	201.29	450.05	237.88	201.29	450.05	-	-	-	19.18	12.05	15.85	-	-	-
Brazil	Rotavirus	Fiocruz	-	33.35	37.35	-	33.35	37.35	-	-	-	-	20.59	14.94	-	-	-
Brazil	Varicella	Fiocruz	-	18.32	-	-	-	-	-	18.30	-	-	9.90	-	-	-	-
Brazil	YF	Fiocruz	-	46.62	39.04	-	43.57	38.94	-	3.05	0.09	-	64.66	46.81	-	10.69	0.21
Brazil	MenC_conj	FUNED	-	207.58	-	-	207.58	-	-	-	-	-	99.80	-	-	-	-
Brazil	BCG	Butantan	0.08	0.04	-	-	-	-	0.08	0.04	-	0.17	0.07	-	0.18	0.07	-
Brazil	HepB_adult	Butantan	21.80	21.80	32.14	21.80	21.80	32.14	-	-	-	53.04	71.71	70.94	-	-	-
Brazil	HPV	Butantan	-	-	195.15	-	-	195.15	-	-	-	-	-	55.28	-	-	-
Brazil	Influenza_Adult	Butantan	113.25	89.32	109.62	113.25	89.32	109.62	-	-	-	50.33	33.96	46.45	-	-	-
Brazil	OPV	Butantan	-	0.21	-	-	-	-	-	0.21	-	-	0.11	-	-	-	-
Brazil	Rabies	Butantan	-	7.61	-	-	7.61	-	-	-	-	-	52.13	-	-	-	-
Brazil	Td	Butantan	4.60	20.65	-	-	20.65	-	4.60	-	-	3.62	8.83	-	-	-	-

Country	Vaccine	Manufacturer	Revenue Size, global (US$ million)			Revenue Size, domestic (US$ million)			Revenue Size, export (US$ million)			Percent market share, global (%)			Percent market share, export (%)		
			2012	2013	2014	2012	2013	2014	2012	2013	2014	2012	2013	2014	2012	2013	2014
Brazil	DT	Butantan	1.7 x 10^-3	1.7 x 10^-3	-	1.7 x 10^-3	1.7 x 10^-3	-	-	-	-	4.9 x 10^-9	4.9 x 10^-9	-	-	-	-
Brazil	DTwP	Butantan	0.06	1.47	-	-	1.44	-	0.06	0.03	-	0.30	6.96	-	-	0.14	-
Brazil	BCG	FAP	3.90	3.90	3.90	3.90	3.90	3.90	-	-	-	7.88	6.67	7.54	-	-	-
Bulgaria	BCG	BB-NCIPD	1.73	10.42	8.97	0.11	0.10	0.11	1.62	10.30	8.86	3.50	17.81	17.35	3.28	17.67	17.18
Bulgaria	DTwPHibHepB	BB-NCIPD	-	0.02	-	-	-	-	-	0.02	-	-	4.4 x 10^-9	-	-	-	-
Bulgaria	Td	BB-NCIPD	5.53	35.68	57.54	1.17	0.85	0.73	4.37	34.80	56.80	4.36	15.25	29.36	3.47	14.94	29.10
Bulgaria	TT	BB-NCIPD	0.68	2.21	1.67	-	-	-	0.68	2.21	1.67	2.86	7.44	5.30	-	-	-
Bulgaria	DT	BB-NCIPD	0.46	0.43	0.30	-	-	-	0.46	0.43	0.30	1.35	0.81	0.97	-	-	-
Bulgaria	DTwP	BB-NCIPD	0.05	-	0.03	-	-	-	0.05	-	0.03	0.25	-	0.11	-	-	-
China	HepA	Sinovac	1.61	4.05	2.95	-	-	-	1.61	4.05	2.95	3.68	2.91	1.19	-	-	-
China	Influenza_Adult	Sinovac	0.07	0.08	-	-	-	-	0.07	0.08	-	0.03	0.03	-	-	-	-
China	JE_LiveAtd	Chengdu	108.52	157.09	394.23	-	-	-	109.00	157.00	394.00	126.04	126.69	124.76	-	-	-
China	Influenza_Adult	Changchun	11.05	6.54	2.65	-	-	-	11.00	6.54	2.65	4.91	2.49	1.12	-	-	-
China	Influenza_Pediatric	Changchun	0.06	0.04	0.07	-	-	-	0.06	0.04	0.07	0.27	0.14	0.19	-	-	-
Cuba	Td	Finlay	1.68	-	-	-	-	-	1.68	-	-	1.32	-	-	-	-	-
Cuba	TT	Finlay	1.00	1.00	1.00	1.00	1.00	1.00	-	-	-	4.22	3.37	3.16	-	-	-
Cuba	Typhoid	Finlay	-	2.71	2.71	-	2.71	2.71	-	-	-	-	34.44	37.73	-	-	-
Cuba	DT	Finlay	0.10	0.09	0.09	0.10	0.09	0.09	-	-	-	0.29	0.16	0.28	-	-	-
Cuba	DTwP	Finlay	0.06	0.04	0.05	0.03	0.04	0.04	0.03	-	0.01	0.30	0.17	0.19	0.14	-	0.06
Cuba	DTwPHibHepB	CIGB	12.96	26.72	24.34	1.39	1.39	1.39	11.60	25.30	22.90	3.47	6.61	5.19	3.11	6.29	4.91
Cuba	HepB_adult	CIGB	2.71	2.19	4.41	-	-	-	2.71	2.19	4.41	6.59	7.21	9.72	-	-	-
Cuba	HepB_pediatric	CIGB	4.19	4.11	6.33	0.05	0.13	0.13	4.14	3.98	6.20	6.22	4.83	8.45	6.15	4.69	8.29
Cuba	Hib	CIGB	0.26	0.37	0.39	0.26	0.37	0.39	-	-	-	12.45	6.01	18.09	-	-	-
Cuba	DTwPHepB	CIGB	4.80	-	-	-	-	-	4.80	-	-	4.36	-	-	-	-	-
Egypt	Td	Vacsera	-	-	7.23	-	-	7.23	-	-	-	-	-	3.69	-	-	-

Country	*Vaccine*	*Manufacturer*	*Revenue Size, global (US$ million)*			*Revenue Size, domestic (US$ million)*			*Revenue Size, export (US$ million)*			*Percent market share, global (%)*			*Percent market share, export (%)*		
			2012	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*
Egypt	TT	Vacsera	-	-	0.28	-	-	0.28	-	-	-	-	-	0.90	-	-	-
Egypt	DT	Vacsera	-	-	0.03	-	-	0.03	-	-	-	-	-	0.08	-	-	-
Egypt	DTwP	Vacsera	-	-	0.18	-	-	0.18	-	-	-	-	-	0.68	-	-	-
India	OPV	Haffkine	22.03	23.12	9.42	11.88	-	-	10.20	23.10	9.42	15.52	11.73	5.35	8.68	14.39	-
India	HepB_pediatric	Immunologicals	-	-	28.50	-	-	28.50	-	-	-	-	-	38.05	-	-	-
India	TT	Immunologicals	-	-	13.03	-	-	13.03	-	-	-	-	-	41.24	-	-	-
India	DTwP	Immunologicals	0.96	1.44	-	-	-	-	0.96	1.44	-	4.57	6.82	-	10.55	20.28	-
India	DTwPHibHepB	Panacea	1.88	-	20.92	-	-	-	1.88	-	20.90	0.50	-	4.46	0.52	-	5.16
India	OPV	Panacea	12.26	0.38	-	11.88	-	-	0.38	0.38	-	8.63	0.19	-	0.32	0.24	-
India	HepB_adult	Bharat	7.34	0.01	-	-	-	-	7.34	0.01	-	17.87	0.03	-	-	-	-
India	HepB_pediatric	Bharat	1.5 x 10^-3	-	-	-	-	-	1.5 x 10^-3	-	-	2.2 x 10^-3	-	-	-	-	-
India	OPV	Bharat	-	36.21	-	-	34.61	-	-	1.60	-	-	18.38	-	-	1.00	-
India	Rabies	Bharat	-	-	1.24	-	-	-	-	-	1.24	-	-	45.46	-	-	-
India	TT	Bharat	-	-	0.00	-	-	-	-	-	0.00	-	-	0.00	-	-	0.01
India	Typhoid	Bharat	-	-	0.11	-	-	-	-	-	0.11	-	-	1.57	-	-	-
India	BCG	IP India	-	1.0 x 10^-5	-	-	-	-	-	1.0 x 10^-5	-	-	1.7 x 10^-5	-	-	2.1 x 10-5	-
India	DTwP	IP India	5.97	-	18.90	5.97	-	18.90	-	-	-	28.42	-	70.79	-	-	-
India	BCG	SII	14.54	22.35	17.13	4.39	11.12	10.66	10.10	11.20	6.47	29.38	38.21	33.13	24.93	23.71	15.79
India	DTwPHibHepB	SII	149.98	196.88	195.19	15.92	-	63.62	134.00	197.00	132.00	40.10	48.73	41.62	37.44	-	32.45
India	HepB_adult	SII	2.0 x 10^-3	0.45	0.50	-	-	-	9.7 x 10^-3	0.45	0.50	4.9 x 10^-3	1.47	1.10	-	-	-
India	HepB_pediatric	SII	2.19	19.33	0.64	-	13.98	-	2.19	5.35	0.64	3.25	22.71	0.85	-	9.37	1.37
India	Hib	SII	0.34	0.42	0.22	-	-	-	0.34	0.42	0.22	16.26	6.93	10.00	-	-	-
India	OPV	SII	2.36	3.93	7.14	-	-	-	2.36	3.93	7.14	1.66	1.99	4.06	2.02	2.45	-
India	IPV	SII	0.01	0.15	3.02	-	-	-	0.01	0.15	3.02	0.01	0.23	4.75	-	-	-
India	Measles	SII	61.34	24.54	46.14	44.96	-	28.15	16.40	24.50	18.00	65.89	50.59	62.95	34.07	-	39.81

Country	Vaccine	Manufacturer	Revenue Size, global (US$ million)			Revenue Size, domestic (US$ million)			Revenue Size, export (US$ million)			Percent market share, global (%)			Percent market share, export (%)		
			2012	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*
India	MenA	SII	1.17	8.40	1.19	-	-	-	1.17	8.40	1.19	100.00	100.00	100.00	-	-	-
India	MMR	SII	46.50	47.62	80.35	-	-	-	46.50	47.60	80.40	19.96	16.83	23.22	-	-	-
India	MR	SII	13.81	33.65	19.50	-	-	-	13.80	33.70	19.50	72.31	101.37	79.59	-	-	-
India	Dip	SII	0.11	-	-	-	-	-	0.11	-	-	89.98	-	-	-	-	-
India	Mumps	SII	-	0.04	-	-	-	-	-	0.04	-	-	4.07	-	-	-	-
India	Pneumo_conj	SII	-	-	2.56	-	-	-	-	-	2.56	-	-	0.09	-	-	-
India	Rabies	SII	-	-	0.04	-	-	-	-	-	0.04	-	-	1.46	-	-	-
India	Rotavirus	SII	-	-	0.51	-	-	-	-	-	0.51	-	-	0.20	-	-	-
India	Rubella	SII	4.2 x 10^-3	0.01	1.2 x 10^-3	-	-	-	4.2 x 10^-3	0.01	1.2 x 10^-3	13.11	20.17	9.32	-	-	-
India	Td	SII	69.30	50.29	55.22	-	-	-	69.30	50.30	55.20	54.57	21.49	28.17	-	-	-
India	TT	SII	6.96	8.77	3.34	-	-	-	6.96	8.77	3.34	29.35	29.53	10.56	40.78	39.38	17.93
India	Typhoid	SII	-	0.06	-	-	-	-	-	0.06	-	-	0.73	-	-	-	-
India	DT	SII	2.30	0.90	2.14	-	-	-	2.30	0.90	2.14	6.82	1.70	6.96	-	-	-
India	YF	SII	-	0.60	4.76	-	-	-	-	0.60	4.76	-	0.83	5.71	-	-	-
India	DTaPHibHepB	SII	-	2.00	0.88	-	-	-	-	2.00	0.88	-	10.19	16.80	-	-	-
India	DTIPV	SII	-	1.62	1.38	-	-	-	-	1.62	1.38	-	100.00	100.00	-	-	-
India	DTwP	SII	3.41	1.20	4.34	-	-	-	3.41	1.20	4.34	16.22	5.69	16.24	37.43	16.91	55.58
India	DTwPHepB	SII	10.52	-	-	-	-	-	10.50	-	-	9.56	-	-	-	-	-
India	DTwPHib	SII	0.08	4.14	5.88	-	-	-	0.08	4.14	5.88	0.72	26.91	88.81	-	-	-
India	BCG	Green Signal	4.39	0.17	-	4.39	-	-	-	0.17	-	8.87	0.29	-	-	0.35	-
India	DTwP	CRI Kasauli	5.97	-	-	5.97	-	-	-	-	-	28.42	-	-	-	-	-
India	DTwPHibHepB	Biological E.	27.20	59.20	98.31	-	-	-	27.20	59.20	98.30	7.27	14.65	20.96	7.60	-	24.25
India	HepB_pediatric	Biological E.	-	13.98	-	-	13.98	-	-	-	-	-	16.43	-	-	-	-
India	OPV	Biological E.	-	-	0.47	-	-	-	-	-	0.47	-	-	0.27	-	-	-
India	Td	Biological E.	-	-	0.01	-	-	-	-	-	0.01	-	-	0.01	-	-	-

Country	Vaccine	Manufacturer	*Revenue Size, global (US$ million)*			*Revenue Size, domestic (US$ million)*			*Revenue Size, export (US$ million)*			*Percent market share, global (%)*			*Percent market share, export (%)*		
			2012	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*	*2012*	*2013*	*2014*
India	TT	Biological E.	7.21	9.07	2.35	6.64	7.43	-	0.57	1.64	2.35	30.43	30.53	7.43	3.34	7.37	12.63
India	DTaPHibHepB	Biological E.	-	-	4.38	-	-	-	-	-	4.38	-	-	83.20	-	-	-
India	DTwP	Biological E.	-	14.00	-	-	14.00	-	-	-	-	-	66.35	-	-	-	-
Indonesia	BCG	Bio Farma	4.78	3.90	3.88	4.77	3.86	3.88	0.02	0.04	-	9.67	6.67	7.50	0.04	0.08	-
Indonesia	DTwPHibHepB	Bio Farma	-	4.21	47.88	-	4.14	45.16	-	0.06	2.72	-	1.04	10.21	-	0.02	0.64
Indonesia	HepB_pediatric	Bio Farma	-	1.79	1.16	-	1.79	1.16	-	-	-	-	2.11	1.54	-	-	-
Indonesia	OPV	Bio Farma	9.75	9.01	10.21	5.92	5.09	4.93	3.83	3.91	5.28	6.87	4.57	5.80	2.82	2.04	3.09
Indonesia	Measles	Bio Farma	13.16	13.90	14.45	8.50	9.04	10.26	4.66	4.85	4.19	14.14	28.66	19.71	5.51	12.30	6.66
Indonesia	Td	Bio Farma	1.16	68.55	18.44	-	64.59	7.08	1.16	3.96	11.40	0.91	29.29	9.41	-	2.34	6.01
Indonesia	TdaP	Bio Farma	24.77	-	-	-	-	-	24.80	-	-	99.87	-	-	-	-	-
Indonesia	TT	Bio Farma	1.62	2.86	2.66	-	0.45	1.28	1.62	2.41	1.37	6.82	9.64	8.41	-	8.25	4.53
Indonesia	DT	Bio Farma	24.13	46.10	13.10	23.83	45.80	12.80	0.30	0.30	0.30	71.61	86.98	42.66	3.00	4.13	1.66
Indonesia	DTwP	Bio Farma	3.38	1.92	1.68	-	-	-	3.38	1.92	1.68	16.08	9.12	6.30	-	-	-
Indonesia	DTwPHepB	Bio Farma	79.56	41.52	-	79.24	41.52	-	0.32	-	-	72.33	63.39	-	1.04	-	-
Iran	BCG	IP Iran	1.95	1.56	1.95	1.95	1.56	1.95	-	-	-	3.94	2.67	3.77	-	-	-
Iran	HepB_adult	IP Iran	2.18	1.09	2.18	2.18	1.09	2.18	-	-	-	5.30	3.59	4.81	-	-	-
Iran	HepB_pediatric	IP Iran	3.22	3.22	4.60	3.22	3.22	4.60	-	-	-	4.78	3.78	6.14	-	-	-
Iran	OPV	Razi	3.40	2.00	3.30	3.40	2.00	3.30	-	-	-	2.39	1.02	1.88	-	-	-
Iran	Measles	Razi	0.21	0.35	0.28	0.21	0.35	0.28	-	-	-	0.23	0.72	0.38	-	-	-
Iran	MMR	Razi	8.62	17.24	12.28	8.62	17.24	12.28	-	-	-	3.70	6.09	3.55	-	-	-
Iran	Rubella	Razi	4.2×10^{-2}	-	0.01	4.2×10^{-2}	-	0.01	-	-	-	13.29	-	90.68	-	-	-
Iran	Td	Razi	13.37	14.58	14.58	13.37	14.58	14.58	-	-	-	10.52	6.23	7.44	-	-	-
Iran	DT	Razi	0.13	0.13	0.13	0.13	0.13	0.13	-	-	-	0.39	0.25	0.43	-	-	-
TOTAL – by year			**1,393.79**	**1,962.16**	**2,476.81**	**827**	**1,179.44**	**1,460.4**	**567.23**	**782.57**	**1016.57**						
GRAND TOTAL				**5,832.76**			**3,466.84**			**2,366.37**							

Note: N = 318 observations; 5.13 billion vaccine doses

Among domestic sales of vaccines, 95% of the suppliers had at least 95% of market share for those markets. This is shown in Table 4.5. The total revenue from vaccine sales in global markets was US$5.83 trillion, where domestic revenue amounted to US$ 3.47 trillion and export market revenue was US$ 2.37 trillion. While on average, DCVM production revenue from vaccine sales was US$ 18.3 million for global markets, US$ 18.1 million for domestic markets, and US$ 13.4 million for export markets. Total market shares were 18.4% for global markets and 10.2% in export markets. Within the three-year study period, local vaccine producers were mostly state-owned enterprises (58%), in countries with a fully functional NRA (91%), had consistent supply to global immunisation programs (61%), produced around 8 different vaccines, produced traditional vaccine technology types (50%), and produced vaccines that were not of prequalified status (63%). These are shown in Tables 4.6 and 4.7. Results of the univariate analyses are shown in Table 4.8.

Table 4.5 Percent market share of developing country vaccine manufacturers in domestic markets (2012-2014)

COUNTRY	VACCINE	MANUFACTURER	YEAR		
			2012	2013	2014
ARGENTINA	Influenza_Adult	Sinergium	-	100.02	99.97
ARGENTINA	Influenza_Pediatric	Sinergium	-	100.00	100.40
MEXICO	HepB_adult	Probiomed	100.00	-	100.00
MEXICO	HepB_pediatric	Probiomed	100.00	-	100.00
PAKISTAN	Measles	NIH Pakistan	-	100.00	-
PAKISTAN	TT	NIH Pakistan	-	100.00	100.00
SENEGAL	YF	IP Dakar	-	-	100.00
THAILAND	HepB_pediatric	GPO-Merieux	100.00	100.00	100.00
THAILAND	Influenza_Adult	GPO-Merieux	100.00	100.00	88.24
THAILAND	OPV	GPO-Merieux	100.00	100.00	100.00
THAILAND	JE_Inactd	GPO-Merieux	100.00	100.00	100.00
THAILAND	MR	Masu, Thailand	-	-	100.00
THAILAND	Td	Masu, Thailand	99.59	100.09	100.00
THAILAND	DTwPHepB	Masu, Thailand	100.00	100.00	100.00
TUNISIA	BCG	IP Tunis	100.00	100.00	100.00
VIETNAM	BCG	IVAC Vietnam	100.00	100.00	100.00
VIETNAM	TT	IVAC Vietnam	100.00	100.00	100.00
VIETNAM	DTwP	IVAC Vietnam	100.00	100.00	100.00
VIETNAM	OPV	Polyvac Vietnam	95.00	95.00	95.00
VIETNAM	Measles	Polyvac Vietnam	100.00	100.00	100.00

VIETNAM	HepB_pediatric	Vabiotech	100.00	100.00	100.00
VIETNAM	Cholera	Vabiotech	-	100.00	100.00
VIETNAM	JE_Inactd	Vabiotech	100.00	100.00	100.00
VIETNAM	Typhoid	DAVAC	-	100.00	100.00
BRAZIL	Hib	Fiocruz	-	100.00	100.00
BRAZIL	OPV	Fiocruz	100.00	-	100.00
BRAZIL	IPV	Fiocruz	99.88	99.91	99.90
BRAZIL	MMR	Fiocruz	100.02	99.77	99.98
BRAZIL	MMRV	Fiocruz	-	-	99.96
BRAZIL	Pneumo_conj	Fiocruz	99.95	100.14	100.01
BRAZIL	Rotavirus	Fiocruz	-	99.85	99.87
BRAZIL	YF	Fiocruz	-	99.94	100.11
BRAZIL	MenC_conj	FUNED	-	99.80	-
BRAZIL	HepB_adult	Butantan	100.00	100.00	100.12
BRAZIL	HPV	Butantan	-	-	100.08
BRAZIL	Influenza_Adult	Butantan	100.22	100.02	99.65
BRAZIL	Rabies	Butantan	-	100.00	-
BRAZIL	Td	Butantan	-	99.77	-
BRAZIL	DT	Butantan	100.00	100.00	-
BRAZIL	DTwP	Butantan	-	100.00	-
BRAZIL	BCG	FAP	100.00	100.00	100.00
BULGARIA	BCG	BB-NCIPD	100.00	100.00	100.00
BULGARIA	Td	BB-NCIPD	100.00	100.00	100.00
CUBA	TT	Finlay	100.00	100.00	100.00
CUBA	Typhoid	Finlay	-	100.00	100.00
CUBA	DT	Finlay	100.00	100.00	100.00
CUBA	DTwP	Finlay	100.00	100.00	100.00
CUBA	DTwPHibHepB	CIGB Cuba	100.00	100.00	100.00
CUBA	HepB_pediatric	CIGB Cuba	100.00	100.00	100.00
CUBA	Hib	CIGB Cuba	100.00	100.00	100.00
EGYPT	Td	Vacsera	-	-	100.00
EGYPT	TT	Vacsera	-	-	100.00
EGYPT	DT	Vacsera	-	-	100.00
EGYPT	DTwP	Vacsera	-	-	100.00
INDIA	OPV	Haffkine	47.50	-	-
INDIA	HepB_pediatric	Immunologicals	-	-	100.00
INDIA	TT	Immunologicals	-	-	100.24
INDIA	OPV	Panacea	47.50	-	-
INDIA	OPV	Bharat	-	95.07	-
INDIA	DTwP	IP India	50.15	-	100.00
INDIA	BCG	SII	50.00	100.15	99.60
INDIA	DTwPHibHepB	SII	100.13	-	100.03
INDIA	HepB_pediatric	SII	-	49.92	-
INDIA	Measles	SII	99.90	-	100.16
INDIA	BCG	Green Signal	50.00	-	-
INDIA	DTwP	CRI Kasauli	50.15	-	-
INDIA	HepB_pediatric	Biological E.	-	49.92	-

INDIA	TT	Biological E.	100.00	100.00	-
INDIA	DTwP	Biological E.	-	100.00	-
INDONESIA	BCG	Biofarma	100.00	100.00	100.00
INDONESIA	DTwPHibHepB	Biofarma	-	100.00	99.92
INDONESIA	HepB_pediatric	Biofarma	-	100.00	100.00
INDONESIA	OPV	Biofarma	95.00	95.00	95.00
INDONESIA	Measles	Biofarma	100.00	100.00	99.57
INDONESIA	Td	Biofarma	-	99.98	100.00
INDONESIA	TT	Biofarma	-	100.00	100.00
INDONESIA	DT	Biofarma	100.14	100.01	99.99
INDONESIA	DTwPHepB	Biofarma	100.05	100.05	-
IRAN	BCG	IP Iran	100.00	100.00	100.00
IRAN	HepB_adult	IP Iran	100.00	100.00	100.00
IRAN	HepB_pediatric	IP Iran	100.00	100.00	100.00
IRAN	OPV	Razi	100.00	100.00	100.00
IRAN	Measles	Razi	100.00	100.00	100.00
IRAN	MMR	Razi	100.00	100.23	99.87
IRAN	Rubella	Razi	100.00	-	100.00
IRAN	Td	Razi	99.74	99.87	99.87
IRAN	DT	Razi	100.00	100.00	100.00

Source: calculated based on JRF and V3P data for 2012 - 2014

Table 4.6 Summary and definition of outcome and explanatory variables

Viability factor	Variable	Definition	Indicator	Mean (Standard Deviation) 2012 - 2014	2012	2013	2014	Data source	Date of access
Proxy of viability	**Revenue size (US$)**	Revenue of vaccine doses sold	**Model 1.** Revenue size, global (US$ million)	18.34 (47.82) N=318	14.83 (35.30) N=94	18.17 (39.25) N=108	21.35 (61.98) N=116	JRF and V3P data, 2012 - 2014	17/01/2017
			Model 2. Revenue size, domestic (US$ million)	18.06 (47.39) N=192	15.04 (38.11) N=55	17.87 (39.41) N=66	20.57 (59.60) N=71	JRF and V3P data, 2012 - 2014	17/01/2017
			Model 3. Revenue size, export (US$ million)	13.44 (40.14) N=176	10.12 (24.73) N=56	13.27 (33.86) N=59	16.66 (54.85) N=61	JRF and V3P data, 2012 - 2014	17/01/2017
	Market share (%)	Revenue of vaccine doses sold as percentage of total revenue of all manufacturers selling the same vaccine type.	**Model 4.** Percent market share, global	18.42 (27.79) N=318	16.78 (26.24) N=94	18.46 (27.94) N=108	19.72 (29.00) N=116	JRF and V3P data, 2012 - 2014	17/01/2017
			Model 5. Percent market share, exports	10.20 (12.68) N=73	9.87 (13.66) N=24	8.43 (9.55) N=26	12.56 (14.77) N=23	JRF and V3P data, 2012 - 2014	17/01/2017
Economies of Scale	**Surviving Infants (per 1,000 live births)**	Birth cohort targeted under immunisation programs, calculated based on crude mortality rates and infant mortality rates	Surviving infants (per 1000 live births)	9.70 (10.73) N=318	10.03 (10.87) N=894	9.69 (10.64) N=108	9.45 (10.79) N=116	World Development Indicator/World Bank and UN Statistical Division, 2012 - 2014	20/11/2016
Economies of Scope	**Number of vaccines produced**	Number of vaccines produced by manufacturer	Number of vaccines produced by manufacturer	8.38 (5.21) N=318	8.46 (5.24) N=94	8.36 (5.27) N=108	8.35 (5.19) N=116	JRF database, 2012 – 2014; Manufacturers' websites, DCVMN Directory (2014); and Kaddar, Milstien, and Schmitt (2014)	20/11/2016
Historical performance/quality	**Supply sufficiency for global demand (%)**	Proportion of vaccine doses sold by each manufacturer to the global market for a particular vaccine	Supply sufficiency for global demand	88.43 (24.94) N=318	90.25 (20.69) N=318	89.26 (25.89) N=318	86.17 (27.13) N=318	JRF database, 2012 – 2014	17/01/2017
Legal status/autonomy	**Number of MoH in last five years**	Number of ministers of health within last 5 years	Number of Ministers of Health over the last 5 years	3.22 (1.58) N=318	2.99 (1.32) N=94	2.98 (1.66) N=108	3.63 (1.63) N=116	Country-related websites	06/08/2016
Purchasing power of producing country	**National Income level (US$**	Gross national income, converted to U.S. dollars using the World Bank Atlas method, divided by the midyear population.	Gross national income (GNI) per capita, Atlas method (current US$)	5031.20 (3,687.04) N=318	4931.80 (3503.45) N=94	5222.83 (4006.78) N=108	4933.33 (3543.60) N=116	World Development Indicator/World Bank, 2012 - 2014	11/02/2016

Table 4.7 Summary and definition of categorical explanatory variables

Viability factor	Variable	Definition	Indicator	2012 – 2014		2012		2013		2014		Data source	Date last access
				N	%	N	%	N	%	N	%		
Consistency of Production/Annual capital expenditure	**Consistent production** (binary: 0= inconsistent, 1= consistent)	Whether vaccine was procured in global market over the study period	Consistent	195/318	61.32	65/94	69.15	65/108	60.19	65/116	56.03	JRF data, 2012 - 2014	17/01/2017
			Inconsistent	123/300	38.68	29/94	30.85	43/108	39.81	51/116	43.97		
New technology	**Vaccine technology type** (categorical: 0: pre-GAVI vaccines; 1: Phase I vaccines; 2: Phase II vaccines; 3: Phase III)	Whether the vaccine is a traditional EPI vaccine or a modern one	Pre-GAVI vaccine types	158/318	49.69	50/94	53.19	52/108	48.15	56/116	48.28	Vaccines introduced in each GAVI Phase, as stated in GAVI website.	17/01/2017
			Phase I GAVI vaccines	84/318	26.42	26/94	27.66	28/108	25.93	30/116	25.86		
			Phase II GAVI vaccines	46/318	14.47	12/94	12.77	16/108	14.81	18/116	15.52		
			Phase III GAVI vaccines	30/318	9.43	6/94	6.38	12/108	11.11	12/116	10.34		
Credibility of quality/ Regulatory infrastructure	**Fully functional National Regulatory Authority (NRA)**	National Regulatory Authorities (NRA) that fulfil six critical functions as identified and assessed by WHO[53].	Fully functional	290/318	91.19	80/94	85.11	101/108	93.52	109/116	93.97	Interview with Regulatory team at WHO/HQ	12/12/2014
			Not fully functional	28/318	8.81	14/94	14.89	7/108	6.48	7/116	6.03		
	Vaccine prequalification status (binary: 0=Prequalified, 1=not prequalified)	Whether vaccine produced has a prequalified status	Prequalified	117/318	36.79	36/94	38.30	39/108	36.11	42/116	36.21	Vaccine prequalification database, WHO	20/11/2016
			Not prequalified	201/318	63.21	58/94	61.70	69/108	63.89	74/116	63.79		

[53] WHO establishes six functions that a national regulatory authority must fulfil to be fully functional, a requirement for the corresponding country's vaccine manufacturer to be allowed to export its vaccine production to other countries. These six NRA functions are: (1) a published set of requirements for licensing; (2) surveillance of vaccine field performance; (3) system of lot release; (4) use of laboratory when needed; (5) regular inspections for GMP; and (6) evaluation of clinical performance.

Table 4.8. Univariate hierarchical linear regression of factors associated with revenue sizes and percent market share of vaccines produced by developing country vaccine manufacturers

	Model 1 (n=318)			*Model 2 (n=192)*			*Model 3 (n=73)*			*Model 4 (n=318)*			*Model 5 (n=73)*		
Explanatory variable	**β**	**(95% CI)**	**P**	**β**	**(95% CI)**	**P**	**β**	**(95% CI)**	**P**	**β**	**(95% CI)**	**P**	**β**	**(95% CI)**	**P**
Constant	14.45			14.67			0.99			1.37			0.99		
Surviving Infants (log)	0.21	0.05–0.37	0.008*	0.73	0.53–0.92	0.000*	0.03	-0.24–0.30	0.812	0.25	0.11–0.38	0.000*	0.03	-0.24–0.30	0.812
GNI per capita (log)	0.41	0.04–0.79	0.029*	0.45	0.01–0.89	0.046*	-0.64	-1.40–0.11	0.096*	-0.04	-0.37–0.29	0.831	-0.64	-1.40–0.11	0.096*
Number of vaccines products	0.47	-0.01–0.10	0.105*	0.16	0.08–0.25	0.000*	0.20	0.08–0.32	0.001*	0.10	0.05–0.15	0.000*	0.20	0.08–0.32	0.001*
Consistent production supply	1.27	0.67–1.86	0.000*	-0.23	-0.93–0.46	0.348	0.40	1.93–4.06	0.000*	1.04	0.51–1.57	0.000*	2.99	1.93–4.06	0.000*
Vaccine technology	0.38	0.08–0.68	0.014*	0.19	-1.11–1.49	0.773	0.017	-0.00–0.04	0.110*	0.67	0.42–0.93	0.000*	0.19	-1.11–1.49	0.773
Sufficient supply against demand	0.34	-0.33–1.01	0.315	0.37	-0.40–1.14	0.348	0.40	-0.73–1.54	0.486	0.58	-0.01–1.17	0.052*	0.40	-0.73–1.54	0.486
NRA	2.00	0.97–3.02	0.000*	1.92	0.78–3.05	0.001*	-0.75	-2.97–1.48	0.511	2.04	1.14–2.94	0.000*	-0.75	-2.97–1.48	0.511
Vaccine PQ status	0.78	0.17–1.39	0.013*	0.35	-0.39–1.10	0.350	2.88	1.92–3.83	0.000*	1.13	0.60–1.66	0.000*	2.88	1.92–3.83	0.000*
Manufacture status	0.24	-0.37–0.84	0.438	1.18	0.43–1.92	0.002*	1.58	0.51–2.65	0.004*	0.46	-0.66–0.99	0.086*	1.58	0.51–2.65	0.004*
Number of MOH, last 5 years	-0.10	-0.29–0.09	0.310	-0.16	-0.37–0.05	0.141*	0.17	-0.16–0.50	0.322	-0.120	-0.36– -0.03	0.019*	0.17	-0.16–0.50	0.322
Proportion of export sales	-0.01	-0.01 - -0.00	0.009*	-0.00	-0.00–0.00	0.540	0.14	-0.00–0.03	0.058*	-0.01	-0.01– -0.00	0.016*	0.014	-0.00–0.03	0.058*

* p value ≤ 0.2. Note: *Model 1*: Revenue size for global market; *Model 2*: Revenue size for domestic market; *Model 3*: Revenue size for export market; *Model 4*: Percent market share for global market; *Model 5*: Percent market share for export market.

4.3.2. Multivariate regression

Determinants of viability in global markets: Revenue size (Model 1)

In the vaccine market, revenue sizes were estimated to increase as a result of a one percent increase in the following factors: the number of surviving infants (0.4%[54]) and the national income level of the producing country (0.83%). Existence of the following factors influence an increase in revenue sizes in global markets: consistent production (122.2%) and the ability to sufficiently meet the need of immunisation programs in procuring countries (2%). Companies with a higher proportion of export sales compared to their domestic sales were associated with 2% lower revenue sizes. The number of vaccine products produced by a manufacturer as well as the rate of changes within the health ministry did not significantly influence global market revenues.

Determinants of viability in domestic markets: Revenue size (Model 2)

Revenue sizes in domestic markets were found to increase in association with the number of surviving infants (0.92%), and national income levels (0.66%). Having consistent production, later stage GAVI vaccines and the ability to sufficiently meet the need of immunisation programs in procuring countries were all positively associated with revenue size in domestic markets at varying degrees: 80%, 64%, and 1%. The number of vaccine products produced by a manufacturer as well as a vaccine's prequalification status were not determinant factors for revenue sizes in domestic markets.

Determinants of viability in export markets: Revenue size (Model 3)

Export market revenue was positively associated with a one percent increase in national income levels (2.37%). Consistency in production supply, as well as the ability

[54] Percentages in brackets represent the percentage change in the outcome variable associated with a one-unit change in the explanatory variable. For instance, if the number of surviving infants changes by one percent, the dependent variable is expected to change by 0.4 percent.

to meet the demand of immunisation programs in procuring countries was associated with increases in export market revenue by 201% and 2%. Prequalified vaccine status and private ownership were positively associated with export market revenue by 139% and 661%, respectively. Changes within the health ministry were also associated with increasing revenues in export markets by 49%. The producer country's birth cohort as well as the technology level of vaccines were not found to be determining factors for revenue sizes in export markets.

Determinants of viability in global markets: Percent market share (Model 4)

Percent market share in global vaccine markets was positively associated with one percent increase in the producing country's birth cohort (0.24%) and number of vaccines produced by a single manufacturer (14%). The consistency in production supply and later stage GAVI vaccines were all positively associated with market share in global markets, by 95% and 67% respectively. The ability to meet the demand of immunisation programs in procuring countries and having vaccine prequalification status were positively associated with a greater percent market share in the global vaccine market (2% and 126%). Having a larger proportion of domestic sales compared to export sales was also associated with a higher percent market share in the global vaccines market (2%). The producing country's national income level was not associated with changes in percent market share in global markets.

Determinants of viability in export markets: Percent market share (Model 5)

Percent market share in export markets were influenced by a one percent increase in the producing countries' national income (2.37%). Having consistent production and the ability to meet the demand of immunisation programs in procuring countries increased a DCVM's export market shares by 200% and 2%. A vaccine's prequalification status, private ownership and changes in ministry of health were positively associated with changes in percent market share for exports (139%, 661%

and 49%). The producing country's birth cohorts as well as later stage GAVI vaccines were not determining factors for percent export market shares. These multivariate regression results are shown in Table 4.9.

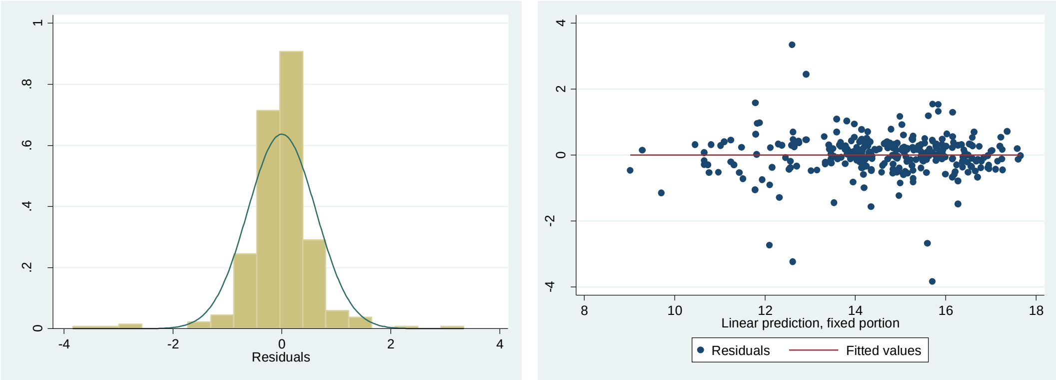
Post-estimation tests on the residuals were performed for each model and presented in Figures 4.7 – 4.11. The residuals show a normal distribution and does not suggest violations to the normality assumption.

Results from the first sensitivity analysis that excluded reported multiple producers from the vaccine procurement data showed that there were not any significant difference in the percent market share for domestic markets or the global and export markets. The two other sensitivity analysis also did not show that there were any significant differences in the results.

Table 4.9. Multivariate hierarchical linear regression of factors associated with revenue sizes and percent market share of vaccines produced by developing country vaccine manufacturers

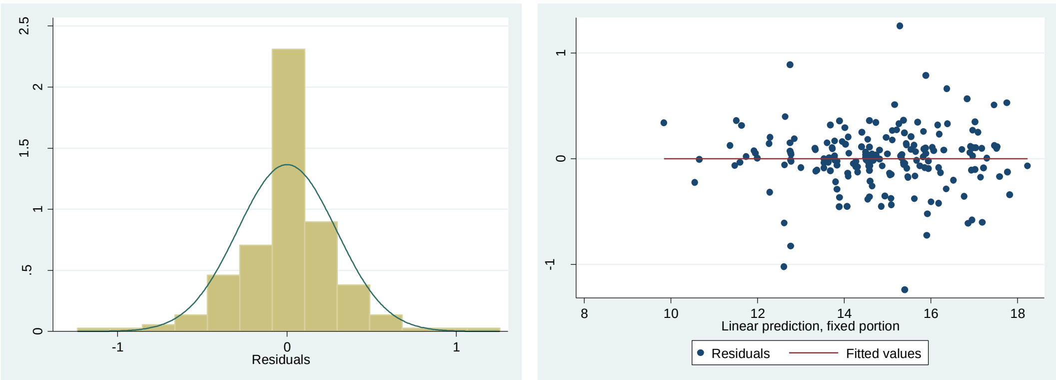
	MODEL 1 (N=318)			MODEL 2 (N=192)			MODEL 3 (N=73)			MODEL 4 (N=318)			MODEL 5 (N=73)		
Explanatory Variable	β	(95% CI)	P	β	(95% CI)	P	β	(95% CI)	P	β	(95% CI)	P	B	(95% CI)	P
Constant	-1.21			-6.69			-24.39			-7.98			-24.39		
Surviving Infants (log)	0.40	0.14–0.65	0.002**	0.92	0.63 – 1.21	0.000***	-0.19	-0.64-0.27	0.427	0.24	0.03 - 0.48	0.047*	-0.19	-0.64-0.27	0.427
GNI per capita (log)	0.83	0.28–1.38	0.003**	0.66	1.72–1.15	0.008**	2.37	0.72 – 4.02	0.005**	0.35	-0.17 – 0.87	0.192	2.37	0.72–4.02	0.005**
Number of vaccines products	0.72	-0.02–0.17	0.131	0.06	-0.03-0.16	0.182				0.14	0.03 - 0.20	0.011*			
Consistent production supply	1.222	0.48–1.97	0.001***	0.80	0.06-1.55	0.035*	2.01	0.82-3.19	0.001***	0.95	0.24 - 1.67	0.009**	2.00	0.82 – 3.19	0.001***
Vaccine technology	0.44	-0.20–1.07	0.178	0.64	0.05–1.23	0.035*	0.24	-0.57 – 1.04	0.563	0.67	0.24 – 1.10	0.002**	0.24	-0.57-1.04	0.563
Sufficient supply against demand	0.02	0.01–0.03	0.000***	0.01	0.01–0.02	0.000***	0.02	0.01 – 0.04	0.002**	0.02	0.01 - 0.03	0.000***	0.02	0.01 -0.04	0.002**
NRA															
Vaccine PQ status	1.59	0.83 – 2.26	0.000***	0.30	-0.05 – 1.05	0.431	1.39	0.66 – 2.12	0.000***	1.26	0.54 - 1.98	0.001***	1.39	0.66- 2.11	0.000***
Manufacture status							6.61	3.93 – 9.28	0.000***				6.61	3.93 – 9.28	0.000***
Number of MOH, last 5 years	0.10	-0.05–0.25	0.181				0.49	0.14 – 0.84	0.006**				0.49	0.14 - 0.84	0.006**
Proportion of export sales	-0.02	-0.03 – -0.017	0.000***							-0.02	-0.03 - 0.02	0.000**			
Random effects	Variance	(95% CI)		Variance	(95% CI)		Variance	(95% CI)		Variance	(95% CI)		Variance	(95% CI)	
Vaccine (Level 1)	1.74	1.18 – 2.55		1.47	0.92 – 2.34		0.15	0.0 – 4.12		0.85	0.43 – 1.70		0.22	0.03–2.08	
Manufacturer (Level 2)	1.26	0.00–1459387		0.91	0.00–2.16e13		0.75	0.00–1.8e34		1.26	0.00–4.6e8		0.75	0.00–1.8e34	
Producing country (Level 3)	1.26	0.00–1459766		0.91	0.00–2.16e13		0.75	0.00–1.8e34		1.26	0.00–4.6e8		0.75	0.00–1.8e34	
Residual	0.82	0.74–0.91		0.41	0.36–0.47		1.14	0.94–1.37		0.84	0.76–0.94		1.14	0.94–1.37	
Log-likelihood	-582.79			-252.89			-123.24			-574.47			-123.24		

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001; bold number: significant. Note: _Model 1_: Revenue size for global market; _Model 2_: Revenue size for domestic market; _Model 3_: Revenue size for export market; _Model 4_: Percent market share for global market; _Model 5_: Percent market share for export market.



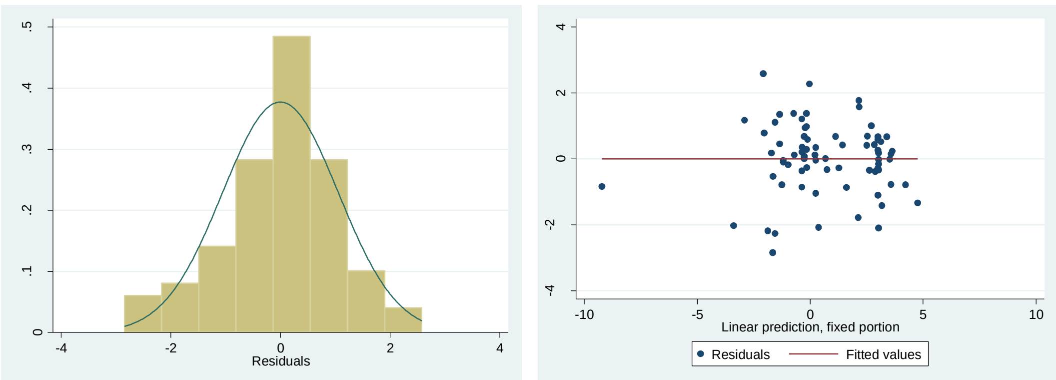
(a) **(b)**

Figure 4.7 Post-estimation tests on residuals of regression of factors influencing developing country vaccine manufacturers' revenue size in global markets (Model 1). Note: (a) distribution of residual values; (b) residuals plotted against corresponding predicted values.



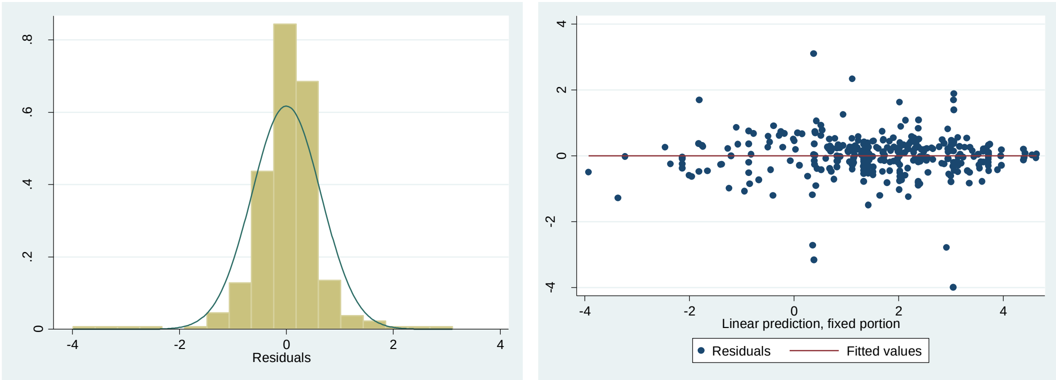
(a) **(b)**

Figure 4.8 Post-estimation tests on residuals of regression of factors influencing developing country vaccine manufacturers' revenue size in domestic markets (Model 2). Note: (a) distribution of residual values; (b) residuals plotted against corresponding predicted values.



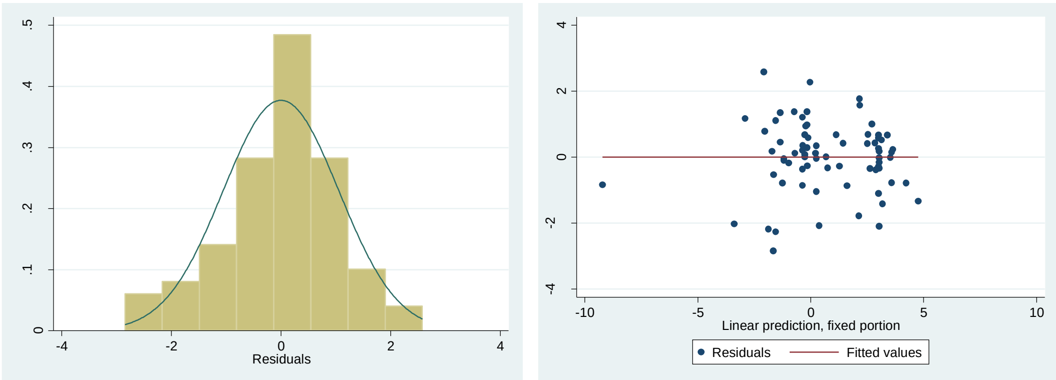
(a) **(b)**

Figure 4.9 Post-estimation tests on residuals of regression of factors influencing developing country vaccine manufacturers' revenue size in export markets (Model 3). Note: (a) distribution of residual values; (b) residuals plotted against corresponding predicted values.



(a) **(b)**

Figure 4.10 Post-estimation tests on residuals of regression of factors influencing developing country vaccine manufacturers' percent market share in global markets (Model 4). Note: (a) distribution of residual values; (b) residuals plotted against corresponding predicted values.



(a) **(b)**

Figure 4.11 Post-estimation tests on residuals of regression of factors influencing developing country vaccine manufacturers' percent market share in export markets (Model 5). Note: (a) frequency distribution of residual values; (b) residuals plotted against corresponding predicted values

4.4. Discussion

During the study period, global market shares for vaccines produced by DCVMs were steady at 15 to 21% and within market types (domestic and export), the data showed a stable market share across the three years observed. The data also showed a contrast between domestic and export markets shares of DCVMs (95% compared to 10%). The very high domestic market share suggests that there is nearly no competition for product sales within domestic vaccine markets.

The multivariate regression identified that all seven characteristics proposed by Milstien et al. (1997) were associated with market share of local vaccine production across markets: economies of scale and scope (surviving infants and number of vaccines), consistency of production, vaccine technology, supply sufficiency, credibility of vaccine quality (vaccine prequalification status), management structure of the company, and changes in health ministries. Additional factors that were included in this Chapter such as national income per capita and proportion of export sales were also found to be associated with vaccine production viability.

Indicators used as proxies for economies of scale and scope were determinant factors for global markets, yet only economies of scale (number of surviving infants) were associated with domestic revenue. In export markets, neither of these factors were influential in increasing revenue. Given that the indicators for economies of scale and economies of scope were that of the producing country and not the procuring country, we cannot establish whether these factors from the procuring countries' perspective were not influential in export markets. In fact, sufficient supply (observed for the procuring country) was shown to be significantly associated with export market share as well as other markets, indicating that economies of scale and scope may in fact be a determining factor in all three market types.

Consistency of production was significant in all three market types that were investigated in the five models. This is an interesting finding given that various supply disruptions occur often in vaccine markets (Gurnani, Mehrotra, & Ray, 2012), (Batson et al., 2003). The impact of this factor in export markets seemed to be greater than in domestic markets, indicating that consistency of production may provide a competitive advantage for manufacturers supplying to export markets.

Production of higher vaccine technology types was found to be a determining factor in global market shares and domestic revenue sizes. Vaccine technology levels not being a determinant factor in export markets may be due to more advanced technology vaccine types being produced by ICVMs, as shown in Figure 4.3. As for vaccine technology levels being a determinant factor in domestic markets, this may be due to the changing landscape in vaccines, where WHO recommendations are issued for countries to shift from certain older vaccine types such as oral polio vaccine (OPV) to newer types, such as inactivated polio vaccines (IPV) in single-antigen and combination vaccines such as the hexavalent vaccine (DTP-HepB-Hib-IPV).

Supply sufficiency was a significant factor in all five models. Given the high market concentrations in individual vaccine markets (i.e.: Hepatitis B vaccine market, hexavalent vaccine market, etc.) it is important for existing suppliers to meet the demand of the immunisation program and avoid the need for multiple vaccine sources, hence avoiding higher transaction costs (Milstien et al., 1997).

Credibility of vaccine quality, identified using the indicator of vaccine prequalification status, was a determining factor in export market revenue and percent market share for global and export markets. A fully functional NRA however was not included in the five models due to being eliminated at the univariable analysis stage. This might be because the prequalification of a vaccine requires that the NRAs in the respective countries be fully functional (Dellepiane & Wood, 2015). Further, the variable for NRA used in the analysis was for NRAs that fulfil all 6 functions. However, procurement may still occur from manufacturing countries with NRAs having less than the six functions (though this is not ideal nor recommended). Detailed information in regards to the number of functions fulfilled by each WHO member-country's NRA however was not publicly available; this research only had access to information identifying fully functional NRAs.

The ownership type, as a proxy for management structure, was a determining factor for export markets, both in terms of revenue size (Model 3) and percent market share

(Model 5). In particular, the results suggested that manufacturers with private status or have private sector involvement such as public-private partnerships have a greater chance of increasing their revenue and percent market share when competing in export markets. This is likely because of the stronger domestic interest and captive market that state-owned manufacturers would have over their private sector competitors, therefore private sector manufacturers may find export markets more attractive.

Health policy leadership in producing countries showed a high tendency for change (with an average of more than three health ministers across a five-year span). The number of Ministers of Health over the last five years as per Milstien et al. (1997) was found to be positively associated with revenue sizes in export markets (Models 3 and 5) but not global or domestic markets. Immunisation programs are normally run with a long-term perspective, where demand is driven by the size of birth cohorts, which do not change over short periods of times. Furthermore, the indicator used for stability of health policy (the number of ministers of health) may not be an accurate proxy. In many countries, the body that regulates and licenses vaccines, the NRA, is often independent from the Ministry of Health structure. Changes in NRA leadership might be a better proxy for vaccine policy stability that should be investigated in future studies.

Proportion of export sales, a proxy for market expansion strategy, was a significant factor in global revenue sizes and percent market share (Models 1 and 4), but not specifically in domestic or export markets. The effect of predominantly selling to export markets was negative, which suggests that having a strong domestic market presence is important in influencing viability.

4.4.1. Limitations

The study by Milstien et al. (1997) used primary data based on 13 country assessments, which provided more detail than the current study. However, the analysis in this chapter was at the vaccine product level, a more disaggregated level than the Milstien study.

In their study, Milstien et al. (1997) used the indicator ‘annual capital expenditure’ to represent production consistency. An attempt was made to include this in the current analysis by assessing capital productivity or capital intensity, which measures the capital intensity of a given industry. Capital productivity is a ratio obtained by dividing capital expenditure by total revenue for a given period (Sinclair et al., 2015), using gross fixed capital formation (GFCF) as a proxy for capital expenditure and manufacturing value added (MVA) for total revenue of the industry in question. These data were provided by the statistics team at UNIDO. However, there was insufficient data encompassing all vaccine producing countries observed. For this reason, capital productivity levels were not included as a representation of production consistency.

Though the data on vaccine doses sold were derived from WHO member states, the corresponding vaccine price data were used based on assumptions derived from the V3P database, and were not identifiable by procuring country. As the vaccine prices in the V3P database varied by transaction, weighted average prices were determined by vaccine product, income level of procuring country and vaccine procurement method, whether directly procured or through a UN procurement agency.

4.4.2. Conclusions

This study was designed to identify and assess the critical factors that influence vaccine production viability among DCVMs. Changes within the vaccine industry, stemming from advances in technological breakthrough and regulatory standards, pose challenges for manufacturers globally. These challenges are even greater for DCVMs, for which markets in developing countries are large in size yet low in fiscal space.

This study adopted a systematic method to evaluate viability of local vaccine producers that was first established by Milstien et al. (1997), and used an updated framework to investigate viability for specific vaccine market types. This was done by identifying revenue sizes and percent market share as proxies for viability at the vaccine product level. To my knowledge this is the first reported study that has used multivariable regression analyses to investigate the determinants of viability of local vaccine production in developing countries.

In general, the findings of this Chapter identified that vaccine viability factors influence a vaccine product's revenue size and market share. The analysis also found that vaccine viability are influenced by economies of scale and scope (surviving infants and number of vaccines), consistency of production, vaccine technology, supply sufficiency, credibility of vaccine quality (vaccine prequalification status), management structure of the company, and changes in health ministries. National income per capita and proportion of export to total sales were also found to be associated with vaccine production viability.

Revenue sizes were found to be influenced by national income levels, consistent production supplies and the ability to meet the needs of immunisation programs in procuring countries, whereas factors identified as influencing percentage of market share were: having consistent production, the ability to meet the needs of immunisation programs in procuring countries and having vaccines with prequalification status.

The data suggest a sharp contrast between DCVMs' market share domestic and export markets, and that production viability in domestic vaccine markets differ from its export markets. Though proxies for economies of scale and scope were determinant factors for global markets, only economies of scale (number of surviving infants) were confirmed to be associated with domestic revenue. In export markets, neither of these factors were influential in increasing revenue. However, we cannot establish whether these factors, because they were observed from the producing countries' perspective, were not influential in export markets. In fact, sufficient supply (observed for the procuring country) was shown to be significantly associated with export market share as well as other markets, indicating that economies of scale and scope may in fact be a determining factor in all three market types.

The findings also suggest that consistency in production is important in maintaining viability in domestic markets, and is even more important for DCVMs interested in venturing into export markets. This may be quite challenging given that various supply disruptions occur often in vaccine markets (Gurnani, Mehrotra, & Ray, 2012), (Batson et al., 2003). Further, the analysis suggests that establishing a strong domestic market prior to expanding globally.

The study indicates that DCVMs' viability in export markets may not be dependent on its technological capacity, however with the changing landscape of vaccine technology due to recent WHO recommendation in switching from more traditional types to safer and more advanced options, DCVMs need to enhance their ability in to produce higher technology type vaccines to maintain its domestic viability

The study also suggest that manufacturers with private status or have private sector involvement such as public-private partnerships have a greater chance of increasing their revenue and percent market share when competing in export markets. This is likely because of the stronger domestic interest and captive market that state-owned manufacturers would have over their private sector competitors, therefore private sector manufacturers may find export markets more attractive.

Chapter 5 A mixed-effects model of the association between procurement factors and prices of vaccines produced by developing countries

5.1. Introduction

Vaccines prices affect a country's decision on adopting a new vaccine into their immunisation program because of the cost implications for the procuring country. Evidence suggests that vaccine price is among the most important factors in determining access of countries to new vaccines (Kaiser, 2008; Munira & Fritzen, 2007; Shearer et al., 2010), however vaccine price transparency remains an issue that WHO argues is key in implementing the Global Vaccine Action Plan (GVAP).

Countries procuring vaccines directly from the manufacturer, as opposed to bulk procurement through an international agency, often do not have a way to know the current market price paid by other countries. Evidence has shown that the prices that countries have paid were not necessarily driven by their income status (Milstien et al., 2003). Milstien et al. (2003) measured the prices that different income level countries were paying for their Hepatitis B vaccine, which at the time was a NUV. They reported that prices middle income countries were paying were often above $1 per dose (which is around the UNICEF price level), and that many of these countries were paying prices at large range (US$0.4 to US$7.85[55]).

This situation of asymmetric information, which often exists in regards to vaccine prices, is defined as a situation where the different parties involved in a transaction do not have the same level of information, therefore making it difficult to achieve an optimal level of pricing that fulfils *Pareto Optimum* (Pindyck & Rubinfeld, 1989). Pareto

[55] Data based on member-country reporting to WHO in 2002.

optimum is an economic concept that defines an allocation to be optimal if no other allocation exists that can make one individual better-off without causing the other parties involved to be worse-off. By providing information to both procuring and producing countries, issues with asymmetric information can be overcome. In effort to increase transparency in prices and reduce the problem of asymmetric information, WHO has established the Vaccine Product, Price and Procurement (V3P) project.

Information is known to be an important economic factor, particularly when economic resources are scarce and in the presence of uncertainty (Stapleton & Nicholson, 1998). Having pricing information may determine the actions of the procurer in their decision to purchase vaccines given the resources/budgets that are available to them, and for manufacturers, their pricing behaviours will also determine how well they can recoup their investment and achieve viability in the vaccines market.

Vaccine pricing policies are often shaped by a complex set of factors. These can range from maximising profits right thought to signalling quality (especially if producer is new to market) or simply recovering costs. Some goals are set for the short-term and some for the long-term. An understanding of the factors that influence the setting of vaccine prices is also important. Knowledge of these factors will help explain how well DCVMs set prices given knowledge of costs, which is important in establishing how effective they are in recouping costs and ensuring profitability and viability. This is important in determining a manufacturer's ability to remain viable in the vaccine market.

This chapter aims to identify and quantify the effect of procurement factors on vaccine prices sold by developing country manufacturers. Though procurement factors is not a theoretical concept, it is defined as the terms and agreements made during a vaccine procurement between a vaccine manufacturer and its clientele. These factors are assumed to influence the pricing decision of vaccine manufacturers, and include but not limited to: size of procured volumes, presentation sizes and formulation types, income level of the consumer, procurement mechanisms used, product type and technology level, contract terms, and competition level. By gaining an understanding of how procurement factors influence vaccine pricing behaviour, this may allow manufacturers to organize themselves to ensure viability. Three outcome variables were investigated that includes all vaccine types as a well as by technology level, defined as traditional and modern vaccines. The findings will allow developing country vaccine producers to align their production plans according to the factors influencing their vaccine sales.

This chapter is organised as follows: a description of the variables used in the analysis along with the econometric methods are presented in section 5.2. Section 5.3 presents the results of the regression model of the association between procurement factors and vaccine prices sold by developing countries, followed by a discussion, summary, study limitations and conclusions in section 5.4.

5.2. Methods

5.2.1. DCVM vaccine prices

Price-per-dose data, self-reported by procuring countries, were obtained from the V3P project. This is the most complete dataset on vaccines prices to date. A subset of the dataset, including prices of vaccines produced by DCVMs for all vaccines sold to immunisation programmes globally as reported to WHO, from 2005 to 2015, was used in the analyses.

5.2.2. Explanatory variables

The following explanatory variables were used in the analysis:

- *Volume:* number of vaccine doses procured in each transaction;
- *UN Procurement*: whether vaccine procurement was facilitated by a UN procuring agency such as UNICEF and PAHO;

- *Contract*: the different contract lengths that may have been arranged, if any, between the vaccine manufacturer and procurer. It was hypothesised that the longer the contract length, the more secure was the demand for the vaccines, resulting in a decreased price;
- *Formulation:* formulation presentation of the vaccine. This included categories such as multi-dose vials, single-dose vials, prefilled syringes and lyophilised vaccines;
- *Formulation size*: the number of doses in the formulation presentation, mostly applicable to vial formulations;
- *Vaccine category:* the different technology categories of the vaccine (i.e.: bacterial, viral, combination, conjugate and recombinant vaccines);
- *Vaccine technology:* the level of new technology accessed by the manufacturer for the vaccine. Vaccines were categorised by traditional and modern vaccines based on WHO and GAVI's classification of vaccine priorities and market-shaping strategies for developing countries[56]. The first category, traditional vaccines, included those introduced through the initial EPI program, prior to GAVI's establishment. All other vaccines were categorised as modern vaccines;
- *Income group (procurer)*: national income level of the purchasing country, based on the World Bank country classification and income thresholds (see Appendix 1 in Chapter 2);
- *Income group (producer)*: national income level of the producing country, based on the World Bank country classification and income thresholds (see Appendix 1 in Chapter 2);
- *Number of prequalified substitutes*: number of competing products. This was the sum of similar vaccine products produced by different manufacturers, plus

[56] Phase I (2000-06), Phase II (2007-10), Phase III (2011-15) and Phase IV (2016-20), please refer to: http://www.gavi.org/about/strategy/

vaccine products by the same manufacturer that were prequalified and had different formulation presentation. Vaccine products that may have the same antigens, for instance Hepatitis B and DTP-HepB, were not considered substitutes because different countries have different preferences in regards to specific antigens that suit their population and epidemiological conditions (Jarrett, 2008; Pauly & Cleff, 1996).

More detail on the variables assessed as procurement factors in influencing vaccine prices of developing countries are provided in Tables 5.4 and 5.5.

5.2.3. Statistical analysis

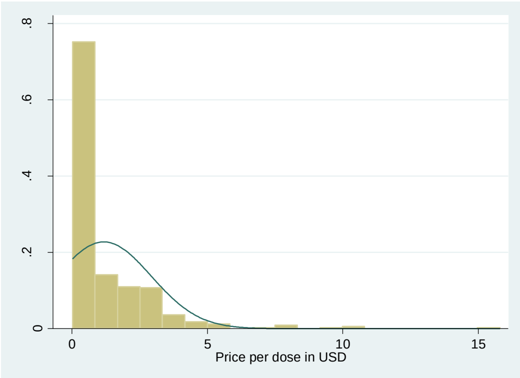
The outcome data were grouped at multiple levels (unit, vaccine, manufacturer, country and year) but not nested (i.e. groups at different levels sat across groups at other levels, for example manufacturer A sold vaccine X to a number of different countries in year Y; these transactions are treated as different data points). Three outcome variables were modelled:

- Price per dose for all vaccines (Model 1)
- Price per dose for traditional vaccines (Model 2)
- Price per dose for modern vaccines (Model 3)

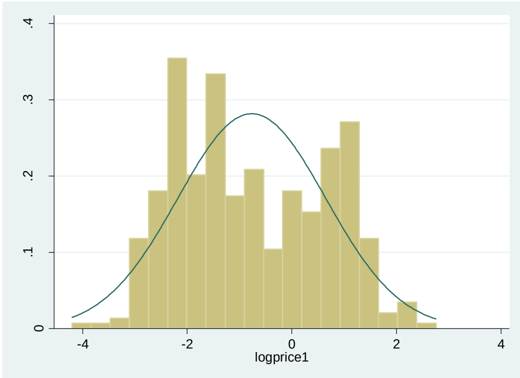
Linear regression models were applied given that the outcome variables were continuous variables. These outcome variables were log transformed to ensure a near-normal distribution, due to the skewness of the data. Volume (i.e. number of doses produced), one of the explanatory variables, was also log transformed. The normal and logarithmic transformation for price and volume data can be seen in Figure 5.1. Graph (1b) in Figure 5.1 shows that the log transformed data for vaccine prices has a bimodal distribution[57]. The subsequent graphs (2b) and (3b) in Figure 5.1 show the log

[57] A bimodal distribution is a continuous probability distribution with two different modes, usually appears as distinct peaks.

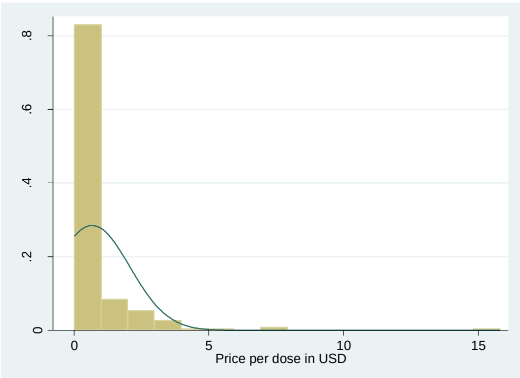
transformed vaccine prices for the different technology types (traditional and modern vaccine) which account for the bimodality distribution in the overall vaccine data.



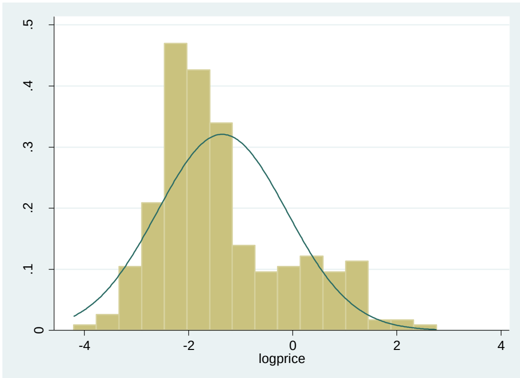
(1a)



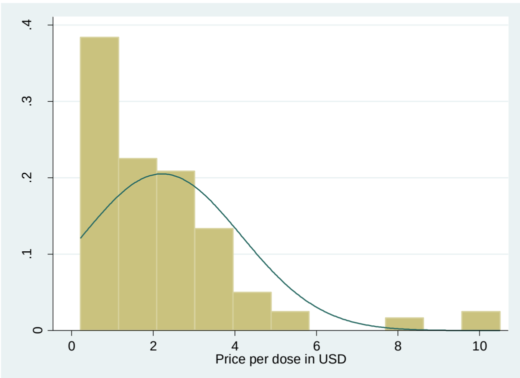
(1b)



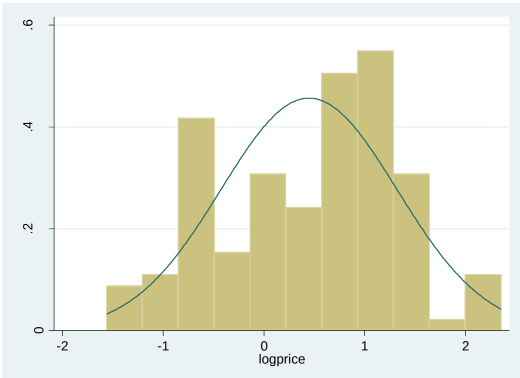
(2a)



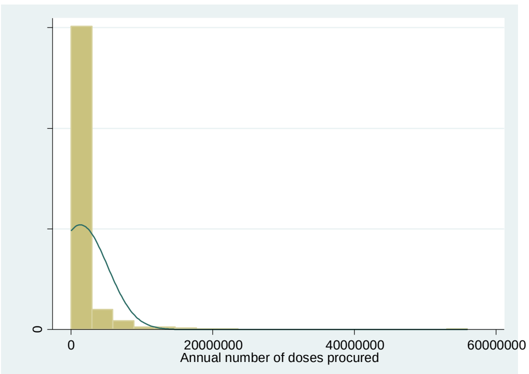
(2b)



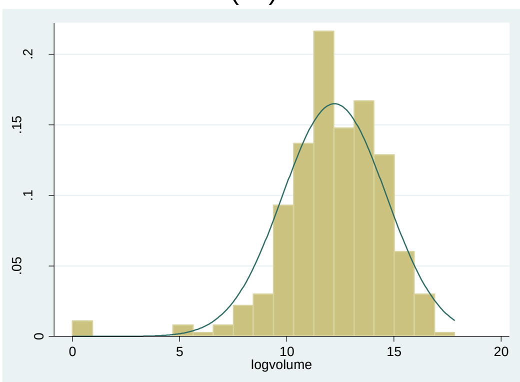
(3a)



(3b)



(4a)



(4b)

Figure 5.1. Logarithmic transformations of outcome and explanatory variables for vaccines produced by developing country manufacturers. Note: (1a) price of all vaccines; (1b) price of all vaccines – log transformed; (2a) price of traditional vaccines; (2b) price of traditional vaccines – log transformed; (3a) price of modern vaccines; (3b) price of modern vaccines – log transformed; (4a) volume of all vaccine transactions; (4b) volume of all vaccine transactions – log transformed.

Data were imported to STATA 14.0 (Stata Corporation, College Station, Texas) where each observation was linked to its corresponding vaccine type-, manufacturer- and country level explanatory variable. In building the model, a univariate analysis was conducted, where a high significance threshold of $P>0.2$ was used for selecting variables for subsequent multivariate analysis, to avoid potential exclusions of false positives (Table 5.1). Multicollinearity was investigated using Pearson's pairwise correlation coefficients (Table 5.2). No pairs of explanatory variables had a correlation coefficient of $>|0.6|$ and thus no variables were excluded due to multicollinearity. Heteroscedasticity was also tested using Breusch-Pagan / Cook-Weisberg (Table 5.3).

Multivariable mixed-effect linear regression models were developed using a backward stepwise variable selection method, with transaction, vaccine type, manufacturer and country level random effects to account for clustering. Variables were excluded from the model if they exceeded the threshold of $P\leq0.2$.

Table 5.1. Univariate regression of factors associated with price per dose of vaccines produced by developing country manufacturers

Explanatory variable	Model 1 (n=284)			Model 2 (n=177)			Model 3 (n=107)		
	β	(95% CI)	P	β	(95% CI)	P	β	(95% CI)	P
Constant	-0.77			-1.13			0.45		
Volume (log)	-0.14	-0.20 - -0.08	0.000*	-1.65	-1.89 - -1.42	0.000*	-0.36	-0.66 - -0.06	0.019*
UN Procurement	-1.32	-1.57 - -1.07	0.000*	-1.57	-1.81 -1.34	0.000*	-0.32	-0.61 -0.04	0.027*
Contract	-0.06	-0.15 – 0.02	0.138*	-0.09	-0.18 – 0.01	0.055*	-0.05	-0.14 - 0.03	0.237*
Formulation type	0.45	0.30 – 0.59	0.000*	0.19	0.01 - 0.36	0.037*	0.33	0.19 - 0.47	0.000*
Formulation size	-0.16	-0.17 - -0.14	0.000*	-0.12	-0.14 -0.09	0.000*	-0.11	-0.14 - -0.08	0.000*
Vaccine technology									
Bacterial	-1.57	-1.82 - -1.33	0.000*	-0.73	-1.16 - -0.30	0.001*	-0.02	-0.75 - 0.70	0.949
Viral	1.54	1.24 - 1.84	0.000*	0.73	0.30 - 1.16	0.001*	0.40	-0.28 - 1.07	0.245
Combination	1.83	1.48 - 2.18	0.000*	–	–	–	0.01	-0.66 – 0.68	0.970
Conjugate	1.15	-1.18 – 3.48	0.333	–	–	–	-0.67	-2.35 – 1.01	0.433
Recombinant	0.98	0.43 – 1.54	0.001*	–	–	–	-0.83	-1.56 - -0.11	0.025*
Income level (Producing country)	0.14	-0.14 – 0.43	0.334	0.54	0.27 - 0.81	0.000*	0.75	0.29 - 1.21	0.002*
Income level (Procuring country)	0.73	0.54 - 0.94	0.000*	0.88	0.67 - 1.09	0.000*	0.56	0.36 - 0.75	0.000*
Number of PQ substitutes	0.04	0.01 – 0.71	0.009*	-0.03	-0.09 - 0.02	0.193*	0.05	0.03 - 0.071	0.000*

*: p-value ≤ 0.2. Note: *Model 1*: Price per dose for all vaccines; *Model 2*: Price per dose for all traditional vaccines; *Model 3*: Price per dose for modern vaccines.

Table 5.2. Correlation matrix of explanatory variables associated with price per dose of vaccines produced by developing country manufacturers

	Volume (log)	*UN Procurement*	*Contract*	*Formulation type*	*Formulation size*	*Vaccine technology*	*Income level (Producing country)*	*Income level (Procuring country)*	*Number of PQ substitutes*
Volume (log)	1.000								
UN Procurement	0.260	1.000							
Contract	0.158	0.225	1.000						
Formulation type	- 0.030	- 0.082	- 0.051	1.000					
Formulation size	0.207	0.199	- 0.049	- 0.347	1.000				
Vaccine technology	0.083	- 0.043	0.084	0.184	- 0.508	1.000			
Income level (Producing country)	- 0.267	- 0.270	- 0.104	0.215	- 0.032	- 0.246	1.000		
Income level (Procuring country)	- 0.578	- 0.424	- 0.278	0.155	- 0.253	- 0.061	0.320	1.000	
Number of PQ substitutes	0.005	0.141	0.111	0.046	- 0.184	- 0.052	- 0.033	- 0.037	1.000

Note: None of the correlation estimations exceeded the correlation coefficient threshold of |0.6|, therefore there are no observed multicollinearity in the model

Table 5.3. Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

Ho	*Constant variance*
Variables	fitted values of logprice
chi2(1)	0.04
Prob > chi2	0.8373

Note: the test statistic has a p-value above 0.05, therefore the null hypothesis of homoscedasticity cannot be rejected.

The form of the mixed-effects multivariate regression models were:

Model 1 (Price per dose for all vaccines):

$$\boldsymbol{Log(VP_{ijkt}) = \beta_{0ijklt} + \beta_{1jkl}Volume_{ijklt} + \beta_2 UNProc_{ijklt} + \beta_3 Formulae_{jkl} + \beta_4 Formulation\ size_{jkl} + \beta_5 VxCat_{jkl} + \beta_6 VxTech_{ijk} + \beta_8 WBcat_{ijkl} + \beta_9 ManufWBcat_{klt} + \beta_{10} Subst_{jkt} + \varepsilon_{ijklt}}$$

Equation 5.1

Model 2 (Price per dose for traditional vaccines):

$$\boldsymbol{Log(VP_{ijkt}) = \beta_{0ijklt} + \beta_{1jkl}Volume_{ijklt} + \beta_2 UNProc_{ijklt} + \beta_4 Formulation\ size_{jkl} + \beta_5 VxCat_{jkl} + \beta_8 WBcat_{ijkl} + \beta_9 ManufWBcat_{klt} + \beta_{10} Subst_{jkt} + \varepsilon_{ijklt}}$$

Equation 5.2

Model 3 Price per dose for modern vaccines:

$$\boldsymbol{Log(VP_{ijkt}) = \beta_{0ijklt} + \beta_{1jkl}Volume_{ijklt} + \beta_2 UNProc_{ijklt} + \beta_4 Formulation\ size_{jkl} + \beta_5 VxCat_{jkl} + \beta_9 ManufWBcat_{klt} + \beta_{10} Subst_{jkt} + \varepsilon_{ijklt}}$$

Equation 5.3

Where:

- VP_{ijkt}, the outcome variable, is vaccine price per dose in unit *i*, vaccine *j*, manufacturer *k*, country *l* and year *t*;
- $Volume_{ijklt}$, is volume level (in number of doses), in log form;
- $UNProc_{ijklt}$, is the mechanism in which the vaccine is procured (direct or bulk procurement);
- $Contract_{ijklt}$, is the number of years of the contract between the procuring entity and manufacturer;
- $Formulae_{jkl}$, is the category of the vaccine presentation, with 6 categories (1=capsule/tube; 2=multi-dose vial; 3=single-dose vial; 4=prefilled syringe; 5= lyophilised; 6=prefilled syringe and lyophilised);
- $Formulation\ size_{jkl}$, is the size of the vaccine presentation;

- $VxCat_{ijk}$, is vaccine technology category, with four categories (1=bacterial; 2=viral; 3=combination; 4=conjugate; 5=recombinant)
- $VxTech_{ijk}$, is vaccine technology level from a developing country perspective[58], with two categories (0=Traditional EPI vaccines; 1=Modern NUV vaccines);
- $WBcat_{ijkl}$, is the vaccine procurer's income level, with four categories as defined by the World Bank (1=low income, 2=lower middle income, 3=upper middle income, 4=high income)
- $ManufWBcat_{klt}$, is the manufacturer country's income level, with four categories as defined by the World Bank (1=low income, 2=lower middle income, 3=upper middle income, 4=high income)
- $Subst_{jkt}$, is the number of manufacturers of the same vaccine that have prequalification.

The level of significance for this mixed-effect linear regression was set at $p \leq 0.05$.

5.3. Results

5.3.1. Descriptive analysis

Tables 5.4 and 5.5 show the summary statistics for the dataset used in this chapter. The dataset used in the analysis contained 392 observations, including vaccine price information from 43 procuring countries in all 5 WHO regions. Among countries that reported their procurement prices, one country was a low income country, 18 were lower-middle income countries, 17 were upper-middle income countries and seven were high income countries. These procurements were for 25 different vaccine types produced by 20 different manufacturers, from 8 different producing countries.

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[58] See section 4.2.2. in chapter 4, under '3.New technology'.

Table 5.4 Summary and definition of outcome and explanatory variables of factors associated with price per dose of vaccines produced by developing country manufacturers.

Variable	Definition	Mean (Standard Deviation)												Data source	Last accessed
		2005 - 2015	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015		
Price-per-dose (US$)	Price of vaccine procured, presented in dose scale	1.17 (1.75) N=392	0.09 (0.05) N=3	0.11 (0.06) N=8	0.14 (0.07) N=6	0.08 (0.04) N=3	0.04 (0.08) N=4	0.90 (1.33) N=5	1.49 (1.97) N=5	0.77 (1.03) N=4	0.77 (1.05) N=46	1.51 (2.31) N=119	1.20 (1.54) N=189	V3P database (WHO)	20/11/2016
Volume (million doses)	Number of doses procured in each transaction	511.76 (75.91) N=392	16.9 (8.66) N=3	1.90 (0.43) N=8	35.98 (11.62) N=6	14.60 (12.02) N=3	4.72 (2.26) N=4	1.76 (0.32) N=5	1.50 (0.27) N=5	2.50 (0.53) N=4	37.18 (16.47) N=46	105.23 (25.12) N=119	289.49 (65.78) N=189	V3P database (WHO)	20/11/2016
Revenue ($ million)	Number of procured vaccine doses multiplied by price per dose	389.88 (105.61) N=392	1.53 (0.83) N=3	0.23 (0.07) N=8	5.18 (2.12) N=6	1.82 (1.67) N=3	0.35 (0.14) N=4	1.95 (1.52) N=5	1.80 (0.96) N=5	1.81 (1.01) N=4	28.61 (15.09) N=46	86.81 (21.91) N=119	259.78 (102.05) N=189	V3P database (WHO)	20/11/2016
No. of PQ substitutes	Number of competing products. Vaccine substitutes are the number of similar vaccine products produced by different manufacturers, with prequalification status.	8.50 (4.83) N=357	6.67 (1.15) N=3	6.13 (2.30) N=8	6.13 (3.27) N=6	5.33 (0.58) N=3	7.25 (3.86) N=4	7.80 (3.11) N=5	8.60 (2.70) N=5	10.75 (3.50) N=4	7.14 (3.25) N=37	8.86 (5.33) N=105	8.84 (5.05) N=117	List of prequalified vaccines (WHO)	20/11/2016

Table 5.5 Summary and definition of categorical explanatory variables of factors associated with price per dose of vaccines produced by developing country manufacturers.

Variable	Definition	Indicator	2005 - 2015		2005		2006		2007		2008		2009		2010		2011		2012		2013		2014		2015	
			N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Procurement mechanism	Whether vaccine was procured directly from manufacturer or through procurement agency, such as UNICEF, PAHO and GAVI.	UN Procurement	220/392	56.12	3/3	100	8/8	100	6/6	100	3/3	100	4/4	100	5/5	100	5/5	100	4/4	100	26/46	56.52	57/119	47.90	99/189	52.38
		Self-Procurement	169/392	43.11	0/3	0	0/8	0	0/6	0	0/3	0	0/4	0	0/5	0	0/5	0	0/4	0	20/46	43.48	61/119	51.26	88/189	46.56
		Other	3/392	0.77	0/3	0	0/8	0	0/6	0	0/3	0	0/4	0	0/5	0	0/5	0	0/4	0	0/246	0	1/119	0.84	2/189	1.06
Contract	Identifies the different contract lengths that may have been arranged, if any, between the vaccine manufacturer and procurer.	Single delivery	47/323	14.55	0/3	0	0/8	0	0/6	0	0/3	0	0/4	0	0/5	0	0/5	0	0/4	0	0/3	0	15/105	14.29	32/177	18.08
		Contractual	276/323	85.45	3/3	100	8/8	100	6/6	100	3/3	100	4/4	100	5/5	100	5/5	100	4/4	100	3/3	100	90/105	85.71	145/177	81.92
Formulation	Formulation presentation of vaccine	Multi-dose vial	290/392	73.98	3/3	100	7/8	87.50	6/6	100	2/3	66.67	3/4	75.00	3/5	60.00	5/5	100	4/4	100	34/46	73.91	80/119	67.23	143/189	75.66
		Single-dose vial	59/392	15.05	0/3	0	0/8	0	0/6	0	0/3	0	0/4	0	1/5	20.00	0/5	0	0/4	0	6/46	13.04	23/119	19.33	29/189	15.34
		Prefilled syringe	4/392	1.02	0/3	0	0/8	0	0/6	0	0/3	0	0/4	0	0/5	0	0/5	0	0/4	0	0/46	0	3/119	2.52	1/189	0.53
		Lyophilised	39/392	9.95	0/3	0	1/8	12.50	0/6	0	1/3	33.33	1/4	25.00	1	20.00	/5	0	0/4	0	6/46	13.04	13/119	10.92	16/189	8.47
Vaccine Category	Identifies the different technology categories of the vaccine (i.e.: bacterial, viral, combination, conjugate and recombinant)	Bacterial vaccines	220/392	56.12	2/3	66.67	4/8	50.00	3/6	50.00	3/3	100	4/4	100	2/5	40.00	2/5	40.00	1/4	25.00	34/46	73.91	68/119	57.14	97/189	51.32
		Viral vaccines	97/392	24.74	1/3	33.33	3/8	37.50	2/6	33.33	0/3	0	0/4	0	2/5	40.00	2/5	40.00	2/4	50.00	8/46	17.39	25/119	21.01	52/189	27.51
		Combination vaccines	55/392	14.03	0/3	0	0/8	0	0/6	0	0/3	0	0/4	0	1/5	20.00	1/5	20.00	1/4	25.00	3/46	6.52	19/119	15.97	30/189	15.87
		Conjugate vaccines	1/392	0.26	0/3	0	0/8	0	0/6	0	0/3	0	0/4	0	0/5	0	0/5	0	0/4	0	0/46	0	0/119	0	1/189	0.53
		Recombinant vaccines	19/392	4.85	0/3	0	1/8	12.50	1/6	16.67	0/3	0	0/4	0	0/5	0	0/5	0	0/4	0	1/46	2.17	7/119	5.88	9/189	4.76

Vaccine technology type	Identifies level of new technology accessed by the manufacturer for the vaccine.	Traditional vaccine	264/392	67.35	3/3	100	7/8	87.50	5/6	83.33	3/3	100	4/4	100	3/5	60.00	3/5	60.00	2/4	50.00	36/46	76.09	79/119	66.39	120/189	63.49
		NUVs	128/392	32.65	0/3	0	1/8	12.50	1/6	16.67	0/3	0	0/4	0	2/5	40.00	2/5	40.00	2/4	50.00	11/46	23.91	40/119	33.61	69/189	36.51
Income group – Procuring country	National income per capita of the procuring and the purchasing country, based on the World Bank country classification and income thresholds	LIC	8/392	2.04	0/3	0	0/8	0	0/6	0	0/3	0	0/4	0	0/5	0	0/5	0	0/4	0	0/46	0	0/119	0	8/189	4.23
		LMIC	204/392	52.04	3/3	100	8/8	100	6/6	100	3/3	100	4/4	100	5/5	100	5/5	100	4/4	100	25/46	54.35	52/119	43.70	89/189	47.09
		UMIC	153/392	39.03	0/3	0	0/8	0	0/6	0	0/3	0	0/4	0	0/5	0	0/5	0	0/4	0	21/46	45.65	56/119	47.06	76/189	40.21
		HIC	27/392	6.89	0/3	0	0/8	0	0/6	0	0/3	0	0/4	0	0/5	0	0/5	0	0/4	0	0/46	0	11/119	9.24	16/189	8.47
Income group – Producing Countries	National income per capita of the procuring and the purchasing country, based on the World Bank country classification and income thresholds	LIC	10/392	2.55	3/3	100	7/8	87.50	0/6	0	0/3	0	0/4	0	0/5	0	0/5	0	0/4	0	0/46	0	0/119	0	0/189	0
		LMIC	270/392	68.88	0/3	0	1/8	12.50	6/6	100	2/3	66.67	3/4	75.00	5/5	100	5/5	100	4/4	100	27/46	58.70	85/119	71.43	133/189	70.37
		UMIC	112/392	28.57	0/3	0	0/8	0	0/6	0	1/3	33.33	1/4	25.00	0/5	0	0/5	0	0/4	0	19/46	41.30	34/119	28.57	56/189	29.63

Note: Data as reported by V3P participating country members to WHO (2005 – 2015); Last accessed: 20/11/2016.

The data accounted for 512 million doses of vaccines and total revenue of approximately US$390 million. The weighted average price of vaccines procured from DCVMs was less than $1 per dose[59], ranging from US$0.01 to US$15.80 (Table 5.6). By contrast, the weighted average price of vaccines for all manufacturers as reported to WHO was $ 3.67[60]. Whilst the data were reported from 2005 to 2015, 92.5% of the responses were from 2013 to 2015 (Table 5.7).

In regards to the income levels of the producing countries, 68.9% of producers in the dataset were lower-middle income countries, while 28.6% were upper-middle income countries and less than 3% were low-income countries. The details of data description are presented in Tables 5.4 and 5.5. Results of the univariate analyses are shown in Table 5.8.

Table 5.6. Summary of vaccine prices-per-dose sold by developing country vaccine manufacturers to V3P participating countries.

Vaccine	Weighted average price per dose (US$)	Minimum price per dose (US$)	Maximum price per dose (US$)	Number of observations
BCG	0.50	0.03	3.55	67
DT-IPV	0.92	8.09	8.09	1
DTwP	0.26	0.09	3.14	43
DTwP-HepB	0.36	3.20	3.20	1
DTwP-Hib	1.24	1.24	2.80	2
DTwP-Hib-HepB	0.37	1.19	5.10	34
Cholera	0.51	0.47	0.47	1
HepB Adult	1.21	0.21	3.80	7
HepB Pediatric	2.68	0.22	1.96	12
Hib	6.02	0.78	0.78	1
Influenza Adult	2.23	1.97	10.40	5
IPV	0.12	1.89	3.36	7
JE Inactd	0.88	0.50	1.50	2
JE LiveAtd	4.45	0.42	10.50	5
DT	1.80	0.11	7.58	32
Measles	3.06	0.14	4.46	29
MMR	0.53	0.50	4.50	27
MR	0.48	0.52	1.73	19
Rabies	8.49	2.86	15.80	4
Rubella	8.29	8.29	8.29	1
Td	0.29	0.01	2.07	34
TT	0.52	0.03	2.55	38

[59] Weighted average price for all observations is approximately $ 0.76
[60] Based on observation of full V3P dataset, which includes vaccine producers from both developing countries and industrialised countries, as presented in Chapter 2, sub-section 2.8.1 and Table 2.3

Typhoid	10.66	0.49	4.22	3
bOPV1,3	0.02	0.13	0.26	4
tOPV	0.37	0.09	2.79	13
Total Average	**0.76**	**0.01**	**15.80**	**392**

Source: Data based on vaccine prices reported to V3P, WHO (2005 – 2015)

Table 5.7. Average vaccine revenue based on sales of vaccines produced by developing country vaccine that were reported by V3P participating countries to WHO during 2005 – 2015 (US$ million)

YEAR	MEAN	STD.DEV	NO. OF OBSERVATIONS
2005 - 2015	389.88	105.61	392
2005	1.53	0.83	3
2006	0.23	0.07	8
2007	5.18	2.12	6
2008	1.82	1.67	3
2009	0.35	0.14	4
2010	1.95	1.52	5
2011	1.8	0.96	5
2012	1.81	1.01	4
2013	28.61	15.09	46
2014	86.81	21.91	119
2015	259.78	102.05	189

Table 5.8. Univariate regression of factors associated with price per dose of vaccines produced by developing country manufacturers

Explanatory variable	***Model 1 (n=284)***			***Model 2 (n=177)***			***Model 3 (n=107)***		
	β	**(95% CI)**	**P**	**β**	**(95% CI)**	**P**	**β**	**(95% CI)**	**P**
Constant	-0.77			-1.13			0.45		
Volume (log)	-0.14	-0.20 - -0.08	0.000*	-1.65	-1.89 - -1.42	0.000*	-0.36	-0.66 - -0.06	0.019*
UN Procurement	-1.32	-1.57 - -1.07	0.000*	-1.57	-1.81 -1.34	0.000*	-0.32	-0.61 -0.04	0.027*
Contract	-0.06	-0.15 – 0.02	0.138*	-0.09	-0.18 – 0.01	0.055*	-0.05	-0.14 - 0.03	0.237*
Formulation type	0.45	0.30 – 0.59	0.000*	0.19	0.01 - 0.36	0.037*	0.33	0.19 - 0.47	0.000*
Formulation size	-0.16	-0.17 - -0.14	0.000*	-0.12	-0.14 -0.09	0.000*	-0.11	-0.14 - -0.08	0.000*
Vaccine technology									
Bacterial	-1.57	-1.82 - -1.33	0.000*	-0.73	-1.16 - -0.30	0.001*	-0.02	-0.75 - 0.70	0.949
Viral	1.54	1.24 - 1.84	0.000*	0.73	0.30 - 1.16	0.001*	0.40	-0.28 - 1.07	0.245
Combination	1.83	1.48 - 2.18	0.000*	–	–	–	0.01	-0.66 – 0.68	0.970
Conjugate	1.15	-1.18 – 3.48	0.333	–	–	–	-0.67	-2.35 – 1.01	0.433
Recombinant	0.98	0.43 – 1.54	0.001*	–	–	–	-0.83	-1.56 - -0.11	0.025*
Income level (Producing country)	0.14	-0.14 – 0.43	0.334	0.54	0.27 - 0.81	0.000*	0.75	0.29 - 1.21	0.002*
Income level (Procuring country)	0.73	0.54 - 0.94	0.000*	0.88	0.67 - 1.09	0.000*	0.56	0.36 - 0.75	0.000*
Number of PQ substitutes	0.04	0.01 – 0.71	0.009*	-0.03	-0.09 - 0.02	0.193*	0.05	0.03 - 0.071	0.000*

*: p-value ≤ 0.2. Note: *Model 1*: Price per dose for all vaccines; *Model 2*: Price per dose for all traditional vaccines; *Model 3*: Price per dose for modern vaccines.

5.3.2. Mixed-effects regression model

Determinants of DCVM vaccine prices: overall

Model 1 identified that a one percent increase in volumes of vaccines procured was associated with a 0.06% decrease in overall DCVM vaccine prices. Lower vaccine prices were also associated with a one-unit increase in the following factors: UN procurement method (44%[61]), vaccine formulation sizes (6%), bacterial vaccines (80%) and prequalified vaccine substitute (1%). By contrast, the following factors were associated with higher vaccine prices: NUVs (24%), viral vaccines (93%), combination vaccines (131%) and higher income level procuring countries (49%). Formulation presentation types, conjugate and recombinant vaccines and the income level of the producing country were not associated with DCVM vaccine prices.

Determinants of vaccine prices: traditional vaccines

For traditional vaccine types, Model 2 found that lower prices were associated with the following factors: UN procurement method (71%), larger formulation sizes (6%), bacterial vaccine types (75%), and number of prequalified vaccine substitutes (4%). By contrast, the following factors were associated with increase in modern DCVM vaccine prices: viral vaccines (75%), higher income level of producing country (20%) and higher income level of procuring country (51%).

Determinants of vaccine prices: new and underused vaccines.

For modern vaccines, Model 3 found that a one-percent increase in the log of volume of vaccines procured was associated with a 0.1% decrease in DCVM vaccine prices. Lower vaccine prices were also associated with larger formulation size (5%) and the recombinant vaccine category (106%). By contrast, vaccine prices increased in

[61] Values in parentheses indicate the percentage change in the outcome variable –log(price per dose) for a one unit change in the explanatory variable

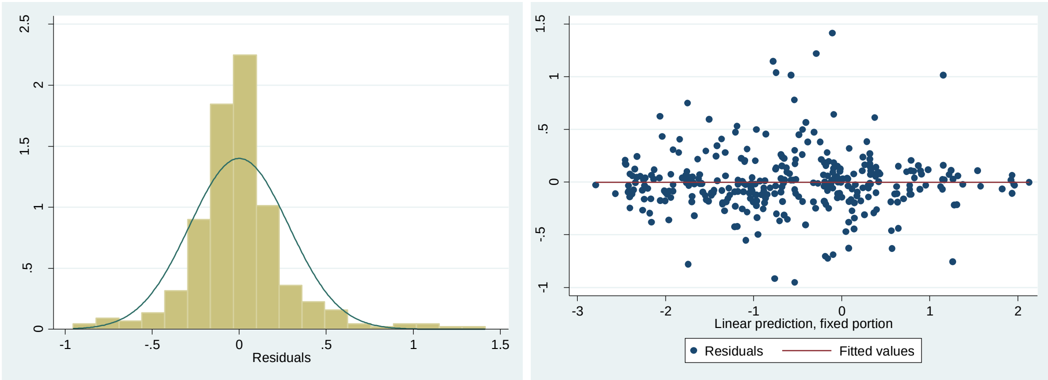
association with a producing country's income level (51%) and prequalified vaccine substitutes (4%).

The mixed-effects regression models are presented in Table 5.9, while post-estimation tests on the residuals were performed for each model and presented in Figures 5.2 – 5.4. The residuals show a normal distribution and there is little to suggest violation of the normality assumption.

Table 5.9. Multivariate mixed-effect linear regression of factors associated with price-per-dose of vaccines produced by developing country vaccine manufacturers

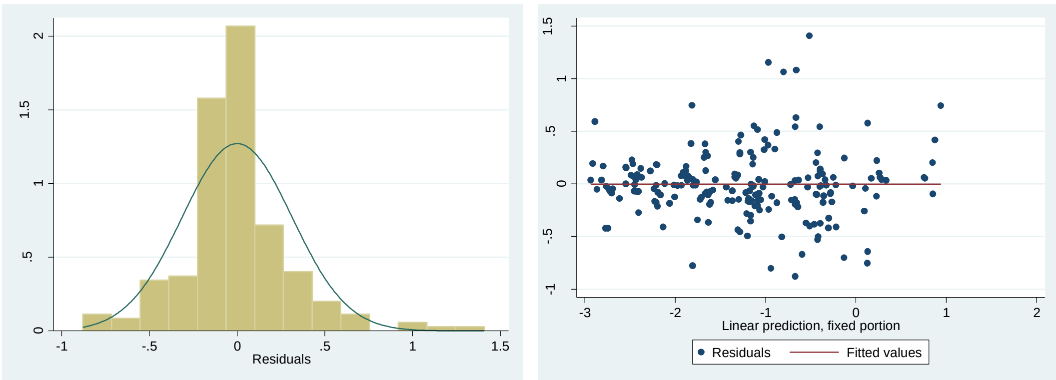
EXPLANATORY VARIABLE	MODEL 1 (N=338)			MODEL 2 (N=213)			MODEL 3 (N=125)		
	β	(95% CI)	P	β	(95% CI)	P	β	(95% CI)	P
Constant	-1.17			-1.14			0.57		
Volume (log)	**-0.06**	**-0.10 - -0.02**	**0.007****	-0.04	-0.09 – 0.02	0.187	**-0.10**	**-0.16 - -0.05**	**0.000*****
UN Procurement	**-0.44**	**-0.67 - -0.21**	**0.000****	**-0.71**	**-1.03 - -0.38**	**0.000*****	-0.19	-0.41 – 0.03	0.089
Contract	–	–	–	–	–	–	–	–	–
Formulation type	-0.01	-0.08 - 0.06	0.782	–	–	–	–	–	–
Formulation size	**-0.06**	**-.074 - -0.04**	**0.000*****	**-0.06**	**-0.08 - -0.042**	**0.000*****	**-0.05**	**-0.08 - -0.03**	**0.000*****
Vaccine category									
Bacterial	**-0.80**	**-1.10 – -0.49**	**0.000*****	**-0.75**	**-1.10 - -0.41**	**0.000*****	0.48	-0.07 – 1.3	0.087
Viral	**0.93**	**0.39 - 0.97**	**0.000*****	**0.75**	**0.41 - 1.10**	**0.000*****	0.02	-0.45 – 0.50	0.942
Combination	**1.31**	**0.25 - 1.11**	**0.000*****	–	–	–	-0.15	-0.64 – 0.34	0.533
Conjugate	-0.04	-2.07 - 0.59	0.960	–	–	–	-0.98	-1.98 – 0.03	0.056
Recombinant	-0.09	-1.52 - -0.50	0.719	–	–	–	**-1.06**	**-1.54 - -0.59**	**0.000*****
Vaccine technology	**0.24**	**0.83 - 1.51**	**0.001*****	–	–	–	–	–	–
Income level (Producing country)	0.12	-0.04 - 0.30	0.184	**0.20**	**0.00 – 0.41**	**0.034***	**0.51**	**0.13 – 0.90**	**0.009****
Income level (Procuring country)	**0.49**	**0.19 - 0.76**	**0.001*****	**0.51**	**0.15 - 0.87**	**0.005****	0.15	-0.05 – 0.36	0.130
Number of PQ substitutes	-0.01	-0.025 - 0.02	0.556	**-0.04**	**-0.08 – 0.01**	**0.014***	**0.04**	**0.02 – 0.06**	**0.000*****
Random effects	**Variance**	**(95% CI)**		**Variance**	**(95% CI)**		**Variance**	**(95% CI)**	
Procuring country (Level 1)	0.45	0.31 – 0.67		0.59	0.42 – 0.84		0.01	0.00 – 1.13	
Vaccine (Level 2)	0.56	0.47 – 0.67		0.46	0.35 – 0.61		0.09	0.03 – 0.24	
Manufacturer (Level 3)	0.00	0.00 – 0.00		0.00	0.00 – 0.00		0.00	0.00 – 0.00	
Residual	0.38	0.34 – 0.43		0.39	0.34 – 0.45		0.12	0.08 – 0.18	
Log-likelihood	-319.00			-191.29					

* p≤0.05; ** p≤0.01; *** p≤0.001; bold number: significant. Note: _Model 1_: Price per dose for all vaccines; _Model 2_: Price per dose for all traditional vaccines; _Model 3_: Price per dose for modern vaccines.



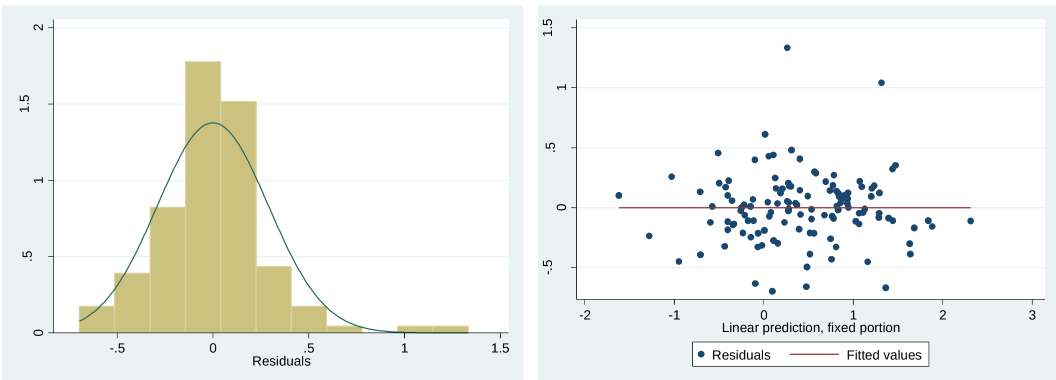
(a) **(b)**

Figure 5.2 Post-estimation tests on residuals of regression of factors associated with price per dose of overall vaccine types produced by developing country manufacturers (Model 1). Note: (a) frequency distribution of residual values; (b) residuals plotted against corresponding predicted values.



(a) **(b)**

Figure 5.3 Post-estimation tests on residuals of regression of factors associated with price per dose of traditional vaccines produced by developing country manufacturers (Model 2). Note: (a) frequency distribution of residual values; (b) residuals plotted against corresponding predicted values.



(a) **(b)**

Figure 5.4 Post-estimation tests on residuals of regression of factors associated with price per dose of modern vaccines produced by developing country manufacturers (Model 3). Note: (a) frequency distribution of residual values; (b) residuals plotted against corresponding predicted values.

5.4. Discussion

Prices of vaccines produced by DCVMs were found to be associated with the following procurement factors for all three vaccine markets observed (overall vaccines, traditional vaccines and modern vaccines): formulation sizes and number of prequalified vaccine substitutes. Formulation type, which was found to be a critical factor in vaccine production costs (Chapter 3 and 4), was not found to influence vaccine prices in this analysis.

Data for overall vaccines however, showed that the log transformed price per dose has a bimodal distribution. The different vaccine technology types seem to be accountable for this bimodality, suggesting that separating the observation by traditional and modern vaccines was correct. Though vaccines can be grouped into three different categories based on their market structure and characteristics (Table 2.1)[62], DCVMs mainly produce traditional vaccines and are expanding into NUVs (Jadhav et al., 2008). NUVs are often much more expensive than traditional vaccines and provide a higher incentive for manufacturers to invest given the increasing number of countries adopting new vaccines and the relatively low number of producers currently in the market (Burchett et al., 2012; Galambos, 2008).

Larger formulation sizes such as multi-dose vial vaccines, relative to single dose vaccines, can result in lower production costs and lower storage space, thereby allowing manufacturers to offer lower prices. The effect of presentation size was also found to be a factor in vaccine prices for manufacturers globally (including ICVMs) in the V3P report of the WHO (WHO, 2016c).

Competing vaccine products with prequalified status impose two issues for a vaccine manufacturer. One is that prequalified vaccines have access to larger vaccine markets

[62] As shown in Table 2.1 of Chapter 2, these categories are: traditional vaccines, NUVs and vaccines in development or also known as pipeline vaccines.

such as those represented by UNICEF, GAVI and PAHO. Second is that prequalified vaccines are usually the recommended and preferred choice for national immunisation programs (Dellepiane & Wood, 2015), particularly due to the assured quality and due diligence placed in the prequalification system. Competition in general, especially in imperfectly competitive markets such that of vaccines, tends to lower prices (Bulow, Geanakoplos, & Klemperer, 1985; Corts, 1998). A large part of the success gained by international health agencies such as GAVI has arisen due to the combined effects of competition and prequalified status in lowering vaccine prices and increasing access to NUVs for developing countries.

Volume of vaccine procured was noted as a significant factor influencing lower vaccine prices globally in the V3P report of the WHO (WHO, 2016c). Though the findings of the current analysis found that a 1% increase in procurement volumes was associated with a 0.06% reduction in prices for overall vaccines and a 0.1% reduction for modern vaccines, the analysis found that, for traditional EPI vaccines in particular, larger volume transactions were not associated with changes in price. This may be due to the fact that traditional vaccines have saturated markets and those produced by DCVMs in general are priced near to their marginal costs.

UN vaccine procurement implements a bulk purchase mechanism, thereby increasing leverage in negotiating prices with individual vaccine manufacturers and subsequently lowering vaccines prices (Berkley, 2014). UN vaccine procurement was found to be significantly associated with lower prices for overall and traditional DCVM vaccines, and was negatively but not significantly associated with prices of modern vaccines in the current analysis. The non-significant finding for modern vaccines could have arisen from DCVMs not yet securing prequalification status for modern vaccines, and thus not being affected by price-lowering effects of UN bulk procurement mechanisms.

Having longer-term contracts in place with procuring countries reduces uncertainty and transaction costs for DCVMs from having to conduct annual re-negotiations (WHO, 2016c). However, this study did not find contracts to be a determining factor in any of the three models observed. Over 50% of the DCVM transactions in this study had a one-year contract, and only 30% were on longer-term contracts, with the remaining having single-delivery arrangements. The large proportion of annual contracts in the study may explain why longer-term contracts did not have a significant impact on vaccine prices.

Another factor that was not found to be a determining factor for vaccine prices was the formulation presentation of a vaccine. Though formulation presentation was found to be a determining factor in production costs of vaccines (Chapter 3), the findings of the current analysis suggest that presentation is not considered by DCVMs as a factor in pricing their vaccines. This in part might stem from the fact that vaccine formulation presentations are often linked to particular requirements of immunisation programs in different countries, such a single-dose presentations being preferred by higher income countries (WHO, 2016c) and lyophilised formulations being preferred in high-temperature countries and those with challenges in sustaining cold-chain systems. Therefore, despite the existence of lower priced vaccine presentations, the particular demands of a country's immunisation programs may prevent different formulation presentations being substituted for each other. The data also showed that the majority (74%) of vaccine presentations in the dataset were multi-dose vial vaccines.

The categories of vaccine technology (e.g. bacterial, viral) as well as having more advanced technology, were found to be associated with prices of vaccines produced by DCVMs. Bacterial and recombinant type vaccines were found to have a lower price, whilst viral vaccines and combination vaccines were found to have higher prices. Vaccine production processes and its cost implications are dependent on the category of vaccine being produced (Mercer Managment Consulting, 2002). However, the dataset did not have enough variability between traditional and modern vaccines within the vaccine category types to generalise these findings.

Finally, procuring countries with higher incomes were associated with higher vaccine prices, both in general as well as for traditional vaccine types; whereas producing countries with higher income levels were associated with higher vaccine prices for traditional and modern vaccines. This may be a result of two phenomenon where: one, given the paradigm of vaccine manufacturers having invested their R&D funding for vaccines catered to the developed world (Milstien et al., 2006; Wilson & Jones, 2010), and two, the tiered pricing mechanisms devised to increase uptake of NUVs by developing countries. Given that vaccine price information is generally asymmetric, vaccine manufacturers may be seeking opportunities to recoup their investments particularly when involving higher income countries (WHO, 2016c),

The overall analysis on vaccine prices reflects a larger underlying question of how countries decide on their vaccine procurement. Factors contributing to a government's decision to introduce and procure a product are known to be complex. In addition to necessary factors such as product availability, disease burden, affordability, programmatic feasibility, and cost-effective studies, a government's decision is often also influenced by swing factors, such as WHO recommendations, regional policies, and the influence of public health champions, both locally and from the international community (Munira & Fritzen, 2007). Prices of vaccines produced by DCVMs differ from vaccines produced by other manufacturers given the different characteristics of the vaccines produced. DCVM vaccines are usually traditional vaccines with prices that are generally lower than those sold by multinational manufacturers.

5.4.1. Limitations

Through the V3P initiative, WHO is making an attempt to increase transparency in vaccine markets, particularly regarding vaccine prices paid by countries (WHO, 2016c).

The V3P dataset provides a subset of all vaccine transactions along with their prices and procurement terms and conditions, as provided by participating countries. In an attempt to confirm the data provided, WHO provides countries with a two-year period to report any necessary changes to the data they have provided. Because the data were a subset of all transactions, general assumptions regarding overall vaccine markets may be limited.

Given that the data does not include the entire number of vaccine transactions, competition among different vaccine types used the number of prequalified status competitors as a proxy. This indicator is justified because these would be strong competitors for manufacturers in general. Ideally, the number of all substituting manufacturers that produce the same vaccines would have been the indicator used, however, this information was not available.

A potential selection bias however may arise from the different types of vaccines being reported to the V3P. Most of the bacterial vaccines reported categories of vaccines data analysis presented this chapter are based on reported vaccine procurement by countries (both higher and lower income) procuring from DCVMs. The dataset used in this chapter indicates most of the bacterial vaccines were traditional vaccines, while most of the viral vaccines reported were NUVs, which the latter is usually more expensive than the traditional EPI vaccines. Given that the data uses a secondary source, it is not entirely clear how randomised was the data collection process. However, the proportion of the data categorised as bacterial and viral as well as traditional and NUVs categories are quite large. It is likely that there is a tendency of DCVMs to produce bacterial vaccines that are traditional and viral vaccines that are NUVs.

5.4.2. Conclusions

The procurement factors that were found to influence lower prices of DCVM vaccines were competing products with prequalification status and formulation sizes. For traditional vaccines in particular, UN procurement transactions were found to have lower prices while transactions involving higher income levels countries, either as a producer or procurer, were associated with higher vaccine prices. Bacterial vaccines were associated with lower prices while viral vaccines were associated with higher prices. For modern vaccines, transactions involving larger volumes as well as recombinant vaccine types were found to be associated with lower prices.

A better understanding of what factors contribute to the pricing of vaccines by developing country manufacturers will help DCVMs assess how that can be translated to the critical factors influencing production costs. This understanding will allow developing country manufacturers to better assess their pricing decisions and be more attuned to the critical factors influencing their costs, which in turn will assist producers to gain and sustain viability and by extension, to support the global supply of vaccines. This may also help navigate dialogue with each manufacturer's local government and other key stakeholder in identifying the support needed to maintain and boost viability of local vaccine production in developing countries.

Chapter 6 Discussion

Developing country producers supply over half of the vaccines used in developing in country immunisation programs. DCVMs vary by size, capacity and quality (CVI & WHO, 1999; Milstien et al., 1997). As the dynamics of the vaccine market have changed over time and will likely continue to change, it is important to identify the critical factors influencing viability of vaccine production in developing countries.

The aim of this thesis was to analyse, from an economics perspective, the viability of local vaccine production, specifically in developing countries. This was achieved through the following assessments:

1. An analysis of the cost structures in establishing vaccine manufacturing facilities in developing countries;
2. An assessment of vaccine viability factors' influence on revenue sizes and percent market shares of developing country production; and
3. An assessment of procurement factors' influence on prices of vaccines produced by DCVMs.

6.1. Overall summary

A review of the existing literature (Chapter 2) found that economic evaluations of vaccine production in developing countries have been limited. Constant changes have been reported to take place in the vaccine market. These changes, which stem from advances in biotechnology and tighter regulatory requirements, pose challenges for vaccine manufacturers to remain economically viable whilst at the same time producing vaccines that are efficacious and of high quality. Maintaining the global supply of vaccines has, therefore, been challenging, particularly to maintain the supply of vaccines to non-premium markets such as those in developing countries.

The cost-per-dose of vaccines produced by DCVMs, over three specified production scale and scope settings[63], was found to be an average of $2.05. The average and range of costs-per-dose ($0.92 - $4.40) were in line with reported costs of vaccines produced by multinationals[64]. The vaccine markets faced by DCVMs however are mostly non-premium markets[65], yet this may be compensated by other features found in developing country vaccine markets, such as the large size of the population and the high need for vaccines due to disease burden profiles[66] and low domestic competition[67]. DCVMs may find particular challenges to sustain their viability when they produce vaccines for the export market, or when they produce new technology vaccines.

From the three analyses conducted in this thesis, the following critical factors were found to influence viability of vaccine production in developing countries.

2. In establishing vaccine manufacturing facilities.
    a. To offset high fixed costs associated with vaccine production, two specific characteristics are important: large production scales (ideally over 20 million annual doses) and a multi-vaccine facility.
    b. Given the step-fixed-cost characteristics of fixed costs, manufacturers should have a high level of certainty over the production scale and scope.
    c. An estimated 10% of cost savings through economies of scale and scope can potentially be achieved by increasing the scale and scope of production

[63] The three settings observed were 1) Scenario A with 20 million annual doses of 1 vaccine product (average cost-per-dose: $2.30); 2) Scenario B with 20 million annual doses of 5 vaccine products (average cost-per-dose: $2.02); and 3) Scenario C with 100 million annual doses of 5 vaccine products (average cost-per-dose: $1.82).
[64] No studies have presented the industry-wide cost of producing vaccines in developing countries. One report based its costing on vaccine production by multinational manufacturers, with costs ranging between $0.05 to $3-$4 per dose (Mercer Management Consulting, 2002). It is not clear however whether those costs included attrition rates, which were included in the calculations in this thesis.
[65] WHO report that vaccine markets in low and middle income countries contribute to only 18% of the total market value of vaccines.
[66] WHO report that 85% of the world's population live in low and middle income countries, while 93% of the burden of disease is found in these countries.
[67] Refer to market shares of DCVMs in their domestic markets (Table 4.5 in Chapter 4)

facilities, regardless of whether they are viral or bacterial vaccines. Recombinant vaccines can achieve higher cost savings (31%) while conjugate vaccines can achieve lower cost savings (15%). If the vaccine is recombinant, economies of scale can be twice as high, whereas if conjugate, only one-third as high. With regards to formulation presentation, economies of scale are achieved in order (from highest to lowest) by: prefilled syringe vaccines, and lyophilised, multi-dose and single-dose vaccines.

d. Almost 20% of cost savings can be achieved if more vaccine products are produced in a facility, regardless of whether they are viral or bacterial vaccines. Recombinant vaccines can achieve higher cost savings (31%) while conjugate vaccines can achieve lower cost savings (15%). Little variation in cost savings was found based on formulation presentations, except for multi-dose types (26%).

3. Once production is up and running, the following aspects were found to be significant in ensuring a DCVM's viability:

   a. In the domestic market: viability is enhanced by: larger scale of vaccines production, production supplies that are sustainable and reliable, producing vaccines with higher technology levels, manufacturers having autonomous management structures, and countries having higher income levels.

   b. In export markets, viability is enhanced by: larger numbers of vaccine types being produced, production supplies that are sustainable and reliable, sizes of production and supply that can sufficiently meet demand, prequalified vaccines, and manufacturers with autonomous management structures.

4. In selling its vaccines, the following procurement factors influence a DCVM's pricing downwards: volume size of procurement, bulk-procurement method, larger formulation sizes, and higher vaccine technology, as well as lower income levels of procuring and producing countries. Also influential towards a DCVM's pricing is the

category of vaccine technology (bacterial, viral and combination vaccine types in particular). The importance of all these factors varied by vaccine technology levels:

a. Traditional EPI vaccines: the downward factors were UN procurement transactions, bacterial vaccine categories and number of competing vaccines. While the upward factors were producing and procuring countries with higher income levels (upwards), and viral vaccine categories.
b. New and underused vaccines: downward factors were volume size of procurement, formulation sizes required and recombinant vaccine types. While upward factors were transactions involving producers with higher income levels[68] and the number of competing vaccines.

6.2. Discussion of critical factors

Joint display (Table 6.1) and the convergent design method proposed by Creswell and Clark (2011), adopted here, can be used to identify the congruence of the findings from the three analyses. This approach is applicable because the analyses explored multiple related themes.

Table 6.1. Congruence design based on the findings of the three viability analyses on cost structures, revenue size and percent market shares; and vaccine prices

Results	Cost	Revenue size and Percent market share			Vaccine Prices		
		Overall	Domestic	Export	Overall	Traditional	Modern
Production Scale and scope	X	X	X		X		X
Vaccine category	X				X	X	
Technology level	X				X		
Procurement method					X	X	
Formulation presentation	X						
Formulation sizes	X				X	X	X
Income level – Producing country		X	X	X		X	X
Prequalification status		X		X			

[68] This refers to higher income countries within the developing country context

The objective of a convergent design method is to obtain an overall interpretation from triangulated results from different analyses conducted on a single topic (Creswell & Clark, 2011). Applying this method on the results in Chapters 3, 4 and 5, two particular factors were consistently found to be significant for viability across the three aspects assessed. These were: production scale and production scope.

6.2.1. Production scale and production scope

A number of studies in the literature report the significance of the scale and scope of production in maintaining the viability of local vaccine production (Mahoney, 1990; Mahoney et al., 2012; Mercer Management Consulting, 2002; Milstien et al., 1997). Across the three analyses conducted in this thesis, both production scope and production scale were found to be influential in minimizing production costs-per-dose, having a positive impact on revenue sizes and percent market shares and allowing manufacturers to offer lower prices to their consumers.

In regards to production costs, economies of scope were estimated to save costs up to an average of 18.7%, and had a larger effect on cost savings than the economies of scale (10.1%). These findings suggest that despite the high fixed cost requirements in establishing new vaccine manufacturing facilities (Sloan, 2012), setting a production scale at 20 million annual doses and above, as well as establishing a multiproduct facility can offset the high fixed costs.

Production scale and scope also affected market shares in overall markets, and specifically in domestic but not export markets. However, given the economies of scale indicator that was used in the regression was based on the producing country, we cannot conclude that economies of scale are not a determining factor in export markets. In fact, ‘sufficient supply’, which is another observed variable derived from the covariate of targeted population in procuring country, was shown to be significant in export markets, implying that economies of scale may in fact be a determining factor in both domestic and export markets.

For the analysis of vaccine prices, the volume of vaccines procured was found to be a significant factor. This can be linked to the size of production of the vaccine, in that large-volume procurements allow manufacturers to offer lower prices to consumers because the manufacturers view this factor as significant in reducing their production costs.

6.2.2. Other driving factors

A number of other factors were also prominent in the research findings, being identified by more than one analysis. These include vaccine categories, national income and formulation presentation.

Vaccine categories

Different vaccine technology categories (i.e.: bacterial, viral, combination, etc.) require different production processes that influence costs (Batson et al., 2003; Sinclair et al., 2015). This has also been found to be the case for medicines in general (Mestre-Ferrandiz et al., 2012). The findings in this thesis were in support of vaccine technology categories having an effect on the production costs and prices of vaccines produced by DCVMs.

Some evidence was found that particular vaccine categories such as viral vaccines required relatively higher fixed costs, yet can have a large cost savings from higher production scales and scope; the effect of this vaccine category appeared to be higher relative to bacterial vaccines. However, to have greater certainty, a direct comparison between a vaccine category’s cost and price levels needs to be undertaken. This was not possible in the current research given the anonimity required for production cost data.

Formulation sizes

Formulation sizes were found to be significant in driving production costs as well as lowering vaccine prices. The largest effects were found for higher-dose vial vaccines, for which transaction costs were lowest, and which require less storage space. However, this vaccine presentation type has also been associated with higher wastage rates, whereby health workers use the multi-dose vials yet cannot use the remaining doses when there are not enough patients for the vaccine to be administered (Drain, Nelson, & Lloyd, 2003; Lee et al., 2010).

Interestingly, formulation presentations were found to be a driving factor for production costs but not vaccine prices. Formulary presentations are often pre-determined by the needs and preferences of the procuring country (Jarrett, 2008; Kristensen, Lorenson, Bartholomew, & Villadiego, 2016). Preferences over certain vaccine formulations are often based on perceptions or risks that a country has, and that the manufacturer takes as a given, and thus are price inelastic. For example, in countries where high temperatures are a major concern for vaccine stability, formulations are required to be heat-stable (e.g.: freeze-dried or lyophilised vaccines). Another example relates to countries where there may be concern over vaccine safety, leading to a requirement for manufacturers to use certain vaccine presentations such prefilled syringes over multi-dose vials, even if these may result in higher priced products (André, 2003; M. M. Levine & Sztein, 2004).

National income levels

An analysis of the effect of national income levels could not be undertaken in the analysis of cost structures (Chapter 3) because of the anonymity required for the respondents. With regards to the effect on market shares, national income levels were found to be a contributing factor for sales in domestic markets. However, the producing country's income level was not found to be significantly associated with export market share. The effect of national income was in line with findings from CVI & WHO (1999), however their study also suggested that what is most important is the commitment to invest in local vaccine production on the part of the government.

With regards to vaccine prices, multiple aspects should be considered. The income level of the producing country was a determining factor for vaccine prices in overall markets as well as for traditional vaccine type markets. Traditional vaccine markets are saturated markets, with supplies dominated by DCVMs. Though DCVMs are keen to expand their production into NUVs (Jadhav et al., 2008; Milstien, Gaule, & Kaddar, 2007; Wilson & Jones, 2010), the results suggested that DCVMs have market power over traditional vaccine types. This needs to be maintained until a strong supply of NUVs can be established.

6.3. Limitations and prospects for future studies

There were several limitations that need to be considered when interpreting the findings of this thesis. Analyses of the three different aspects of viability were based on different datasets, making it difficult to draw direct comparisons across the different aspects observed (cost, revenue sizes and market shares and vaccine prices). For instance, information regarding production costs was not available in the datasets for vaccine sales and vaccine prices. However, to date there are no single data sources that would cover all aspects of production costs, revenue and prices. This is the first study to assess all three aspects, industry-wide, from an economic perspective.

Data collection for vaccine supply is known to be a relatively challenging task. Though much information has been collected on vaccine sales, this may not cover all vaccines sold in the market. This research limited its scope to where most data are available: the public vaccine market. Though the data covered may not have exhausted the full range of information on vaccine production, the thesis attempted to access and analyse data that were as complete as possible, given the resources available to the study.

A manufacturer's viability is often quite specific to the context of the vaccines being produced or the market that the manufacturer faces. Ideally, a case study on a particular vaccine manufacturer would help confirm the industry-wide findings made in this thesis. Several attempts to engage a vaccine manufacturer for a detailed case study were made, however given the timeframe and other technical constraints, this was not possible for the thesis. The range of different viability aspects covered in this thesis however provides an overall assessment that is needed to answer the research questions. Whilst an in-depth case study did not materialise through the undertaking of this thesis, there would be value in engaging individual vaccine manufacturers for future research.

Many vaccine manufacturers in developing countries are either public or private sector entities. Whilst this was not explored in detail in the thesis, there is scope for future research to explore and distinguish further the effects of a vaccine manufacturer's status on their viability. Further, analysis on trends across regions or country types may also be explored in future research.

Though the scope of this thesis was limited to the industrial perspective of vaccine production, it is acknowledged that efforts to address other determinants of vaccine demand, such as the extent and trajectory of disease epidemics, funding from national health care system, capacity and effectiveness to reach and vaccinate target population, regulatory, infrastructural, financial and political constraints could vastly increase the uptake of new vaccines and influence the global supply of vaccines. Future research of vaccine viability would benefit from exploring and incorporating the impact of these issues.

6.4. Conclusions

The interest in vaccine production viability in developing countries stems from the need to secure global supply of vaccines. Vaccine manufacturers in developing countries vary by capacity, quality and structure. These manufacturers however must all face stringent international GMP standards and local regulatory requirements in producing vaccines for public health programs. Domestically, there is not much competition in producing vaccines. However, as DCVMs expand their production to export markets, they are in direct competition with multinational vaccine manufacturers, which often have larger R&D and production capacities.

In the past, it has been assumed that vaccines can be produced at a much lower cost in developing countries than in high-income countries (CVI & WHO, 1999). The cost analysis in this thesis however, suggest that the overall cost per dose of vaccines produced in developing countries are only slightly lower than what is found in developed countries. The findings also suggest that higher production scale and scope contribute to cost savings. Countries with large population sizes and high burden of infectious diseases would therefore have a competitive advantage in lowering vaccine production costs compared to smaller countries. This has also been suggested by previous studies (Batson et al., 1994; van Noort, 1992).

However, even when a vaccine is produced at an economical cost, the producer's viability will also depend on how well it can compete with other manufacturers in the market. The viability factors found in the thesis as the most influential factors were (in descending order): having autonomy in the manufactures' management structure, higher national income levels, having consistent and reliable supply of production and prequalified vaccine status.

Finally, viability is also dependent on how manufacturers price their vaccines, and whether these are in line with the factors influencing their production costs. The findings in this thesis suggest that the volumes of vaccines procured are not a large contributing factor in DCVM pricing behaviour, though UN procurement methods have a larger effect on how DCVMs price their vaccines. More advanced vaccines are set at a higher price, however the descriptive analysis in Chapter 4 shows that half of the vaccines produced by DCVMs are EPI traditional vaccines, and a large proportion of their vaccine production (63%) is not prequalified.

Based on these findings and a review of the literature, this thesis recommends that to achieve and sustain viability in producing vaccines, developing country manufacturers need to secure sufficient production scales and identify multiple vaccine products that can be produced within their facilities. Manufacturers need to establish strong domestic sales and consistent supply before expanding into export markets. The ability to fulfil the global demand for a given vaccine does not contribute as much in increasing revenue sizes or market shares. In order to establish competitiveness in export markets, developing country manufacturers should consider investing in the prequalification processes, especially when considering supplying UN vaccine markets.

In addition to these, developing country manufacturers must also explore potential support from key stakeholders and health advocates such as the WHO, World Bank, BMGF among others, especially given the role of DCVMs in sustaining the global supply of vaccines. Governments in developing countries must enable policies that support viable vaccine production in developing countries. Though the thesis findings suggests that viability in domestic markets are currently established, strong national regulatory authorities (NRAs) need to be maintained. This is especially important given the changing landscape of vaccine technology and in regards to DCVM efforts in expanding production to export markets once strong domestic presence is established. Equally important are industrial policies that support manufacturers in obtaining higher technology capacity. Information provision regarding vaccine market prices needs to continue, such as those collected and disseminated through the V3P project.

Further, given the importance of production scale and scope on the viability vaccine production, proposals for regional vaccine manufacturing, in cases where a single country production may not be viable, should be considered as an option and explored further for its feasibility. Dialogue and exploratory research among existing networks such as the Developing Country Vaccine Regulator's Network, Health Impact Fund and other initiatives need to continue with the goal of strengthening vaccine production capacity and may explore potential funding solutions to increase the incentives and reduce the risks of investing in vaccines for developing countries.

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