The University Of Sheffield.

{An Economic Evaluation of the A(H1N1) Flu Vaccine in Mexico}

Armando Vargas-Palacios

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Medicine, School of Health and Related Research, University of Sheffield

ABSTRACT

During 2009 Mexico experienced an A(H1N1) pandemic with a rapid increase in the number of observed cases. To reduce transmission, the Mexican Government purchased 30 million A(H1N1) vaccines that were under production. There was considerable uncertainty in whether this large expenditure represented value for money. The primary aim of this thesis is to estimate the cost-effectiveness (CE) of vaccination programmes using the information known at the time of the decision. This objective utilised an ordinary differential equations (ODE) approach calibrated via a Markov chain Monte Carlo (MCMC) algorithm. Additional objectives included: assessing whether the observed number of reported cases could also be replicated using discrete event simulation (DES) methodology and documenting the type and prevalence of models used to estimate the CE of an infectious disease vaccine intervention.

There was inherent uncertainty regarding the anticipated CE of the vaccine at the time the decision to purchase was made, primarily as no definitive value for the reporting rate (RR), the number of cases that come to clinical attention could be estimated. Three RR values, for the 0-15-year-age group, were explored (0.75, 0.01 and 0.001) with RR in other age groups being estimated through the MCMC calibration. In two of the RRs (0.75 and 0.01), the vaccination programme was cost-effective, for the assumed threshold value for Mexico ($110,000 MXN per QALY gained). In contrast, when a low RR was assumed (0.001) the vaccine was dominated, being more expensive and producing less health due to the adverse events of the vaccine. These results were robust to most sensitivity analyses. When a pessimistic scenario was applied (low vaccine effectiveness, longer time required to apply the vaccines -an additional 55 days compared with the base case-, and vaccine arriving 31 days later) did the vaccine interventions become non-CE assuming an RR of 0.01. For the 0.001 RR scenario, when longer times of latent and infectious periods were assumed the vaccine became CE. As the Mexican Government anticipated an RR of approximately 0.09, it was concluded that the decision to purchase the vaccines would have been considered a cost-effective use of resources.

The DES model was found to be an unsuitable approach to predict the pandemic as the calibration attempt was unsuccessful and running times were lengthy. There are clear advantages in using an ODE approach rather than a DES approach in a pandemic setting.

The analysis of the papers identified in the literature review has indicated most of the published literature are based on static approaches, although the use of dynamic models has increased over time. Analyses indicated that the year of publication was a significant predictor for the use of dynamic models. The decision to construct a dynamic, rather than a static model, however, was neither influenced by the GDP per capita of the effected country or the location of the lead author.

Table of contents

List of Figures

List of Tables

Abbreviations

Agent-based model	ABM
Biologics and Reagent Laboratories of Mexico	BIRMEX
Centre for Disease Control and Prevention	CDC
Contact matrix	CM
Confidence interval	CI
Cost-effectiveness	CE
Cost-utility	CU
Cost-benefit	CB
Current international dollars	CID
GlaxoSmithKline	GSK
Decision tree model	DTM
Discrete event simulations	DES
Great Britain Pounds	GBP
Gross domestic product	GDP
Guillain-Barre syndrome	GBS
Herd immunity effect	HI
Discrete event simulation model	DES
Dynamic hybrid	dHybrid

Dynamic Markov model	dMM
Incremental cost-effectiveness ratio	ICER
Intensive care unit	ICU
Interquartile range	IQR
Latin America	LA
Markov model	MM
Markov Chain Monte Carlo	MCMC
Metropolis-Hastings	MH
Mexican Institute of Social Security	IMSS
Mexican Ministry of Health	MMH
Mexican Pesos	MXN
National Institute of Public Health Mexico	INSP
National Centre for the health of the childhood and adolescence	CeNSIA
National Council of Population	CONAPO
Net or effective reproduction number	R
Next generation matrix	NGM
NHS Economic Evaluation Database	NHS EED
North America	NA
Odds ratio	OR
Ordinary differential equations	ODE
Pan-American Health Organisation	PHO

Quality-adjusted life years	QALY
Reporting rate	RR
Simulated patient level decision tree model	iDTM
Simulated patient level Markov Model	iMM
Simulated patient level dynamic Markov model	idMM
Standard deviation	SD
Static Discrete event simulation	sDES
Static hybrid model	sHybrid
Static Simulation	sSim
Susceptible-Exposed-Infectious-Recovered	SEIR
System dynamics	SD
Technical consultation group for the vaccination against the pandemic virus	TCG
United States	US
United Kingdom	UK
Vaccine adverse events reporting system	VAERS
World Health Organisation	WHO

Glossary of terms

Basic reproductive number	Average number of secondary infectious persons resulting from an infectious individual following their introduction in a totally susceptible population
Cost-effectiveness	Comparative analysis of alternative courses of action regarding both cost and consequences. The cost-effectiveness analysis measures the effects of the intervention on health outcomes
Cost-utility	Comparative analysis of alternative courses of action regarding both cost and consequences. The cost-utility analysis measures the effects of the intervention using Quality adjusted life years
Cost-benefit	Comparative analysis of alternative courses of action regarding both cost and consequences. The cost-benefit analysis measures the effects of the intervention on health outcomes in monetary terms
Endemic infection	Infection that is present in a population at a similar level over a prolonged period
Epidemic	Occurrence in a community or region of cases of illness in excess of normal expectancy
Force of infection	Rate at which susceptible individuals become infected per unit time
Heard immunity effect	the indirect protection conferred to an unvaccinated individual by the presence of immune individuals conferred by either by vaccination or natural immunity
Heterogeneous mixing	An infectious disease model that assumes that contacts between individuals are not random but based on a set of characteristics such as age, sex, location
Homogeneous mixing	An infectious disease model that assumes that contact between individuals is random or equally likely, irrespectively of age or other characteristics
Lab-confirmed individual	An individual infected with the 2009 A(H1N1) virus with a confirmatory A(H1N1) influenza test
Incubation or latent period	Period between infection and onset of infectiousness
Infectious individuals	An individual that has an infection and can transmit the disease to others
Infectious period	The period during which individuals are infectious
Net reproductive number	Average number of secondary infectious individuals resulting from one infectious individual in a population in which some individuals are already immune
Next generation matrix	Matrix denoting the number of secondary infectious individuals generated by an infectious individual for each group of individuals considered in the model
Pre-infectious or exposed individuals	Individuals who have acquire the disease but have not yet able to transmit the disease
Pandemic	An epidemic occurring worldwide or over a very wide area, crossing international boundaries and usually affecting many people

Prophylaxis	Medical treatment provided to an individual before or after being exposed to an infectious person aimed to prevent the development of the disease
Susceptible individuals	A person who has not yet been infected and is at risk of acquiring an infection

Dissemination of the thesis

Part of the work produced for this thesis has been presented at the last conference of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) for Latin America in its oral format: ISPOR 3rd Latin America Conference. The presentation is available online on the ISPOR website:

Vargas-Palacios, Stevenson M, Duenas A, Wailoo A (2011). Comparing the use of dynamic and static infectious disease models in Latin America with North America, Europe, Asia and other regions.

ISPOR 3rd Latin America Conference, 8-10 September 2011. Mexico City, Mexico: http://www.ispor.org/research_study_digest/details.asp

Acknowledgments

I would like to thank my academic supervisors: Matt (Prof. Stevenson), Dr. Pete Dodd, Alejandra (Dr. Duenas) and Allan (Prof. Wailoo), Dr. Sophie White, Dr. Paul Tappenden for their valuable contribution to this thesis. Also want to thank Claire Hulme, Pete Hall and David Meads for all their support during the conclusion of my thesis

A special thank you to my lead supervisor Prof. Matt Stevenson and your wonderful family: Louise, Isabella, and Sebastian. Thank you for dedication, valuable comments, endless help and support that drove me to achieve higher goals during the entire PhD process. This journey would not have been possible without your valuable support.

During this challenging journey, I have met valuable persons with whom I have shared the joys and tears of the PhD process. Sharing the room 1.03 with you guys have been a very joyful experience.

A special thank you to Elton Chanakira whose friendship has been one of the most precious things that my Wife and I got from this experience. To my very dear friend Robert Akparibo and his family for their valuable friendship and companionship during the last length of my process.

On a personal note to my Mom, Dad and my Brother. Mum *"Muchas gracias por todo tu apoyo y amor incondicional, siempre has sido una fuente de inspiración y entrega. ¡En particular muchas gracias por creer en mí, esa confianza me ha llevado a lograr lo que a la fecha he logrado, créeme sin ello este nuevo paso no hubiese sido posible!"* Dad: *"Tu constancia, dedicación y trabajo fuerte han sido siempre un gran ejemplo para mi progreso en la vida. Te agradezco infinitamente todo el apoyo (moral, económico e intelectual) y los valiosos consejos que me has brindado para lograr llegar a este nivel académico".* Brother: *"Muchas gracias por tu apoyo incondicional, en particular en momentos difíciles durante todo mi proceso educativo (los casi 22 años completos) tus palabras de apoyo más de una vez me han dado fuerzas para continuar". ¡Espero haberlos hecho sentir orgullosos de mí!"*

To my parents and brother-in-law*: "Lic. Campos, muchas gracias por todo su apoyo incondicional. Esta tarea ha sido más sencilla gracias a ello. Sra. Alicia, contar con su*

apoyo siempre me ha dado energías para ser mejor para su hija. Aymard, gracias por toda tu ayuda aún en los momentos más estresantes. Muchas gracias en particular por cuidar de nosotros aún en la distancia."

As Bilbo Baggins said *"It is a dangerous business going out the door. You step the road, and if you do not keep your feet, there's no knowing where you might swept off to"* More than ten years ago I asked the most beautiful person in the world to share an adventure with me. My dear Zarevna this ride has been full of joys, laughter, tears and sad moments. We lost our precious furry boy "Mooi," and we welcome our little Princes Ulrika. I acknowledge all the efforts and sacrifices you have made along the way. I will always be thankful for endless words of support, your encouragement, your dedication and your love for me, Ulrika and Mooi. This hasn't been easy, and you have always been there for me. I'm so grateful to have you in my life. It has been a privilege! Believe my words, without your support this would not have been possible. This degree, my love is yours as much as mine!

To my gorgeous little girl Ulrika, you are my strength and motivation, your endless joy and happiness can transform a bad day into a gorgeous one. Watching you born and open to the world has been a marvellous experience in my life. I hope this immense task would someday be an example of dedication and resilience for all the goals you set in your life. Know that I will always love you and that I'll be there for you now and ever! I love you with all my heart my darling; this is also for you!

Your sad loss has left an empty space in our hearts. Thank you, my dear Mooi, for all the moments you share with us. You always knew when I needed you the most. I will never forget you as your unconditional love drove me to finish this PhD. This thesis my boy is dedicated to you!

This is the end of a Chapter in our lives now as Gandalf said: *"All we have to do is decide what to do with the time that has been given to us."*

Chapter 1. Introduction

1.1 Overview of the Chapter

This Chapter provides the background information that motivated this thesis. The Chapter begins with a description of the 2009 A(H1N1) influenza pandemic events that led to the purchase of a commercially available vaccine by the Mexican Government (Section 1.2). This Chapter presents the aims and objectives of the thesis (Section 1.3), before concluding with a description of the thesis structure (Section 1.4).

1.2 Introduction to the A(H1N1) pandemic and the Mexican experience.

Seasonal flu caused by the influenza virus occurs around the world every year during the Autumn and Winter months. According to the World Health Organisation (WHO) (2009), influenza causes approximately three to five million illnesses annually with a resulting 250,000 to 500,000 deaths. In the United States (US) alone the estimated direct medical costs of seasonal influenza were estimated to be $10.4 billion in 2003 (Molinari et al., 2007).

Occasionally a mutation of the influenza virus occurs, resulting in a strain to which a large proportion of the population has no natural immunity, this could result in an influenza pandemic (Morens et al., 2010). Pandemic, defined as “the occurrence of cases of illness excess in a community or region expanding worldwide or over a very wide area, crossing international boundaries, and usually affecting a large number of people” (Porta, 2008). Unlike seasonal influenza, the highest risk of complications in a pandemic influenza could occur in young adults or adolescents (WHO, 2009). In the 20th century, three great influenza pandemics took place (1918, 1957 and 1968).

In April 2009, the WHO announced the appearance in North America of a novel influenza virus designated as A(H1N1), commonly known as “swine flu.” The disease spread quickly around the world, by June 2009 there were more than 28,000 cases reported across 74 countries with a death toll of 144 people. At this stage the WHO had declared the A(H1N1) a global pandemic, with a pandemic alert at phase six.[1] The

[1] The WHO has defined six phases to allow incorporation of new recommendations to the existing national preparedness and response plan in case of a pandemic emergency. Phases one to three are related to preparedness. Phases four to six clearly signal the need for response and mitigation efforts (WHO, 2011).

WHO definition of this phase is that "The same identified virus has caused sustained community level outbreaks in two or more countries in one WHO region and at least another country in another WHO region" (WHO, 2010b). By August 2010 when the WHO declared the end of the pandemic, 213 countries were affected with an estimated death toll of nearly 18,000 people (Reuters, 2010)

Mexico was one of the earliest countries to be affected by this virus. Mexico experienced a marked increase in the number of influenza-like illnesses (ILI) and acute respiratory infections (ARI) between the 12th of April and the 2nd of May 2009 compared to the same period in the previous year (SINAIS/SINAVE/DGE/SALUD, 2011)[2]. Between these dates the number of ILI/ARI cases represented an increase of 162% on average.[3] In the light of these figures, the Mexican Ministry of Health (MMH) feared an outbreak of 2 million cases that would result in one million deaths within a three month period (El Universal Online, 2010).

In response to these fears, the Mexican Federal Government and the MMH undertook several measures to contain the outbreak. Between the 24th of April and the 5th of May 2009, the Government ordered school closures. Subsequently, the Government also ordered the closure of museums, cinemas, theatres, libraries, restaurants and any other public gathering events, followed by the closure of non-essential economic activity (for both the public and private sector) from the 2nd to the 5th of May).[4,] The mitigation strategies slowed the progression of the disease[5,6] However, at the end of the mitigation strategies another wave arose. By the end of May, a total of over 6,918 and 97 lab-confirmed and deaths had been reported by the MMH.

The MMH anticipated a bigger third wave would occur due to the beginning of the 2009-2010 school term and the Autumn and Winter months. Estimations made by the MMH based on previous pandemics suggested that the number of deaths could range between 9,000 to 49,000, while outpatient care and hospitalisations could range

[2] An ILI is defined by the European Centre for Disease and control as sudden onset of symptoms and at least one of the following: fever, malaise, headache, Myalgia and at least one of the following respiratory symptoms: cough, sore throat, shortness of breath. ARI, is defined an individual with sudden onset of symptoms and any of the following respiratory symptoms: cough, sore throat, shortness of breath or coryza plus a clinician judgment that the illness is related to an infection (ECDC, 2016).
[3] Information obtained from the daily reports performed by the Economic Analysis Unit part of the Ministry of Health.
[4] While all non-essential activities resumed on the 6th, schools remain closed and were resumed progressively until the 29th of May.
[5] The MMH reported a reduction in the number of confirmed cases at the end of this period from 400 to 100 per day. Rapid tests (rRT-PCR) were performed in a number of ILI and ARI cases that seek medical attention
[6] The economic implications of the closures and of the outbreak were considerable. The tourism and services sectors were severely affected during the activity closure. The Ministry of Public Finances (2009) estimated the economic loss to be between 0.3% to 0.5% of the Gross Domestic Product (GDP)

between 3 to 14 million and 50,000 and 250,000 respectively (Córdova-Villalobos et al., 2010).

In response, the Mexican Government began negotiations to acquire the A(H1N1) vaccines under development by international pharmaceutical companies. The MMH announced an agreement to purchase vaccines on the 18th of July 2009. The MMH bought 30 million doses of the vaccine for a total cost of $2,850 million MXN (approximately 130 million British Pounds (GBP)) (El Universal Online, 2009a).[7] Vaccines were purchased from Sanofi-Pasteur™ (67%) and GlaxoSmithKline™ (GSK) (33%) (BIRMEX, 2009). The total cost of the purchase represented 0.024% of the 2009 Mexican GDP.[8]

There was little information on the effectiveness or availability of the vaccine, however, and therefore in August 2009, a technical consultation group (TCG) for the vaccination against the pandemic virus was formed. This group had as its objective to formulate recommendations and advice over the vaccination campaign to be launched. Based on the information known at that time, the group determined that the pandemic in Mexico have the following characteristics. First, the highest incidence had occurred in the young (children between 2 to 15 years). Second, the highest lethality to date occurred in people over 45-year-olds. Third, the highest number of non-fatal complications occurred in middle age groups (25 to 60 years). Fourth, the highest number of hospitalisations occurred in those less than 1-year-old and those who were 60 years and over. Lastly, pregnant women and individuals with co-morbidities such as diabetes, obesity, being overweight or asthma represented a high-risk group (Córdova-Villalobos et al., 2010).

Based on those characteristics and the absolute number of lab-confirmed cases up to August 2009 (20,502 with 163 deaths), the group concluded that: i) the pandemic did not put a risk to the national security. However, it could jeopardise the functioning of the Mexican health system; ii) the transmission was likely to increase during the winter months and iii) there was a relationship between having diabetes, obesity, asthma, heart diseases and the incidence of complications of the disease.

As such, they proposed that the vaccination strategy should have as objectives: a reduction in the number of fatalities; and a decrease in the transmission of the disease to prevent the overload of the health service. The group also developed a cost-

[7] The price of each vaccine was of S95.00 MXN or £4.46 GBP. The exchange rate considered was from December 2009 using the www.oanda.com currency convertor
[8] The total GDP in Mexico in 2009 was of $11,822,986 million pesos (MXN)

effectiveness (CE) analysis.[9] Three scenarios were tested: vaccination of 1 to 24-year-old only (with a population of 49 million people); vaccination of 25 and 59 years old only (with a population of 47 million people) and third, universal vaccination (total population in Mexico during 2009: 107 million people). All scenarios were compared to no vaccination. The first scenario estimated an expected reduction of 1,149 cases or 11.2% and a 5.2% reduction in the mortality rate. The second scenario, a reduction of 573 cases or 5.6% and 3.0% in mortality rate. The universal vaccination, however, resulted in a reduction of 5,128 cases (or a 50% reduction) and 50% in the mortality rate. The absolute number of cases was not clear in the no vaccination strategy.

The TCG determined that universal vaccination strategy was cost-effective only if the total number of cases and deaths was 15 times bigger than the cases notified to date (nearly 300,000) and more than 2,400 deaths, therefore considered this vaccine strategy unlikely to be cost-effective. The details described here were the only information available on the CE analysis performed by the consulting group. No published or unpublished information about this analysis was found.[10] Uncertainty existed regarding the type of model developed, the method used and if under-reporting was assumed.

It was suggested that the best distribution of the already agreed vaccine purchases was as follows: medical personal (2% of the population); pregnant women (1% of the population), 6 to 23 months infants (3% of the population) and individuals with co-morbidities between the age of 2 years and 64 (14% of the population).[11]

The initial agreement made by the MMH expected the vaccines to arrive by the end of October (El Universal Online, 2009b) when the Government expected an increase in the number of cases and a third wave of the pandemic. However, the initial batch of vaccines (around 600,000) was not received until late November 2009 (Cordova-Villalobos et al., 2017). At this point, the number of daily cases in the third wave was already in decline (with less than a 100 lab-confirmed cases per day compared with the peak of this wave where the numbers of identified cases reached nearly 1,000 cases per day).[12]

[9] A cost-effectiveness analysis is a comparative analysis of alternative courses of action in terms of both their costs and consequences. The cost-effectiveness analysis measures the outcomes in terms of health outcomes (Drummond et al., 2015)
[10] Information about this study was requested from the MMH. Despite several attempts to track this document no information was provided.
[11] Vaccination to population at risk (medical personal) and individuals at high risk was considered elsewhere as a cost-effective strategy (Baguelin et al., 2010)
[12] No information of the daily numbers of ILI or ARI was available

The vaccination programme started on the 24th of November according to the previously described plan (initially vaccinating medical personnel and pregnant women). Shortly after a second batch arrived (December 2010) and was applied to infants (6 to 23 months) and people with co-morbidities between 2 and 64 years of age. The vaccine was applied progressively, to anyone who requested it. According to the MMH, approximately 28.5 million people were vaccinated by the end of the pandemic (August 2010) (Cordova-Villalobos et al., 2017).

The vaccine to the vulnerable and high-risk population (as performed by the MMH) has been estimated as a potential CE strategy in England (Baguelin et al., 2010). However, the purchase of additional doses necessitates the exploration of population-based vaccine strategies (as the ones analysed by TCG).[13]

1.3 Aim and objectives

This thesis has six key objectives although the primary aim of this thesis is to estimate the CE of a population-based vaccine strategy of the 2009 A(H1N1) pandemic in Mexico using the information available at the time the decision to purchase the vaccine was made. The six objectives, in order of appearance in the theses, are:

1. To document the different models used to estimate the CE of an infectious disease vaccine intervention
2. To construct a model to simulate the spread of the A(H1N1) vaccine in Mexico during the 2009 pandemic using an ODE approach
3. To construct a model to simulate the spread of the A(H1N1) vaccine in Mexico during the 2009 pandemic using a DES approach
4. To calibrate both models (ODE and DES) so that the data observed within Mexico could generally be replicated
5. To determine the estimated CE of a population vaccine strategy at the time the decision to purchase the vaccine was made using the ODE model
6. To comment on the use of the DES methodology to guide future researchers working in a similar area.

[13] By population based strategies refers to those applied to the general population irrespectively of their vulnerability or risk group.

1.4 Structure of the thesis

The thesis is divided into seven chapters. This section describes the contents of each one

Chapter 1. Background

This Chapter provides a short background on the events of the 2009 A(H1N1) pandemic in Mexico, highlighting uncertainties surrounding the decision to purchase the vaccine and describes the structure of the thesis.

Chapter 2. Characteristic of the A(H1N1) pandemic in Mexico

This Chapter details the epidemiological patterns and clinical characteristics of the 2009 A(H1N1) pandemic in Mexico. Relevant information on key characteristics that need to be considered when constructing the models and performing the CE analysis are provided.

Chapter 3. Literature review

This Chapter describes the literature review performed during the thesis. The methodology used and the results obtained are described and presented. The aim of the review was to document the different type of methods used to estimate the CE of a vaccine intervention. A review of relevant CE analysis performed on the 2009 A(H1N1) is also presented.

Chapter 4. Model structure: ODE model

This Chapter describes the design, construction, and calibration of the ODE model, compartmentalised into susceptible, exposed, infectious and recovered individuals and calibrated via a Markov Chain Monte Carlo routine

Chapter 5. Model structure: DES model

This Chapter describes the design, construction, and calibration of the DES model.

Chapter 6. Cost-Effectiveness of the A(H1N1) vaccine intervention

This Chapter details the development of the CE analysis of the 2009 A(H1N1) vaccine intervention. The main characteristics, the methodology used, assumptions, limitations, and results are detailed. Only results from the ODE model are presented as a DES approach was deemed unsuitable.

Chapter 7. Summary, contribution of the thesis, discussion, and areas of future research

This Chapter summarises all the elements of the project. It concludes with a discussion of the limitations of the thesis and recommendations for future work

Chapter 2. Characterisation of the A(H1N1) pandemic in Mexico

2.1 Overview of the Chapter

This Chapter aims to explore the epidemiological patterns and clinical characteristics of the 2009 A(H1N1) pandemic in Mexico. It interrogates several data sources and analyses the available information to offer a picture of the events that occurred during the 2009 A(H1N1) pandemic in Mexico. The characteristics of the vaccine are also discussed (regarding the effectiveness and the occurrence of adverse events). This information was used to populate the infectious disease model and CE analyses.

The Chapter is divided into four sections. Section 2.2 describes the general characteristic of the pandemic in Mexico. Section 2.3 briefly describes the vaccine purchased by the MMH. Lastly, Section 2.4 provides a summary of the Chapter.

2.2 Characteristics of the 2009 A(H1N1) pandemic in Mexico

Influenza is an acute viral infection that transmits via close contact between individuals. This disease can be caused by one of the three known influenza viruses: A, B or C. on this thesis the most relevant is the type A virus, as the type of virus that caused the pandemic in 2009: A(H1N1) (Garten et al., 2009).

During 2009, Mexico had a population of 107.5 million people. The country is divided into 31 states and one Federal District (Mexico City). Most of the population concentrate in the central states (61%) which include Mexico City, followed by the northern states (26%) and southern states (13%) (CONAPO, 2012).

The MMH maintained a record of the number of identified or lab-confirmed cases from the beginning to the end of the pandemic. The datasets covered the period between March and the end of November 2009 and contained information on the daily number of lab-confirmed individuals with A(H1N1) by age, sex and region.

The data was collected directly from different hospitals and health institutions via the InDRE (National Institute of diagnostic and epidemiologic reference: "*Instituto de Diagnostico y Referencia Epidemiológica" in Spanish).* Only data up to the moment the decision to purchase the vaccine was announced (18th July 2009) was required. Figure 2.1 shows the lab-confirmed data available from the start of the data collection up to the decision point.

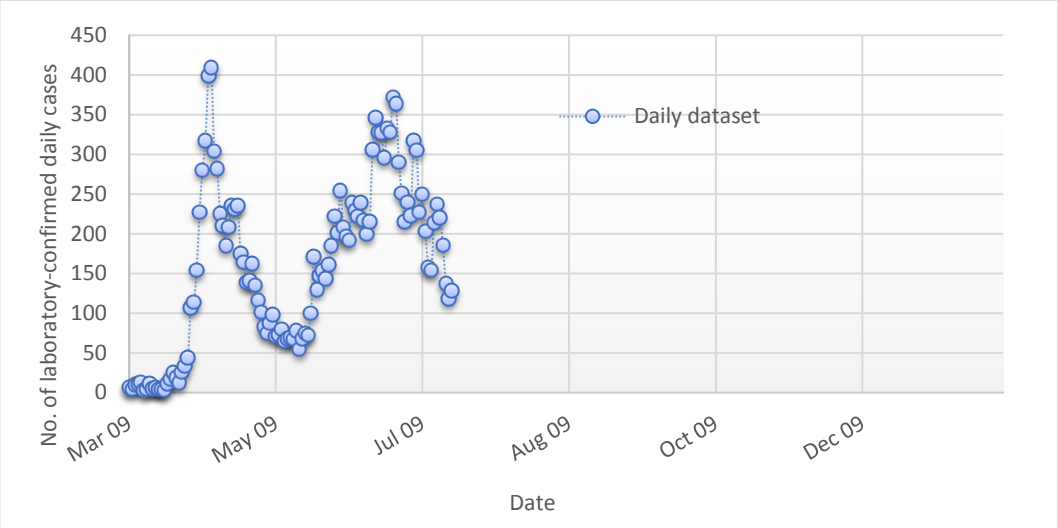
These data, however, were likely to be an under-estimate of the true number of cases in the population as it was probable that many cases went under-reported. The MMH suggest that approximately 10% of the cases of influenza could be asymptomatic (Córdova-Villalobos et al., 2010).[14] However, there are other reasons of under-reporting which if not considered can dramatically underestimate the true size of the influenza pandemic such as mild infections where the patient did not seek medical attention or those who were wrongly diagnosed or had a false negative test result. Furthermore, some test might have been compromised (due to timing or contamination of the collected sample. Estimations made by Elizondo-Montemayor et al., (2012) confirmed the under-estimation of lab-confirmed cases reported by the MMH as in a small sample between November and December 2009, the authors found a seroprevalence of A(H1N1) antibodies between 36.7-40.7%[15]

Furthermore, some authors have suggested that the A(H1N1) pandemic is similar to the HA viruses isolated from swine in North America that were first detected in 1930 (Couch et al., 2012). The 2009 A(H1N1) pandemic virus could be related to influenza A(H1N1) viruses that have circulated previously (from 1918 to 1977), therefore is more likely that older individuals would have a lower susceptibility to the pandemic virus (Couch et al., 2012). These strains have been included in the annual influenza vaccine since 1977. Therefore, it is possible that some immunity to a similar class of virus such as the 2009 pandemic A(H1N1) could have been generated.

Technically any diagnosis of influenza without serological tests is a diagnosis of ILI or ARI. A diagnosis of ILI or ARI can later be confirmed as influenza (or in this scenario) as an A(H1N1) pandemic case. During the pandemic, swabs were taken to test for A(H1N1) from those patients who sought medical attention and were diagnosed with ILI or ARI. The patients with a positive test for A(H1N1) were reported, and this information was compiled in a data set by InDRE.

[14] Córdova-Villalobos et al., (2010) is an editorial. However, this was used as source of information for several components, parameters and assumptions of the models as this editorial refer to what happened in Mexico during the 2009 A(H1N1) pandemic. This is a compilation (lead by the Minister of Health at the time of the pandemic: Dr. Jose Angel Cordova-Villalobos) of the information and estimations available to the MMH that provided evidence to the discussion and the decision to purchase of the vaccine.
[15] The study was based on a small sample of 2,222 individuals categorised by age groups and focused on a school setting in a community in Mexico.

Figure 2.1 Number of lab-confirmed reported cases during the 2009 A(H1N1) pandemic in Mexico up to the 18th July 2009



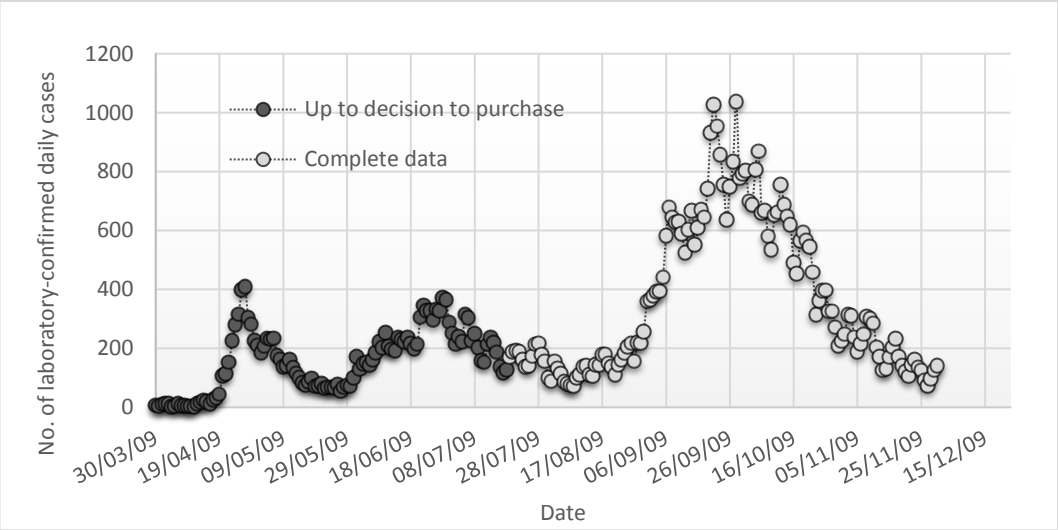
At the time when the decision was made, the lab-confirmed data suggested that the pandemic had two waves a Spring wave (from the beginning of April until the 19th of May) and a Summer wave (from the 20th of May). The pandemic seems to have been influenced by social distancing generated by both school terms and Governmental actions (described in Chapter 1) (Mexican Ministry of Health, 2009a; Chowell et al., 2011)[16]. As it can be observed in Figure 2.1, it is highly likely that the decline observed in the lab-confirmed data at the end of April and the beginning of May was related to Governmental actions. Based on this same data, the Summer wave seems to have started soon after the resumption of activities. The peak of lab-confirmed cases was observed around the time when the school term finished towards the end July 2009 (Figure 2.1). As discussed in Chapter 1, the MMH expected a third wave triggered by the Autumn and the start of the school term, which had an influence on the decision to purchase the vaccine.

The lab-confirmed data after the decision was made, shows a third wave between August and December 2009. The lab-confirmed cases reached its peak at the end of September 2009. The decline could not be attributed to the vaccination campaign since it began at the end of November neither to the end of the school term as this occurred in mid-December. Therefore, it is likely that the decline was attributed to the depletion

[16] Eames et al., (2012); Chao et al., (2010) and Cauchemez et al., (2009) found an elevated percentage of outpatient visits for influenza-like diseases 14 days after schools open in autumn 2009. Eames et al. (2012) also concluded that changes in school terms influenced the pattern of the 2009 influenza pandemic in the UK)

on the number of susceptible individuals in the population.[17] This wave had the highest number of lab-confirmed cases per 100,000 individuals: 95% confidence interval (CI) 36.04 – 67.45 versus the 7.18-16.57 for the Spring and 6.22-22.11 Summer waves.[18] Figure 2.2 shows the complete lab-confirmed data.

Figure 2.2 Complete lab-confirmed data

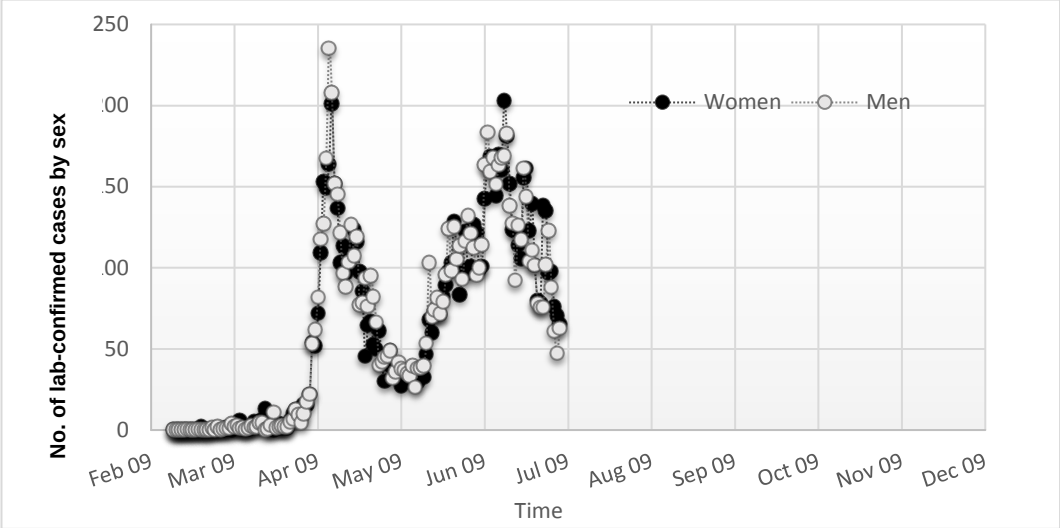


The graph includes the lab-confirmed cases between March and November 2009

Although the Autumn and Summer lab-confirmed observed waves were driven by different regions in the country, Chowell et al., (2011) found no association between the rates of morbidity, hospitalisation, and deaths between regions. Furthermore, no difference was found in lab-confirmed cases between gender and the spread of the disease, with 51% of the cases occurring in women up to the decision time nor through the pandemic (Figure 2.3). Furthermore, a positive correlation was found in the trend of infections between genders (Pearson's rho = .99 p-value <0.005) (author's calculation). Data reported in Echevarría-Zuno et al., (2009) corroborate these findings as their estimation found that 50% of the lab-confirmed cases were women. Additionally, they found no association between inpatient care between gender (odds ratio (OR) 0.84 95% CI 0.70-1.02) or deaths (OR 1.62 95% CI 0.93-2.82).

[17] This suggests that the confirmed number cases reported by the MMH was a gross underestimation of the actual size of the pandemic.
[18] A t-test was performed to test for statistical significance. The third wave was significantly bigger compared the two other waves (p<0.01). These numbers were based on estimations made from the available database.

Figure 2.3 Number of lab-confirmed cases by sex in Mexico up to the decision time



2.2.1 General description of the on lab-confirmed data

The median age of lab-confirmed cases was 17 years old with a range from 0 to 100 years old and interquartile range (IQR) between 9 and 29 years. Only 10% of the lab-confirmed cases was observed in children below four years of age or people aged over 45 years old.[19] The highest morbidity rate was found in the 6 to 14 years age group (102.9 cases per 100,000), whilst the lowest was observed in the 60 years and over population (13.4 cases per 100,000). These figures were estimated at the end of the pandemic and are similar to those described by Echevarría-Zuno et al., (2009) where the median age was 18 years old, and the highest morbidity was found in the 5-14 years old (115.7 per 100,000 cases).

By the time the decision was made an estimated number of 20,502 lab-confirmed cases, and 195 deaths had been reported. At the end of the pandemic, the MMH reported 72,548 lab-confirmed cases and 1,316 deaths, implying an overall fatality rate of 1.84% (95% CI 1.93-1.74%). This value is higher than the expected deaths from seasonal influenza (0.1%) (Córdova-Villalobos et al., 2010). Estimations made by

[19] Author's estimation using the above-mentioned dataset.

Echevarría-Zuno et al., (2009) calculated that the highest mortality occurred in the 60 and over age group (39.2% 95% CI 35-43.3%).

The MMH however, did not provide an actual number of total ILI during the pandemic. The PHO suggested an approximate number of ILI or ARI cases of 280,000 identified by the health services.[20]

2.2.2 Epidemiology of the A(H1N1) pandemic in Mexico

The average duration of symptoms for those patients infected with A(H1N1) range between 3 to 7 days for mild cases. For severe cases, however, the symptoms could last up to 14 days with an average period of six days before admission hospital (Córdova-Villalobos et al., 2010; Dominguez-Cherit et al., 2009).

Data on the mean generation time (defined as the mean latent period plus one-half the mean infectious period (Cummings and Lessler, 2014) [21] was obtained from Fraser et al., (2009). The author estimations were made with Mexican data during the early stages of the pandemic (between the start of the pandemic and the 30th of April 2009) and suggest a mean generational interval of 1.9 (95% CI 1.30-2.71).[22]

Mild symptoms of the A(H1N1) are similar to those of general influenza but may develop suddenly. These are unusual tiredness, muscle pain, headache, runny nose, rhinorrhea, fever, chills, frequent and intense cough. Diarrhoea and vomiting can be present (NHS Choices, 2013c; Mexican Ministry of Health, 2009b; CDC, 2009). The study performed by Echevarría-Zuno et al. (2009) in the clinics and hospitals pertaining to the National Institute of Social Security (IMSS)[23] described the most common symptoms for almost 7,000 patients treated. In 92% of the cases, the patient had a fever, 91% had a cough, 88% had a headache, 72% muscle aches, 77% rhinorrhoea, 60% nasal congestion and 50% a sore throat.

Poor oxygenation episodes (tachypnea, hypoxia and laboured breathing), low blood pressure, confusion, severe dehydration, or exacerbation of chronic conditions such as asthma, chronic obstructive pulmonary disease, chronic renal failure, diabetes, or cardiovascular conditions usually accompany the progression of symptoms (NHS Choices, 2013c; Mexican Ministry of Health, 2009b; CDC, 2009).

[20] Presumably this was the population that sought medical attention.
[21] The following definition of mean generational time was used: *"If infectiousness is evenly distributed across the infectious period, then the mean generation time will be equal to the mean latent period plus one-half the mean infectious period"* from Cummings and Lessler, (2014).
[22] The study does not estimate the latent or infectious period.
[23] The IMSS is the biggest social insurer for Mexican workers in the private sector. It covers almost half of the total Mexican population.

Lower respiratory tract diseases requiring supplemented oxygen, an abnormal chest radiography and the use of mechanical ventilation are usually characteristics of severe cases. Patients might have developed encephalitis or encephalopathy, complications of low blood pressure such as shock or organ failure, myocarditis or rhabdomyolysis or invasive secondary bacterial infection (NHS Choices, 2013c; CDC, 2009).

The treatment guidelines developed by the MMH, the World Health Organisation (WHO), the Centre for Disease Control and Prevention (CDC) and the Department of Health UK, suggest the use of antiviral medication for mild cases or when risk factors are present.[24] If the symptoms are low to moderate and the person has no risk factors, then antiviral treatment was not considered necessary. If the disease does not improve after 72 hours, the patient is recommended to return to the clinic to re-evaluate the condition (INSP, 2009; CDC, 2009).

The antiviral of choice in Mexico during the pandemic was the oseltamivir (although zanamivir was also available if necessary).[25] Oseltamivir can be given to children under one year of age and pregnant women if necessary. The treatment was recommended for a period between 5 to 10 days depending on the severity of the condition (INSP, 2009).

Patients showing a progression of symptoms may require immediate hospital care. Once in hospital, patients would receive treatment with antivirals if not already treated. If the patients develop a bacterial infection treatment with antibiotics is given accordingly. If the disease is severe or progresses further, patients could be admitted to the intensive care unit (ICU). Here, ventilation support might be offered (INSP, 2009). Antiviral treatment could be used as chemoprophylaxis for family members (for out and inpatient care patients) to prevent further transmission. This was only recommended for family members with underlying risk factors (obesity, overweight, asthma, diabetes, pregnant women, and those with chronic obstructive pulmonary disease, chronic renal failure, diabetes, or cardiovascular conditions).

Lastly, Elizondo-Montemayor et al. (2012) suggest that there are no significant differences in symptoms profile between ILI and lab-confirmed patients.[26] Figure 2.4 shows an interpretation of the treatment pathway followed by the MMH.

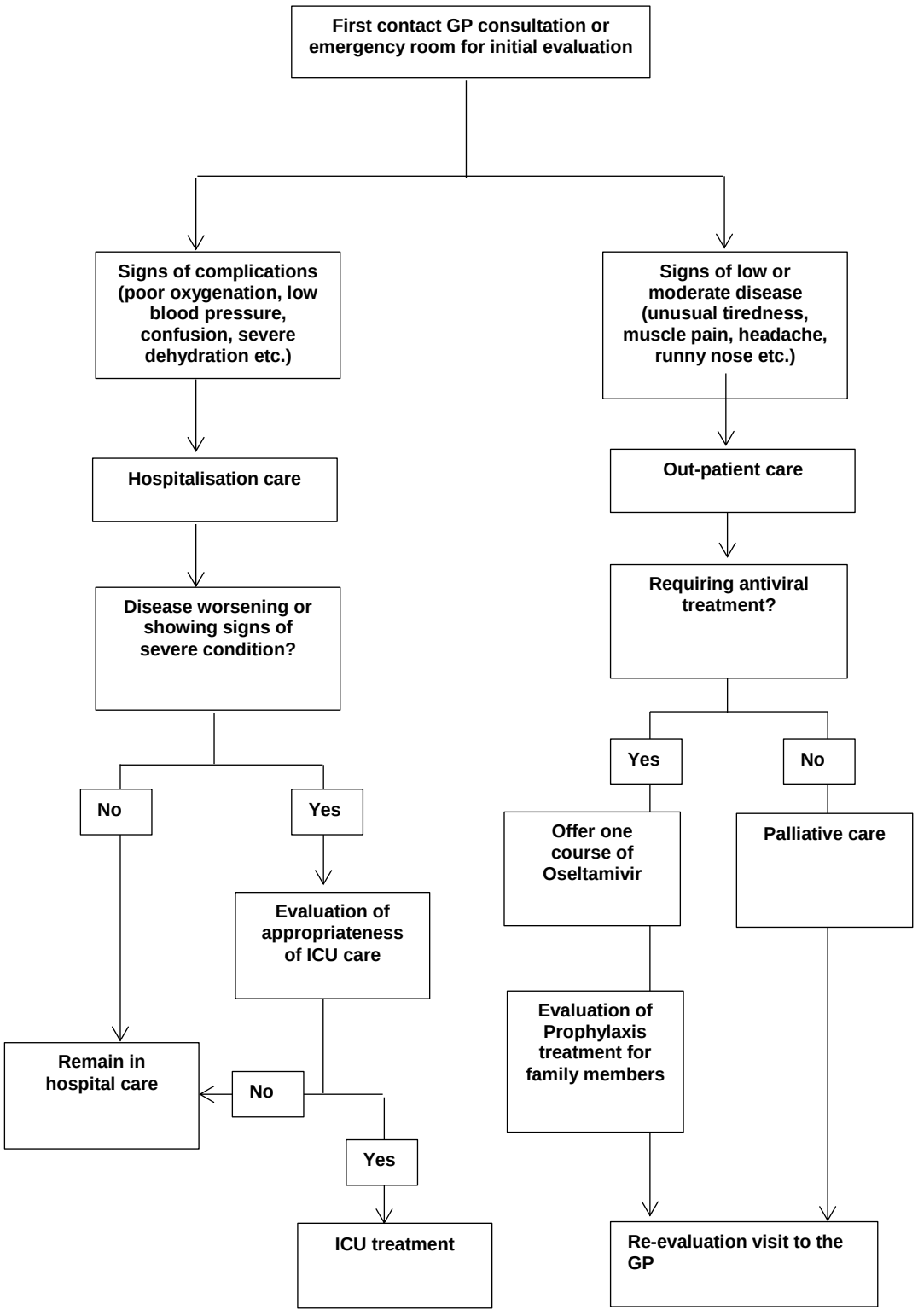
---

[24] Risk factors: obesity, overweight, asthma, diabetes, pregnancy, chronic obstructive pulmonary disease, chronic renal failure, diabetes, or cardiovascular conditions

[25] Oseltamivir is an antiviral used to treat some types of influenza in adults, children and infants (Medline Plus, 2013).

[26] The study analysed the difference between ILI, respiratory illnesses and non-respiratory illnesses. The author's findings suggested that no significant difference in were found in the symptom profile of those confirmed to have had A(H1N1) and those who experience ILI.

Figure 2.4 Flow chart for the treatment of H1N1 patients



Author's interpretation based on the MMH guidelines

2.3 Vaccination

The Sanofi-Pasteur vaccine was a pre-filled syringe with no co-adjuvant (0.5 ml doses containing 15μg hemagglutinin of influenza A/California/07/2009 A(H1N1 v-like virus) (FDA, 2013). The GSK, however, was packed in a ten dose vial and required co-adjuvant (3.75μg haemagglutinin per 0.5mL dose) (GSK, 2010).

The influenza vaccine can produce antibodies against the disease one week after vaccination, but the maximum immunity levels will usually be reached between the two and four weeks after immunisation (Córdova-Villalobos et al., 2010). At the time when the MMH made the purchasing decision, the effectiveness and average time to immunogenicity for A(H1N1) were unknown. As described by the compilation editorial by the Minister of Health at the time of the decision (Córdova-Villalobos et al., 2010), the MMH based its estimations of its potential effectiveness on seasonal influenza and several other published sources. These have been summarised here by age group:

For people aged 60 years and over, it was estimated that the effectiveness of the vaccine to prevent influenza or influenza-like disease was between 6 to 58% (Govaert et al., 1994).

Jefferson et al., (2005); Hak et al., (2005); Nordin et al., (2001); Fleming et al., (1995); Mullooly et al., (1994); Fedson et al., (1993); Foster et al., (1992) estimated that the effectiveness of the vaccine in preventing hospitalisation in individuals of 60 years or older could lie between 19 and 72%.

Hak et al., (2005); Nordin et al., (2001); Fleming et al., (1995); Mullooly et al., (1994); Fedson et al., (1993); Foster et al., (1992) estimated the vaccine can prevent between 27 to 72% of deaths.

For individuals between 18 and 65 years estimates by Jefferson et al., (2007) have located the efficacy of a vaccine between 47 to 100% in the prevention of influenza. Hak et al., (2005) estimated an effectiveness of 26% in the prevention of medical consultations, 87% of hospitalisations and 78% of deaths.

Jefferson et al. (2005), estimated that the inactive vaccine has an effectiveness of 28% for children between 2 and 16 years old but found no conclusive evidence for children aged 2-years and younger.

Based on this information, at the time of the decision, the MMH considered the potential effectiveness of the 2009 A(H1N1) vaccine would be of 50% ranging between 30% and 70% in preventing cases of A(H1N1).

The actual effectiveness of the vaccine has been studied in several recent publications. Osterholm et al. (2012); Yin et al. (2012) both performed a meta-analysis on the effectiveness of the monovalent 2009 A(H1N1) vaccine. Osterholm et al. (2012) included five studies all conducted in Europe or Canada: Hardelid et al. (2011); Valenciano et al. (2011); Skowronski et al. (2011); Puig-Barberà et al. (2010). The results suggest that the vaccine effectiveness in preventing A(H1N1) influenza cases has a median of 69% and range between 60-93%. The five studies were based on single doses, and most of the vaccinated participants received a vaccine containing an adjuvant.

Yin et al., (2012), however, estimated the effectiveness from 11 studies. The authors estimated a vaccine effectiveness of 90% (95% CI 25-99%) for those studies using a single dose of adjuvant monovalent vaccine. When including those studies without adjuvant doses of the A(H1N1) monovalent vaccine, the effectiveness estimate became 84% (95 IC% 68-92%). The summary effectiveness of the 2009 A(H1N1) vaccine was estimated based on three studies using non-adjuvant vaccines only and single and double doses. The reported effectiveness of those studies was 86% (95% CI 73-93%) (Yin et al., 2012).

2.3.1 Vaccine adverse events

The adverse events of influenza vaccines including that for 2009 A(H1N1) are low. The most common local reactions are pain and tenderness or redness at the site of injection, while the most common systemic reactions (adverse reactions that spread to one organ -skin- to other organ systems of the body) include: fever; headache, malaise, and myalgia. Severe conditions defined as life threatening or that which require hospitalisation include anaphylaxis; convulsions; Bell's palsy; Guillain-Barre syndromes (GBS); encephalomyelitis and vasculitis or neuritis (Fiore et al., 2009; Folkenberg et al., 2011). Some of these conditions can leave permanent disabilities or be fatal in particular GBS which might require hospitalisation treatment for up to 94 days of (NHS Choices, 2013a, 2013b; Carroll et al., 2003; CENETEC, 2016).

The MMH main concern at the time of the decision was GBS. According to the MMH guidelines (IMSS, 2008), most patients recover from this disease (80%) although between 25% and 85% of the recovered patients might face long-term health implications or disabilities. The recovery rate, however, is believed to be related to the

age of the patients as 90% to 95% of those less than 18 years of age with the syndrome regained full health (Cho et al., 2010).

The MMH, based estimates of vaccination-induced GBS from a previous swine flu outbreak in 1976, where ten cases per 1,000,000 vaccinated individuals were reported (McGrogan et al., (2009)).

Whilst the GSK vaccine has subsequently been shown to have a risk of narcolepsy (Miller et al., 2013; Partinen et al., 2012), a scooping search in Medline® and Embase® found no published papers linking an influenza vaccine with narcolepsy before 2009. As such, the MMH was not expecting any case of narcolepsy.

The actual adverse events reported by the MMH at the end of the campaign were mild. Up to the end of April 2010 (when the vaccination campaign was almost over), 354 cases of adverse events were reported: 288 low, 52 mild and 14 severe. Most of the adverse events occurred in the 20-49 years age group (225 cases) followed by the 50-64 age group (51 cases). Only 165 were directly related to the vaccine of which 157 (95%) were low to moderate, including fever, pain at the injection site and headache (MMH (Censia), 2010). Of the 14 severe cases of adverse events, three were identified as GBS, but none was assumed to be associated with the A(H1N1) vaccine. No deaths due to the vaccine were reported (MMH (Censia), 2010).

2.4 Summary

This Chapter aimed to explore the epidemiological patterns and clinical characteristics of the 2009 A(H1N1) pandemic in Mexico. The vaccine characteristics were also discussed (effectiveness and adverse events). This information was used to inform the infectious disease model and CE analyses.

The lab-confirmed data reported by the MMH showed three waves: Spring, Summer, and Autumn of 2009. When the decision to purchase the vaccine was announced, the Summer wave was almost over (18th July 2009) although the MMH expected a third wave once the school term began.

The first reduction in lab-confirmed cases was most likely the effect of Government actions (Mexican Ministry of Health, 2009a; Chowell et al., 2011). The second wave of lab-confirmed cases started soon after the resumption of activities, and its peak was observed near the conclusion of the school term in July 2009.

The third wave of lab-confirmed cases peaked at the end of September (two months and a half before the end of the term in mid-December). This decline was most likely related to a depletion in the number of susceptible individuals in the population (Chowell et al., 2011).

Although the lab-confirmed waves were driven by different regions in the country, no association was found between the rates of morbidity, hospitalisations, and deaths between regions. Furthermore, no difference was found by gender (number of cases or shape of the spread) (Chowell et al., 2011).

The treatment guidelines developed by the MMH suggested the use of antiviral medication for mild or severe cases when risk factors are present. The antiviral of choice in Mexico during the pandemic was oseltamivir. Patients with an increase symptomatology were evaluated and if required were referred to hospital care If the disease was severe or progressed further, with some patients admitted to the ICU. Antiviral treatment was considered for those family members of infected individuals with underlying risk factors.

Mexico purchased 30 million monovalent A(H1N1) vaccines in total from Sanofi-Pasteur (with no adjuvant) and GSK (with coadjuvant) based on an inactivated A(H1N1) influenza virus. Based on the information of several published articles the MMH expected that the vaccine effectiveness to be between 30 and 70% with a mean of 50%.

Regarding adverse events, the major concern the MMH had was on GBS as a previous vaccine for a similar virus reported 10 cases per 1 million vaccinated individuals. Although most of the patients are expected to recover, a sizeable number can develop long term implications or disabilities. The actual adverse events reported by the MMH at the end of the pandemic were low or mild (with 95% of those attributed to the vaccine itself). Only three cases of the GBS were reported however none was directly attributed to the vaccine.

Chapter 3. Literature review

3.1 Overview of the Chapter

The literature review aim was to provide information on the techniques used to estimate the CE of vaccine interventions in an epidemic, pandemic outbreak or an endemic disease. A classification of the different types of techniques based on whether the model was static or dynamic and type of method used (e.g. decision tree (DTM), Markov (MM), Hybrid models) was made. A secondary aim was to explore the articles published to estimate the CE of the A(H1N1) vaccine during the pandemic event in 2009.

The literature review was a lengthy process. Since this section of the project was performed at the start of the thesis, a cut-off date of mid-2010 was applied for the classification process mentioned above. However, an update of the literature (from mid-2010 until the end of April 2017) was performed[27].

Section 3.2 describes the methodology used to perform the search, retrieve the relevant publications and to classify models according to the approach and method used. Section 3.3 describes the results obtained. Section 3.4 provides a summary by broad methodology category. Section 3.5 explores the articles published to estimate the CE of the 2009 A(H1N1) vaccine. Lastly, Section 3.6 provides a general summary of the Chapter.

3.2 Methodology

The literature review had the following steps:

1. Selection of the electronic databases
2. Identification of the search topics and construction of the search terms
3. Development of the search strategy inclusion and exclusion criteria
4. Processing and interpretation of the results

[27] The cut-off date of the search was December 2016; however, a monthly auto-alert was set up to flag relevant papers. Additionally, a scoping search early in May 2017 was performed covering January to April 2017 aimed at retrieving all new papers published during that time frame.

3.2.1 Selection of the electronic databases

According to Sassi et al. 2002, Medline is the key source for economic evaluation within healthcare studies since it comprises information about medicine, health care system, and preclinical sciences among other disciplines. Royle & Waugh, 2003 suggests that the use of this electronic database could retrieve approximately 85% of the published economic evaluation literature.

The Embase® and CINAHL® databases are an important source of healthcare literature. Embase®, contains biomedical literature while CINAHL® specialises in nursing and allied health literature (Centre for Reviews and Dissemination, 2011; Embase, 2010) Although both databases are mainly focused on healthcare literature they provide a good source of information for economic evaluation health care (McKinlay et al., 2006).

A further electronic database from which to retrieve economic evaluations for health care literature is the NHS Economic Evaluation Database (NHS EED). The NHS EED focuses primarily on the economic evaluation of health care interventions.

Two additional electronic databases were used to capture papers using simulation techniques: The Web of knowledge interface and SCOPUS. Web of knowledge comprises web of science (compiles literature in science, social science, arts, and humanities); BIOSIS (includes life science and biomedical research, pre-clinical experimental research, methods and instrumentation and animal studies) and Medline (Thomson Reuters 2002). Due to the type of topics covered BIOSIS was not considered in the search.

SCOPUS, however, comprises literature in scientific, technical, medical, social sciences and arts and humanities (SciVerce, 2010). Econlit® was also considered as it represents an important source of information for economic peer-reviewed articles.

According to Royle & Waugh 2003, a search strategy that combines Medline with Embase and NHS EED could return around 95% of the peer-review published economic evaluation literature when adequate search filters are used. The inclusion of CINAHL, web of knowledge, SCOPUS and Econlit was expected to increase the retrieval percentage further. Table 3.1 presents the databases within their specific interfaces.

Table 3.1 Databases used in the literature review

Interface	Database
Ovid SP®	MEDLINE(R) In process & other Non-Indexed Citations and Ovid MEDLINE® from 1946 MEDLINE(R), from 1946 Embase®, from 1980 Econlit®, from 1969
Centre for Reviews and Dissemination (CRD)	NHS Economic Evaluation Database (NHS EED)
EBSCO®	CINAHL®, from 1981
Web of Knowledge®	Web of Science®, from 1899 Medline® from 1950
SciVerse®	SCOPUS®, from 1966

3.2.2 Search topics and search terms

Search terms are a series of keywords that are used to retrieve specific types of articles from the electronic databases. A collection of search terms is known as a search filter. A search filter should be constructed considering the objectives of the review; for example, they can be highly sensitive or precise (sensitive: proportion of relevant records retrieved; precise: number of relevant records retrieved as a proportion of the total records retrieved). An appropriate search strategy would be both highly sensitive with good precision.

For this literature review, 34 search filters were constructed. The first two were: Economic evaluation and vaccination and these constitute pivotal filters. The remaining 32, correspond to a selection of relevant vaccine interventions. The combination of the first two with the 32 vaccine specific search filters was used to retrieve the proposed literature.

The economic evaluation search filter was constructed to be highly sensitive. A review of pre-designed economic evaluation search filters was performed (Intercollegiate, 2012) to guide its construction. The NHS Quality Improvement Scotland filter, NHS Economic Evaluation Database filters (NHS EED) and the Scottish Intercollegiate Guidelines Network filter (SIGN) for Medline, CINAHL®, and Embase® offer a comprehensive collection of search terms for CE models. According to Glanville et al. 2009, these filters have a sensitivity between 90% and 100%.

A combination of pre-defined search filters (NHS Quality Improvement Scotland filter, NHS EED, and the SIGN) were used in Medline®, CINAHL®, and Embase®. Additional terms were added such as discrete event simulation (DES), computer simulation and

System Dynamics (SD) as they were methods that were deemed to be used. The filters can be found in Appendix VII.

Web of Knowledge, SCOPUS, Econlit and NHS EED electronic require specific filters to perform the searches. Those filters contained terms related to CE, cost-utility, cost-benefit, cost-minimisation, cost, cost and consequences analysis as well as health-related quality of life sub-topics.

The objective of the vaccination search filter was to capture literature related to vaccine interventions from immunisation programs to prevention strategies. No pre-defined search filters were found for these. Most of the selected search terms were based on the MeSH headings classification system. Several vaccines terms were also included such as attenuated, conjugated, acellular and synthetic. Other relevant sub-topics such as immunisation programs, booster vaccination, and mass vaccination were also considered (Appendix VII).[28]

There are several vaccines available in the market. Therefore, it was thought that performing individual searches for relevant vaccines would retrieve more articles that a general search for all vaccine interventions. Chosen vaccines were those intended to prevent infectious disease where the human-to-human contact plays an important role in the transmission of the disease, and thus a herd immunity effect (HI) was expected to be a relevant factor[29]. In total 32 infectious diseases with vaccines were selected (Table 3.2).[30] Their corresponding filters were constructed based on the most relevant terminology for each topic and on the electronic database used and were based on MeSH headings classification of the different interfaces plus relevant terms to broaden the search (Appendix VII).

[28] The MeSH terms used the US spelling of the word immunisation. The term using UK spelling was used to in the NHS EED database.
[29] Herd immunity defined as *"the indirect protection experienced by unvaccinated individuals resulting from the presence of immune individuals in a population"* (Vynnycky and White, 2010)
[30] Yellow fever virus, Japanese encephalitis, Thick-borne encephalitis, rabies, Typhoid fever, Cholera, Lyme disease, Malaria and Q fever were not considered since their transmissions mechanisms are not directly related to human to human contact. Tetanus is not transmitted via direct human to human contact and Rotavirus can also be transmitted via an external agent. However, since the recent development of the Rotavirus vaccine several cost-effectiveness analyses have been developed. While Tetanus vaccination have been combined with several other relevant humans to human transmitted diseases such as Diphtheria and is considered as a regular vaccination in national vaccination programs around the world.

Table 3.2 List of diseases included

Individual Vaccines	Combined vaccines
Adenovirus	Diphtheria-Tetanus
Diphtheria	Diphtheria-Tetanus-Pertussis
Haemophilus influenzae type b (Hib)	Diphtheria-Tetanus-Pertussis-HBV
Hepatitis A virus (HAV)	Diphtheria-Tetanus-Pertussis-Hib
Hepatitis B virus (HBV)	Diphtheria-Tetanus-Pertussis-Hib-Polio
Hepatitis C virus (HCV)	HAV-HVB
Human Papillomavirus (HPV)	HBV-Hib
Influenza and Influenza A(H1N1)	Measles-Mumps
Measles	Measles-Mumps-Rubella
Meningococcal	Measles-Mumps-Rubella-Chicken Pox/Varicella
Mumps	Influenza-pneumococcal
Pertussis	Pneumococcal-meningococcal
Plague	
Pneumococcal	
Poliomyelitis	
Rotavirus	
Rubella	
Tetanus	
Tuberculosis (BCG)	
Chickenpox/Varicella	

The filter to retrieve literature on the CE of the A(H1N1) vaccine included the terms bird flu A(H1N5), the A(H1N1), the 2009 A(H1N1) swine flu, the B, C virus sub-type, the common cold and pandemic influenza.

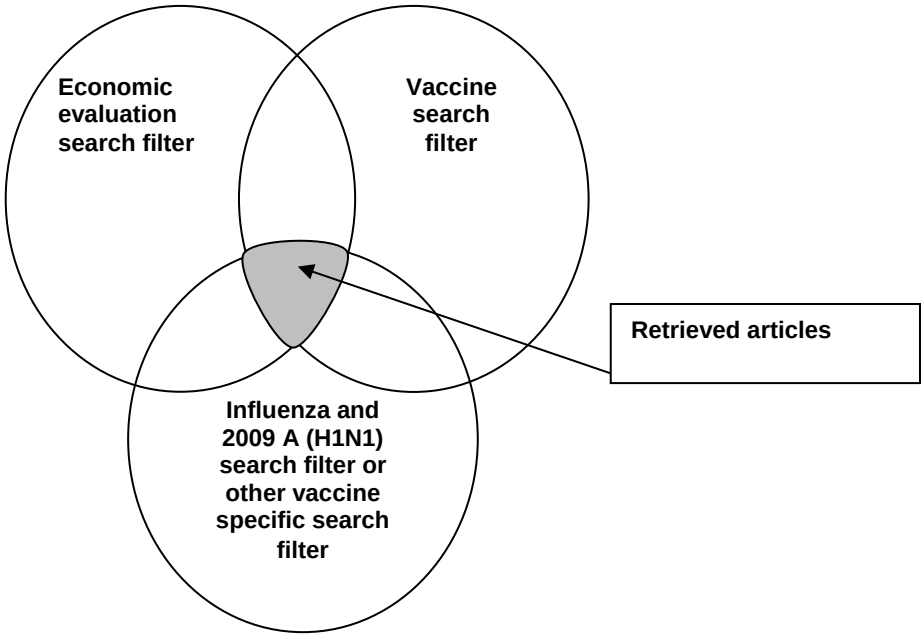
The search terms were based on the MeSH headings system used by the Ovid interface such as influenza human, common cold, and influenza virus B. Some terms were exploded to include all possible sub-headings. Other search options such as text words or truncation symbols were also employed. Several sources were consulted to confirm the filters validity: Glanville et al. (2009), McKinlay et al. (2006), The University of York (2012).

3.2.3 Definition of the search strategy and selection criteria

The first step was to combine the economic evaluation and vaccine search filters with the Boolean operator “AND”. At the end of this process, the results were aggregated in EndNote X© (1988-2006 Thomson ResearchSoft) to remove duplicates. Mendeley© (Mendeley Desktop Version 1.17.9 2008-2016 Mendeley Ltd London United Kingdom)

was used for processing and citing. Figure 3.1 uses the Influenza and A(H1N1) search filter to illustrate the process.

Figure 3.1 Search strategy



3.2.4 Selection process

After eliminating duplicates, a first sift was made based on the title. Articles not making any reference to an economic evaluation study (costs, health-related quality of life and economic evaluations literature reviews) were discarded.

Following this, a more detailed second sift was performed. This selection was based on the published abstract or in some cases reviewing the full text of the article in conjunction with pre-defined inclusion and exclusion criteria.

The inclusion and exclusion criteria were defined based on the aims and objectives of the project and literature review. The definition of economic evaluation cited by NHS EED was used for this propose: *"Full economic evaluations are studies in which a comparison of two or more treatments or care alternatives is undertaken and in which both costs and outcomes of the alternatives are examined. This includes cost-benefit analyses, cost-utility analysis and cost-effectiveness analyses"* (Centre for Reviews and Dissemination, 2011).

Inclusion criteria

1. Studies that fulfil the above-mentioned definition of a full economic evaluation study
2. Studies that report or estimate the utility gains or losses from influenza or influenza-like disease (including swine flu, bird flu or common flu)
3. Studies that consider vaccination as one of the alternatives under analysis
4. Studies related to an infectious disease
5. Studies published in English or Spanish

Exclusion criteria

1. Costs of illness or other types of costing studies
2. Studies related to animals or veterinary science settings
3. Studies that explore the CE of a vaccine intervention in a group of patients such as those with diabetes, a cancer diagnosis, who are HIV positive or who are pregnant.
4. Studies related to bioscience, biochemistry, genetics, physics, virology or molecular science
5. Conference proceedings
6. Studies not in English or Spanish

After completion of the first and second sifts, the next step was the identification of the different methods used to estimate the CE of the vaccine interventions in the context of an infectious disease.

3.2.5 Classification by type of method used

One of the main elements in the classification of the different type of models available is whether the model was dynamic or static. A static model assumes that the risk of infection is constant and thus not dependent on the effective contact rate between susceptible and infectious individuals.

The development of a model to estimate the CE of a vaccine intervention in the context of an infectious disease such as the 2009 A(H1N1) influenza pandemic requires a methodology capable of simulating the transmission of the disease. It is essential to recognise that the risk to of a person who has not yet been infected and is at risk of infection of acquiring the disease is related to the number of infectious population in the population (Vynnycky and White, 2010). Modelling techniques capable of incorporating this feature are often known as dynamic. In a dynamic model, the risk of infection is a

function of the number of infectious individuals in the population at a given point in time, multiplied by the effective contact rate between susceptible and infectious individuals (more details on the relevant characteristics of CE models for infectious diseases can be found in Appendix I).

Some authors using a static approach have attempted to incorporate the HI effect by approximating its possible impact using strategies such as employing a percentage reduction in the probability of acquiring the disease. This percentage can change from cycle to cycle depending on the number of susceptible or the age and sex of the population. These types of models, however, are not dynamic as the infection rate is not dependant on the number of susceptible or infectious individuals at any given time point. Whilst these models are not technically static as the infectious rate changes across time this has been classified as static for the purposes of the thesis.

Another type of static model referred as “catalytic model” may offer similar results to those of a compartmental model except that they do not explicitly describe transmission between individuals. Instead, individuals are assumed to become infected at a constant age, or time-dependent rate. These methods estimate the trace of incidence through time rather than via direct contact between individuals (Vynnycky and White, 2010). The main assumption of catalytic models is that in the absence of vaccination or other intervention, the average value of the force of infection remains approximately constant (Grenfell & Anderson, 1985; Griffiths, 1974). The basic model could be modified to estimate the age-specific force of infections via a non-linear regression model (Vynnycky and White, 2010; Bauch et al., 2007).

After classifying articles as static or dynamic, models were classified according to their model structures. Table 3.3 and Table 3.4 show these structures.

Table 3.3 Static model classification

Approach	Modelling techniques		Main characteristics
Static	Aggregate level models: These models follow a group or a cohort of individuals. Transmission rate is fixed or not related to the contact between susceptible and infectious.		
	Decision tree (DTM)		Tree like structure to outline decisions Transition probabilities are used to estimate the expected values for patients Recursion or looping is not allowed
	Markov Model (MM)		Transitions probabilities per unit time to change from one state to another Mutually exclusive and mutually exhaustive states Independence of progressive stages (memory-less property)[31] Clearly defined time cycles Recursion or looping is allowed
	Hybrid model (sHybrid)		DTM followed by MM or vice versa
	Individual-level models: Patients are modelled individually. Transmission rate is fixed or not related to the contact between susceptible and infected.		
	Individual sampling models (ISMs)		These types of models include the simulated patient DTM (iDTM) and simulated patient level MM (iMM): • iDTM: same characteristics as DTM, but patients are modelled or simulated individually • iMM: same characteristics as MM, but patients are modelled or simulated individually
	Computer simulations[32]	Simulation models (sSIm)[33]	• Continuous/discrete time model • States can be dependent on each other • Involve different types of computer simulation models, such as discrete event simulation models or agent-based models • DES: use of entities, labels, resources, queuing structure (subclasses as sDES)
	Hybrid model (iHybrid)		Any combination of static models with individual static models

[31] There are subtle ways to extend the Markovian assumption. If sufficient number of states are considered the MM can effectively account for previous events, or by using different transmission matrices as time, transitions probabilities can depend on certain attributes. Nevertheless, the most common approach of a MM follows the memory less assumption

[32] Time handling is a key element of computer simulations. If time moves forward in pre-defined time intervals it is said that the simulation is based on the time slicing technique. Alternatively, when the model is evaluated only when it is known that a state is about to change then the simulation is based on the next event technique and is categorised as a continuous time model.

[33] Discrete event simulation, was treated as a separate category however, as this method has specific elements to distinguish it from other simulation techniques

Table 3.4 Dynamic model classification

Approach	Modelling techniques		Main characteristics
Dynamic	Aggregate level models: These models follow a group or a cohort of individuals. Transmission rate is assumed to be a function of the number of infectious individuals in the population at a given point in time, multiplied by the effective contact rate between susceptible and infectious individuals.		
	Markov model (dMM)[34]		Same characteristics as MM
	Compartmental or system dynamic models (SD)		• Difference equations (discrete time) • Ordinary or partial differential equations (continuous time) • Fractions of individuals can occur • Model can be complemented with a static section to measure disease progression • The SD component is usually deterministic • Compartmental, SIR, and SEIR, SEIRV and related models included
	Dynamic Hybrid model (dHybrid)		dMM or SD followed by any static model
	Individual-level models: Patients are modelled Individually (fully or partially) Transmission is assumed to be a function of the number of infectious individuals in the population at a given point in time, multiplied by the effective contact rate between susceptible and infectious individuals		
	Simulated Patient Level Dynamic Markov Models (idMM)		• Similar characteristics as MM • Can follow a continuous time approach: the distribution of time to the next event is exponentially distributed
	Computer simulations	Discrete event simulation (DES); Simulation and agent-based models[35] (dSim)	• Continuous/discrete time model • States can be dependent on each other • Accounts for individual behaviour or individuals acting autonomously • DES use of entities, labels, resources, queuing structure
	Individual dynamic Hybrid (idHybrid)		Any individual level dynamic model with a static model

A series of flow charts was constructed to aid the classification process. The flow charts were based on relevant characteristics of dynamic and static approach and of

[34] A dMM can be classed as a compartmental or system dynamic model as they share the memoryless assumption.
[35] Agent-based models were classified as simulation models (dSim) as simulation models share similar components. DES was treated as a separate category however, as this method has specific elements to distinguish it from other simulation techniques.

the relevant modelling techniques. Figure 3.2 shows a flow chart to distinguish between static and dynamic models. Figure 3.3 and Figure 3.4 show flow charts to classify the static and dynamic models according to the type of modelling technique used. The flowcharts distinguish between key characteristics and assumptions of the different types of models listed in Table 3.3 and Table 3.4. These flowcharts were followed when the paper did not clearly specify the type of modelling method used.[36]

Additionally, articles were classified by year of publication: pre-1991; 1991-1995; 1996-2000; 2001-2005, 2006-2010 and 2010-2017. A logistic regression analysis to estimate the relationship between static and dynamic models was undertaken.

[36] Hybrid models were not distinguished in the flow chart) as all hybrid models were clearly identified as such.

Figure 3.2 Flow chart static or dynamic approach

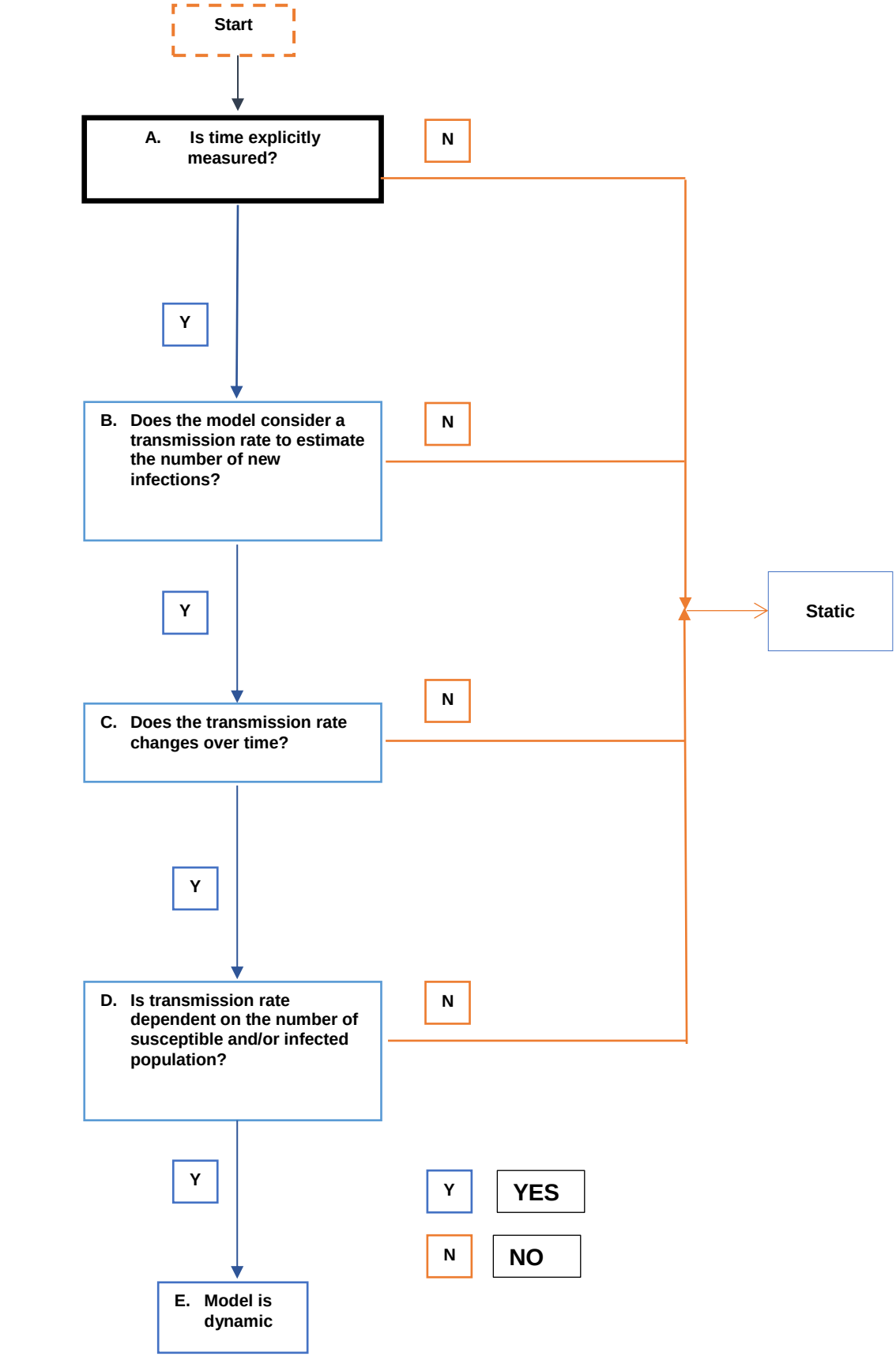
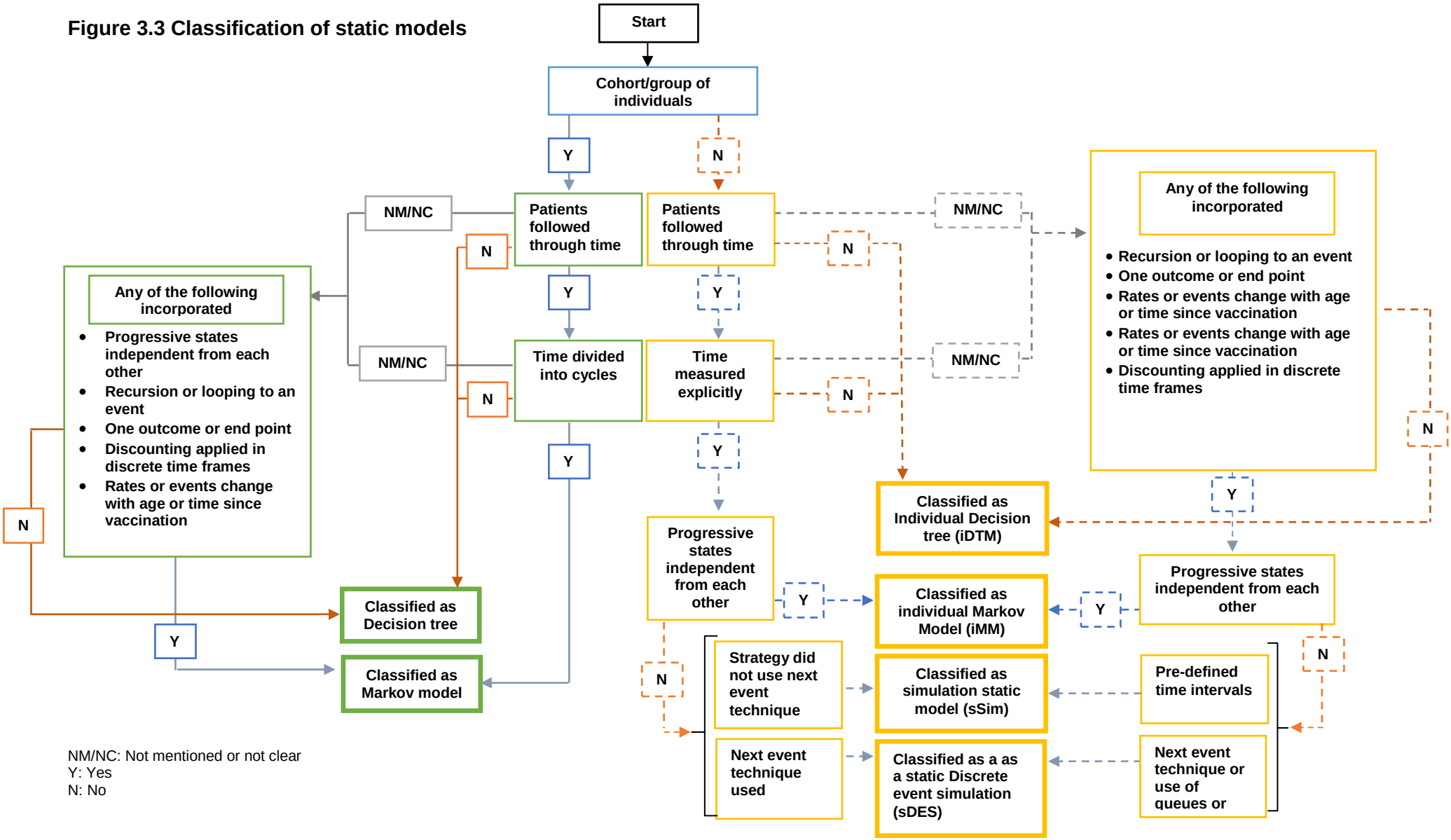
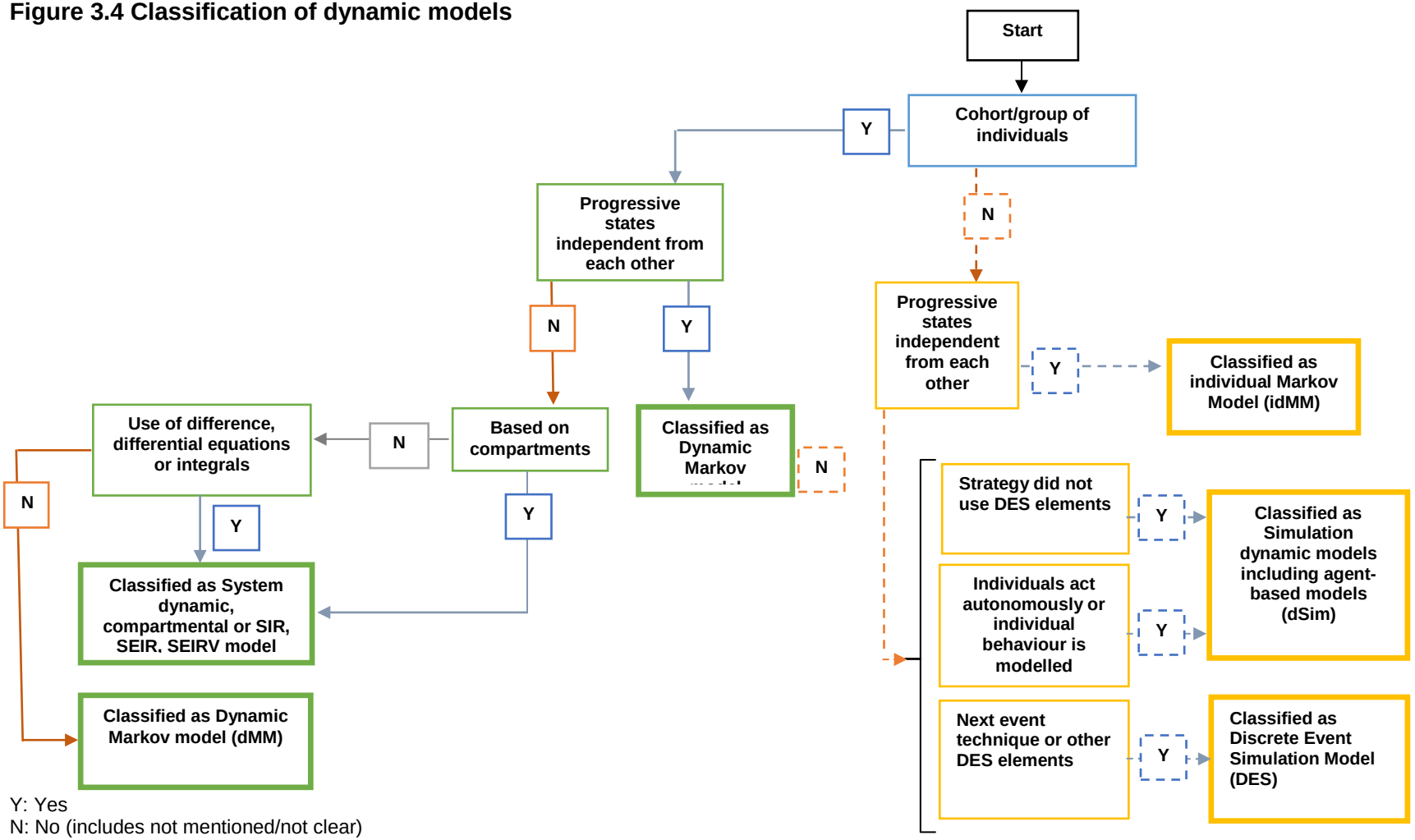


Figure 3.3 Classification of static models



NM/NC: Not mentioned or not clear
Y: Yes
N: No

Figure 3.4 Classification of dynamic models



Y: Yes
N: No (includes not mentioned/not clear)

3.2.6 Update of the literature review

An update of the literature review was undertaken identifying papers published between mid-2010 to April 2017. The cut-off date of the full review was December 2016. However, a monthly auto-alert was set up to flag relevant papers, and a scoping search was run at the beginning of May 2017 to retrieve all papers between December 2016 and April 2017. The update had the objective of ascertaining if any recently published materials affected the aim and objectives of the thesis.

Compared with the initial search, only the CE and vaccine filters were used; and only two databases were searched: OVID SP®, Embase®. This amendment was based on the experience gained from the initial search, where using the CE and vaccine filters (instead of one specific for each included disease) in those datasets offer the same accuracy regarding the relevant hits retrieved but had more precision. Results of the two searches are presented separately due to the differences in the search filters and databases used. However, the analysis and results based on the type of methodology and year of publication contain the results of both searches.

3.3 Results

3.3.1 Results of the initial literature review comprising the years 1976-2010

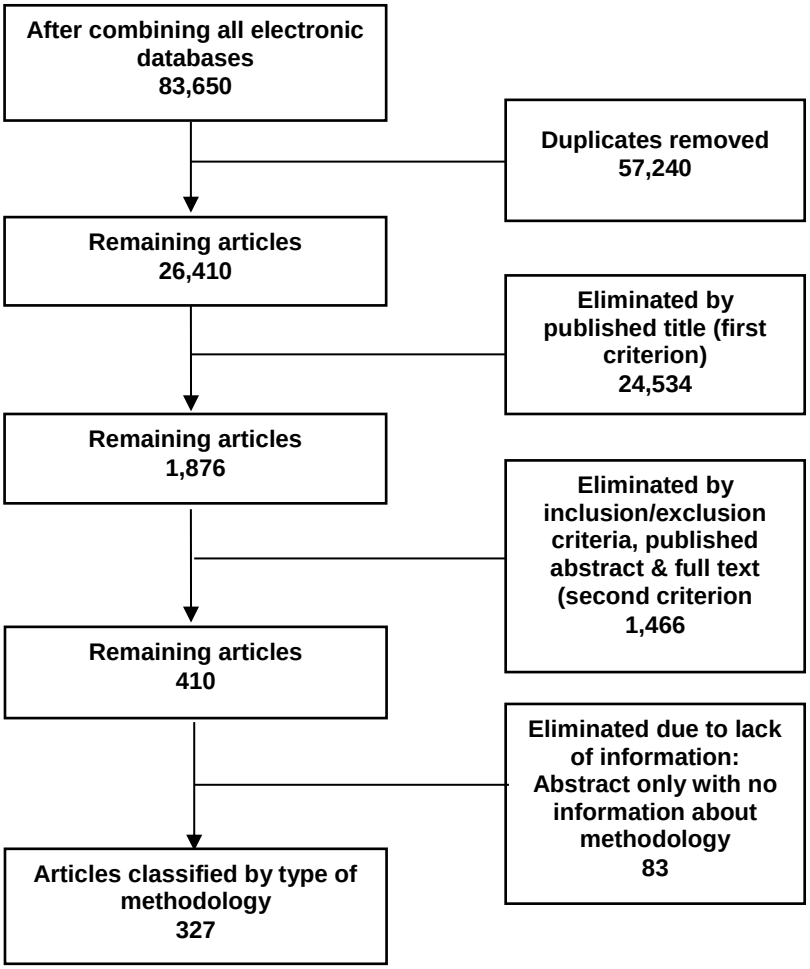
Table 3.5 shows the number of retrieved articles. The date of the publications ranges between 1976 and 2010. The number of articles retrieved is significant: 83,650. Since the search was designed to be sensitive, the number of duplicates was significant (68%). Only 7% were retained following de-duplication and examination by title. The second selection, based on published abstract, published articles and inclusion and exclusion criteria eliminated 78% of the remaining articles. From the 410 remaining articles, 327 were classified according to the type of methodology used. The remaining 83 were eliminated due to lack of information since only the published abstract was available (Figure 3.5).

Table 3.5 Retrieved articles after applying search filters

Vaccine	Medline, Embase, Econlit, CINAHL, Web of Knowledge, SCOPUS, NHS EED
Adenovirus	1,976
Diphtheria	3,922
Haemophilus influenzae type b (Hib)	2,479
Hepatitis A virus (HAV)	3,843
Hepatitis B virus (HBV)	5,434
Hepatitis C virus (HCV)	1,358
Human Papillomavirus (HPV)	3,954
Influenza	8,866
Influenza A(H1N1)	2,440
Measles	4,212
Meningococcal	1,790
Mumps	1,479
Pertussis	2,899
Plague	476
Pneumococcal	3,921
Poliomyelitis	2,601
Rotavirus	280
Rubella	1,967
Tetanus	3,096
Tuberculosis (BCG)	4,644
Varicella	3,430
Combined vaccines	
Diphtheria-Tetanus	2,829
Diphtheria-Tetanus-Pertussis	2,568
Diphtheria-Tetanus-Pertussis-HBV	1,057
Diphtheria-Tetanus-Pertussis-Hib	1,188
Diphtheria-Tetanus-Pertussis-Hib-Polio	1,045
HAV-HVB	2,927
HBV-Hib	919
Measles-Mumps	2,143
Measles-Mumps-Rubella	1,472
Measles-Mumps-Rubella-Varicella	1,067
Influenza-pneumococcal	999
Pneumococcal-meningococcal	369
Total (single and combined vaccines)	**83,650**

Articles ranging from 1976 to 2010

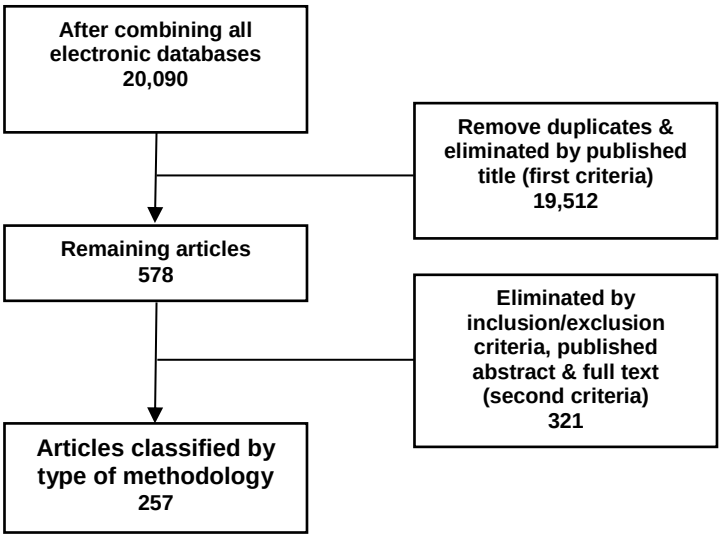
Figure 3.5 Processing of the retrieved results



3.3.2 Results of the update of the literature search comprising the years 2010-2017

In total 20,090 articles were retrieved. From those, 97% (19,512) were eliminated due to being duplicates or not fulfilling the first selection criteria. Following the second selection criteria, 257 articles were retained (Figure 3.6).

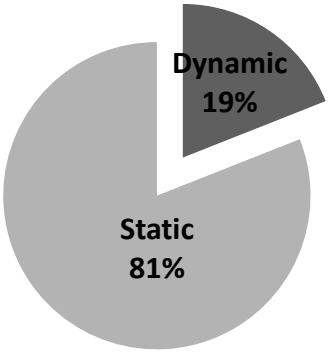
Figure 3.6 Processing of the retrieved results: literature review update



3.3.3 Classification by static and dynamic models

In total 584 articles were retrieved, 327 from the initial search and 257 from the update. Most models used in the literature were classified as Static (81%). The breakdown of study type is displayed in Figure 3.7.

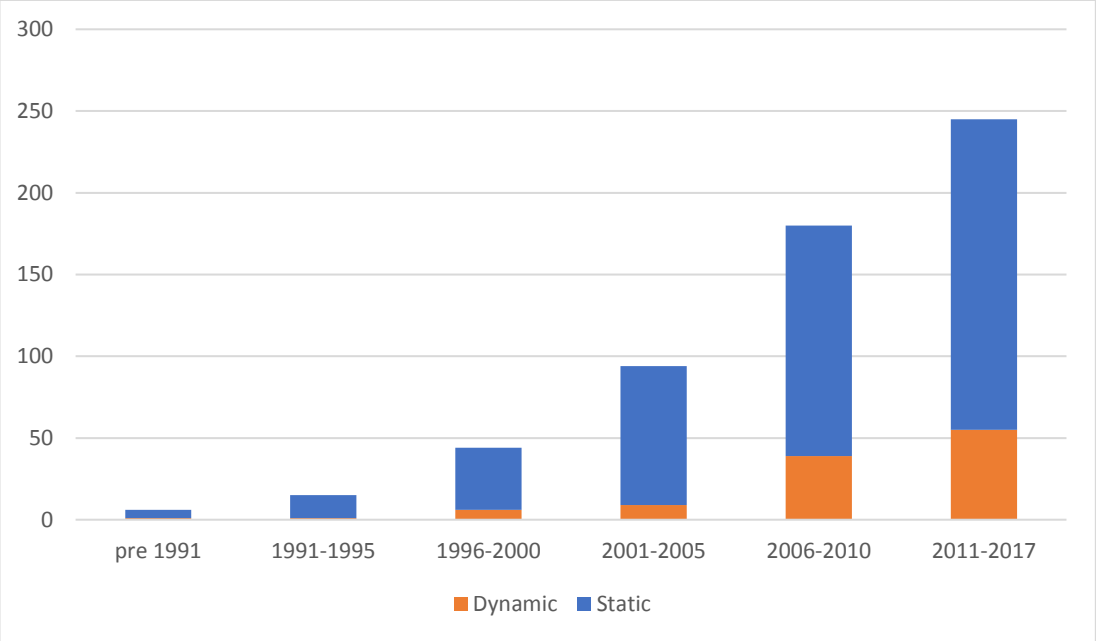
Figure 3.7 Static and dynamic model



The earliest selected article was published in 1981, was set in the US and followed a static approach (Patrick and Woolley, 1981). The first recorded dynamic article selected was performed in Italy, Europe (Carducci et al., 1989). Few articles were published before 1995 (6.4%), with the majority published after 2000 (80%).

Figure 3.8 shows the trend of published articles exploring the economic evaluation of vaccine interventions over time. Figure 3.8 also shows that the number of dynamic models has increased over time, however between 2011 and 2017, 71% of the retrieved articles still followed a static approach.

Figure 3.8 Static and dynamic models over time



The logistic regression (Table 3.6) showed that if the article was published after 2006 the odds of the model being dynamic were 2.3 times greater than if the article was published before 2006. If the cut-point was 2010, the odds ratio reduces to 1.5 for the latter group and is no longer statistically significant at the 5% level.

Table 3.6 Regression analysis: year of publication and approach

Logistic regression: Static *vs.* Dynamic Model reference: Static			
Before and after 2006		**Before and after 2010**	
Variable	**Odds ratio (95% CI)**	**Variable**	**Odds ratio (95% CI)**
Publication after 2006	2.3 (1.3 - 4.1)	**Publication after 2010**	1.5 (0.96 - 2.2)
Reference: Publication before 2006		**Reference: Publication before 2010**	
LR Chi^2 =10.38 p-value=0.0013* Pseudo R^2 = 0.018		**LR Chi^2 =2.89 p-value=0.072** Pseudo R^2 = 0.005**	

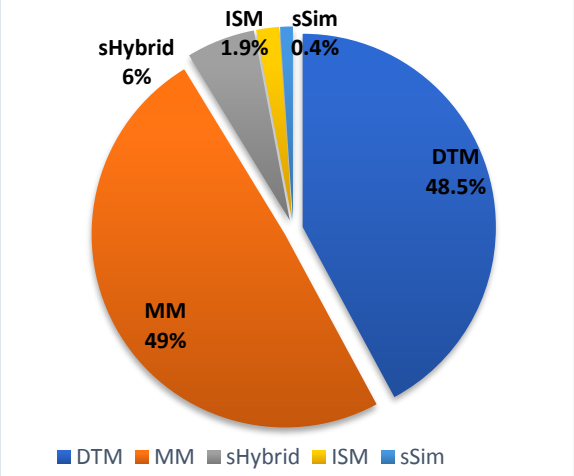
**Suggest that the model is statistical significant against a model with no independent variables*
***Suggest that model is only significant at 10% level against a model with no independent variables*

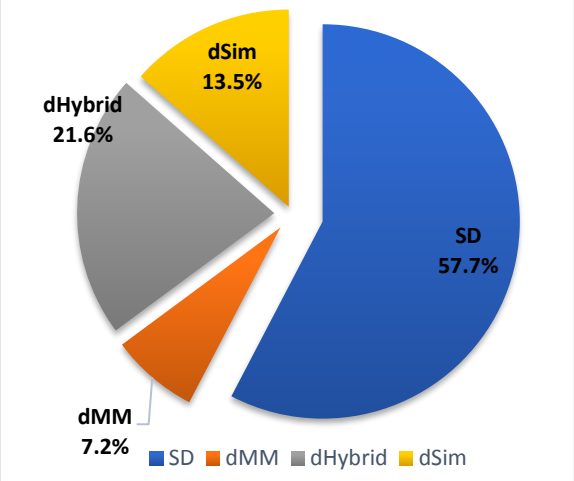
3.3.4 Classification by modelling technique

Static models can follow DTM, MM, sHybrid, ISMs, sSim and sDES while dynamic models follow an SD or compartmental, dHybrid, dMM, idMM, dSim, and DES approach. Figure 3.9 shows the type of methodologies used within the static and dynamic approaches.

The left-hand pie chart in Figure 3.9 shows the distribution of articles using static models. The majority followed an MM, DTM sHybrid approaches (97%). Nine studies followed an iMM technique: Sharma et al., (2012); Coupe et al., (2012); Goldie et al., (2012); Goldhaber-Fiebert et al., (2008); Diaz et al., (2010); Kim et al., (2009); Diaz et al., (2008); Goldie et al., (2008); Kim et al., (2008). Five used a simulation model (sSim): Aguilar et al., (2015); Kiatpongsan and Kim, (2014); Novaes et al., (2015); Walwyn et al., (2015); Najafzadeh et al., (2009).

Figure 3.9 Type of methodology used





Static	471*	Dynamic	111
MM	231	SD	64
DTM	198	dHybrid	24
sHybrid	27	dMM	8
ISM	9	dSim	15
sSim	5		

**Three articles were not possible to be classified as no access to the full text was possible*

The right-hand pie chart in Figure 3.9 details the results of dynamic models. Most of the dynamic models followed an SD, dHybrid or dMM approach (86.5%)[37], while 15 followed a simulation approach. Of those, two used an

[37] dMM could be considered a SD method as a SD approach is memoryless and is based on compartments.

agent-based model (ABM) (Olsen and Jepsen, 2010; Usher et al., 2008), and only one was clearly defined as DES (Vanni et al., 2012).

3.3.5 Regional Comparison of methods to estimate the CE of vaccine interventions

An analysis of how the type of approaches (static and dynamic) and methodologies (such as DTM, MM, sHybrid) are used around the world was developed. This analysis was only performed for the initial literature search (between 1976-2010). The full details and the analysis are shown in Appendix VI.

The main results showed that the greatest proportion of models around the world followed a static approach. Most static methods used a DTM or an MM technique. When dynamic methods were used, the preferred technique was SD; these results were maintained when analysed by first author's location.

The use of dynamic models was greater in Europe than North America (NA) or Latin America (LA). However, LA had the biggest proportion of dynamic models (26% vs. 24% and 13% in Europe and NA).

A logistic regression analysis showed that the geographical location or GDP per-capita had no influence on the type of model shown. It also showed that the use of dynamic models has increased over time. However, static models still predominate.

3.4 Summary of the papers by broad methodology category

3.4.1 Static models

The most analysed diseases were Pneumococcal related illnesses (Pneumococcal pneumonia, Meningococcal, Otitis), Influenza, Papillomavirus and cervical cancer and Hepatitis A, B or C. The vaccines were analysed for at-risk populations, (infants, elderly, general population, women) and in new, endemic and pandemic diseases.

In general, the authors has considered different attack rates depending on certain characteristics of the population under analysis (e.g. age, sex, risk

groups) as in this papers: Baltussen et al., (1997); Clark et al., (2009); Lee et al., (2010b).

The force of infection was estimated using different techniques depending on available data. Aballea et al., (2007a, 2007b) adapted the incidence rate from a different county to estimate the attack rate for a specific age group in their countries of interest. Beutels et al. (1996); Chodick et al. (2005) and Getsios et al., (2002) estimated *a priori* the attack rate based on the number of susceptible individuals at the beginning and end of the analysed age interval.

Secondary transmission was taken into account by some authors. Ellis et al., (2007); Purdy et al., (2004); Pechevis et al., (2003); Hibbert et al., (2007); Shiell et al., (1998); Valenzuela et al., (2005) considered intra-household transmission, whilst Suarez et al. (2008) took into consideration cross protection and waning effect.

The nine ISM models found were developed to estimate the CE of the Human Papilloma Vaccine (HPV): Goldie et al., (2012); Sharma et al., (2012); Diaz et al., (2010, 2008), Kim et al., (2008, 2009); Goldie et al., (2008); Goldhaber-Fiebert et al., (2008) were based on the modelling structure defined in Goldie et al., (2007) and Kim et al., (2007b). This model estimated the CE and natural history of cervical cancer via an individual-based stochastic model based on a Markov-like structure. The transmission rates were based on data for age-related HPV incidence rather than calculated through the actual transmission dynamics in the analysed population. The authors suggest that the model has the capability to be linked to an independent transmission model to measure the dynamics of the diseases properly. The latter is done in other articles performed using this methodology classified as dHybrid (Kim and Goldie, 2009, 2008a; Goldie et al., 2007; Kim et al., 2007a).

The only sSim identified explored the CE of Herpes Zoster (HZ) vaccine in Canada (Najafzadeh et al., 2009). The model is a DES and simulates individuals allocated to receive either the HZ vaccine or not. Individual characteristics such as age, sex, and medical history were randomly sampled. Probabilities of events were adjusted to account for vaccination status, age at vaccination and time since the vaccine was applied. The model also considered the waning effect of the vaccine. However, the risk

of acquiring the infection was not related to the proportion of infectious people in the population.

A common estimation of the potential HI effect was by comparing the incidence of the disease before and after the introduction of the intervention (Rubin et al., 2010; Poirier et al., 2009; Lloyd et al., 2008; Silfverdal et al., 2009; Ray et al., 2006, 2009). Some authors used the coverage, time since last vaccination, averted cases, the percentage of non-vaccinated population and gender to estimate an adjustment factor to mimic the HI effect (Chesson et al., 2008; Beutels et al., 1999; Lee et al., 2007).

Others accounted for the HI as a percentage reduction in the incidence of the analysed disease or as a case scenario in the sensitivity analysis: Akumu et al., (2007); Claes et al., (2009); Caro et al., (2005); Ginsberg et al., (1992); Giglio et al., (2010); McIntosh et al., (2005); Hubben et al., (2007); Hsu et al., (2003); Lee et al., (2008); Vespa et al., (2009); Tormans et al., (1998); Tilson et al., (2008); Welte et al., (2004).

Three catalytic models were identified; Zhuang et al., (2008); Thiry et al., (2004); Pham et al., (2012).

3.4.2 Dynamic models

SD models using partial differential equation and realistic age-structured transmission models to incorporate age structures were identified in several published articles e.g.: Gerlier et al., (2017); Shim et al., (2016); Meeyai et al., (2015); Knight et al.,(2014); Lenne et al., (2006); Trotter and Edmunds, (2006); Brisson and Edmunds, (2003, 2002); Wutzler et al., (2002); Coudeville et al., (1999); Pelletier et al., (1998); Williams et al., (1996a, 1996b)

Stevenson et al. (2002); De Wals et al. (2007) and Vanagas et al. (2010) resemble a SEIR (susceptible-exposed-infectious-recovered) type of model using a dMM. In each transition, the model estimates the number of effective contacts made by a person with an infected individual to estimate the number of expected cases in the next cycle. The number of effective contacts refers to an interaction between two individuals that result in an infection.

A total of 15 studies were found using dSim: Doroshenko and Qian, (2016); Brisson et al., (2016); Laprise et al., (2016); Drolet et al., (2014); Laprise et

al., (2014); Halder et al., (2014); Kelso et al., (2013); Vanni et al., (2012); Hontelez et al., (2011); Sander et al., (2010); Olsen and Jepsen, (2010); Robin de Vries et al., (2010); Sander et al., (2009b); Tediosi et al., (2009); Usher et al., (2008).

Sander et al., (2010, 2009b) considered different contact ratios depending on the location of the individuals (workplace, household, school or day care). The articles published by Olsen and Jepsen, (2010) and Usher et al. (2008), used an agent-based simulation where simulated individuals could choose partners, duration of their relationships and frequency based on their characteristics. Doroshenko and Qian, (2016) used an ABM to simulate Pertussis to explore the role of individual behaviour in an outbreak.

The most recurrent combination of dHybrid models was SD with DTM, followed by SD with MM and SD with iMM. The model known as Economic varicella vaccination tool for analysis (EVITA) was a recurrent structure. It combines a dynamic infectious disease model with an MM. SD was used to estimate the spread of the disease over time while the MM describes the course of varicella and its potential complication and the associated health-care resource utilisation (Hammerschmidt et al., 2003). The dynamic component is a partial differential equation model based on Halloran et al., (1994). Five articles were found using this approach: Bonanni et al., (2008); Hammerschmidt et al., (2007); Banz et al., (2009, 2003, 2002).

Four papers were identified that estimated the CE of HPV used a combination of SD and iMM (Burger et al., 2015; Kim and Goldie, 2009, 2008a; Kim et al., 2007a). The SD model was an open-cohort, age-structured compartmental model in which men and women form sexual partnership over time. The generated information was used to populate the iMM model which was used to compare multiple strategies for the prevention of cervical cancer.

3.5 Articles on the CE of the A(H1N1) pandemic vaccine

These were selected from the 583 retrieved articles. As shown in Figure 3.10, 74 articles were found to estimate the CE of seasonal influenza or pandemic influenza including the H1N1 and H5N1 virus subtypes. From

those, only pandemic influenza or A(H1N1) articles were selected resulting in 11 identified articles. Eighth were later discarded as not being related to the 2009 (H1N1) pandemic, being static or based on a specific population (Table 3.7 and Table 3.8).

Figure 3.10 Selection of the CE of A(H1N1) relevant articles

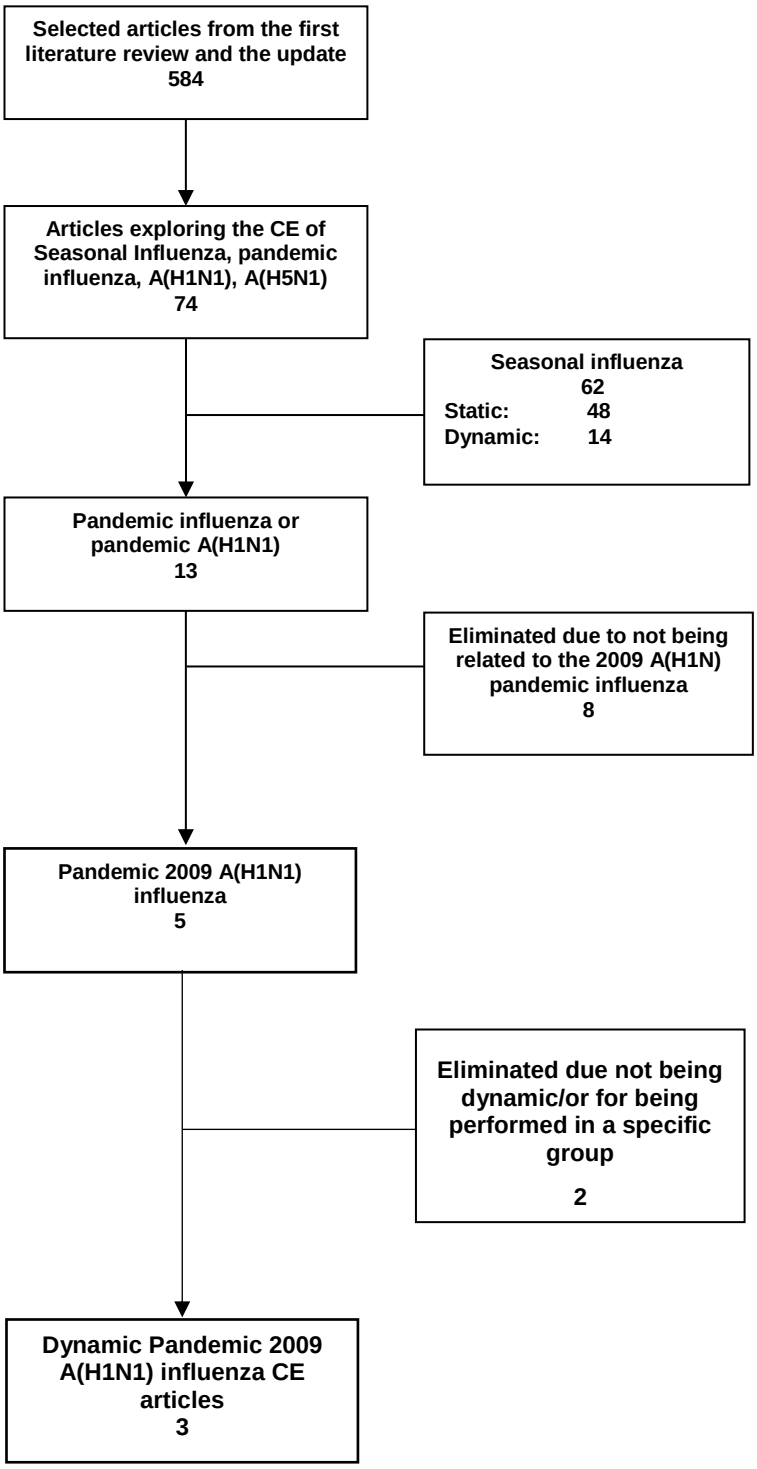


Table 3.7 List of rejected papers for not being related to the 2009 A(H1N1) influenza pandemic

Title	Authors (year)	Country	Disease	Type of methodology
A model-based economic analysis of pre-pandemic influenza vaccination cost-effectiveness	Halder et al., (2014)	Australia	Pandemic influenza	dSim
Vaccination strategies for future influenza pandemics: a severity-based cost effectiveness analysis	Kelso et al., (2013)	Australia	Pandemic influenza	dSim
Cost-effectiveness of vaccination against pandemic influenza in European countries: Mathematical modelling analysis	Lugner et al., (2012)	Germany, Netherlands & UK	Pandemic influenza	SD
Cost-effectiveness of Pharmaceutical-based Pandemic Influenza Mitigation Strategies	Newall et al., (2010)	Australia	Pandemic influenza	dHybrid: SD followed by DTM
Economic evaluation of influenza pandemic mitigation strategies in the United States using a stochastic micro-simulation transmission model.	Sander et al., (2009b)	US	Pandemic Influenza	dSim
Economics of employer-sponsored workplace vaccination to prevent pandemic and seasonal influenza	Lee et al., (2010)	US	Pandemic Influenza	DTM
Effectiveness and cost-effectiveness of expanded antiviral prophylaxis and adjuvanted vaccination strategies for an influenza A (H5N1) pandemic	Khazeni et al., (2009a)	US	Pandemic Influenza	dHybrid: SD followed by an MM
Economic Analysis of Pandemic Influenza Vaccination Strategies in Singapore	Lee et al., (2009)	Asia	Pandemic Influenza	DTM

Table 3.8 Rejected for being static/pertaining a group

Title	Authors	Country	Disease	Type of methodology
Economic evaluation of the vaccination program against seasonal and pandemic A/H1N1 influenza among customs officers in Greece	Mamma and Spandidos, (2013)	Greece	2009 A(H1N1) Pandemic influenza against customs officers	DTM
Cost-effectiveness of 2009 pandemic influenza A(H1N1) vaccination in the United States.	Prosser et al., (2011)	US	2009 A(H1N1) Pandemic influenza	DTM

Table 3.9 Selected articles exploring the 2009 A(H1N1) vaccine intervention

Title	Authors	Country	Disease	Type of methodology
Vaccination against pandemic influenza A/H1N1v in England: A real-time economic evaluation	Baguelin et al., (2010)	UK	Pandemic influenza A(H1N1) virus sub-type	SD
Is a mass immunization program for pandemic (H1N1) 2009 good value for money? Evidence from the Canadian experience[38]	(Sander et al., 2010)	Canada	Pandemic influenza A(H1N1) virus sub-type	dSim
Effectiveness and Cost-Effectiveness of Vaccination Against Pandemic Influenza (H1N1) 2009	Khazeni et al., (2009b)	US	Pandemic influenza A(H1N1) virus sub-type	dHybrid: SD and MM

Although not related to A(H1N1) the eight articles reported in Table 3.7 were reviewed to determine whether the conclusions could apply to the models developed in the thesis.

Lugner et al., (2012) concluded that the CE of a strategy was dependent on the time of vaccination, prior immunity, and the demographics of the country in which the outbreak occurs. The authors also state that typically strategies which targeted individuals defined by the authors as high transmitters (5-19 years old) were the most CE. However, in a population with a high proportion of older adults, where vaccines were available early, and where pre-existing immunity was assumed, vaccinating the elderly was

[38] An early version of this model was published in 2009 (Sander et al., 2009a), only the 2010 published version was included and commented on below

the most CE strategy. The model assumes heterogeneous mixing based on Mossong et al., (2008)

The paper published by Sander et al., (2009b) analysed 16 different strategies (including combinations of antiviral prophylaxis of the infected household or work/school contacts, pre-vaccination with a low-efficacy vaccine and school closures). The authors concluded that antiviral prophylaxis of the infected household and work/school contacts with unlimited stockpiling of antivirals and pre-pandemic vaccination is a cost-effective strategy. Adding school closures to this strategy is costlier but reduces the negative impact of the pandemic, reducing the infection rate, and morbidity and mortality.

The article published by Newall et al., (2010) suggested that a vaccination strategy before the start of the pandemic combined with antiviral treatment could be a CE strategy, but the results are uncertain as just over 50% of the probabilistic sensitivity analysis (PSA) iterations found this to be the case.

The article published by Khazeni et al., (2009a) explored three interventions to tackle a possible influenza A(H5N1) or bird flu virus. The authors concluded that the most CE intervention was one which assumed a sufficient stock of the adjuvanted vaccine to cover 40% of the population (expanded adjuvanted vaccination). Expanded antiviral prophylaxis, however, was dominated by expanded adjuvanted vaccination.

Kelso et al., (2013) examined the CE of plausible combinations of social distancing, antiviral and vaccination interventions in the event of influenza pandemic assuming a delay of 6 months between the start of the pandemic and the availability of the vaccine. Halder et al., (2014), however, estimated the CE of a pre-emptive vaccination strategy before a pandemic, assuming different levels of vaccine efficacy. The publications used the individual level simulation model, which focuses on a population of 30,000 people in Australia. The model assumed that potential infectious contacts would occur in households, workplaces and randomly in the community. Three different severities of the pandemic were analysed: mild; moderate, and extreme. Kelso et al., (2013) found that a vaccine intervention (arriving six months after the onset of the pandemic) was not CE on its own for any of the pandemic scenarios analysed. Only when the pandemic-size was

assumed moderate adding vaccination to long-term social distancing was CE. Halder et al., (2014), however, found that a pre-emptive vaccine of at least 30% effectiveness is more cost-effective than a reactive vaccination strategy. However, these results were sensitive to the population covered.

Lee et al., (2009) developed a DTM to estimate the cost-benefit and CE analysis of vaccination versus treatment with antivirals alone in a potential pandemic influenza event in Singapore. The authors suggest that the pandemic vaccination is only cost-effective in severe pandemics with vaccines of high efficacy and low cost. However, the study did not consider the potential impact of HI as the model used was static.

One of the rejected articles estimating the CE of a vaccine against the 2009 A(H1N1) performed by Mamma and Spandidos, (2013) explored the 2009 A(H1N1) vaccine in a specific group of the population. The total number of individuals analysed was 3,309. Since this was not an enclosed population group, the general population HI effect of vaccination is negligible. However, if this strategy is part of a greater intervention the HI from vaccinating other groups of individuals might be a factor in determining the vaccine effectiveness of the intervention, although the authors did not consider this.

Research performed by Prosser et al. (2011) examines the CE of the 2009 A(H1N1) in the US population using a DTM model. The authors did not include HI as they consider this effect to be uncertain under the circumstances that surrounded the vaccine intervention. Their results suggest that the vaccine was cost-saving for persons aged six months to 64 years, but that their results were sensitive to the number of vaccines doses needed; costs of vaccination; illness rates; and timing of vaccine delivery.

As seen in Table 3.9, the three selected studies were published in high GDP per capita countries. Two were based on SD approach performed in England and the US (Baguelin et al., 2010; Khazeni et al., 2009b) and one using dSim based in Canada (Sander et al., 2010).

The article published by Baguelin et al., (2010) performs a CE analysis of alternative influenza A(H1N1) vaccination strategies. The model used was an age and risk group structured ODE model (classed as SD in the terminology of this Chapter). The model considered three risk groups:

seasonal influenza risk groups, pregnant woman, and individuals not at risk. The population was split into seven age groups (from under one year to 64 years and over). The model assumes heterogeneous mixing based on Mossong et al., (2008). The authors used data they had collected themselves to determine the QALY losses for an episode of A(H1N1).

The analysis was performed in real-time whilst the pandemic was ongoing. It is likely that the data available, was an underestimate of the actual number of infections. Therefore, the number of susceptible individuals still available in the population was unknown. To account for this, the authors tested different rescaling factors to predict the Autumn wave of the pandemic. A multiplier of 10 provided a '*reasonable fit*' to both epidemic waves, the autumn growth rate, and proportion of children who seroconvert and was used as the base case, while two other multipliers were used as sensitivity analysis (7.5 and 12.5). The authors showed that lower reporting levels (higher multiplication factors) result in a smaller second wave. The model was calibrated by minimising the Poisson deviance between the available data and the model estimations. The best-fitting 1% iterations were used to predict the impact of different vaccine interventions.

Costs and outcomes (measured in QALYs) followed the NHS perspective and using the National Institute for Health, and Care Excellence (NICE) reported thresholds (£20,000 and £30,000), to determine CE. The author's conclusion suggests that vaccinating the high-risk groups is the most CE strategy. The probability of this strategy to be CE is over 90% for a £20,000 threshold. However, the conclusion when the costs of the vaccine are assumed not to be sunk, and the Government can decide not to purchase the vaccine is not as clear, as the probability of CE is reduced to 15% and 43% for the £20,000 and £30,000 threshold. All other sensitivity analyses performed, show that vaccinating only the at-risk groups is highly CE. If the strategy is extended to groups considered not to be at risk, extending it to those aged 5 to 14 years was shown to be the most CE alternative. However, this result was more sensitive to model assumptions such as vaccination timing.

The article published by Khazeni et al., (2009b) used an ODE model (classed as SD) and an MM model to estimate the CE of the influenza pandemic A(H1N1) vaccine. The study compares two vaccination strategies against the no-vaccination scenario (different levels of

vaccination coverage either starting mid-October or mid-November 2009). The model assumed homogeneous mixing. The authors found that the CE was dependent on the speed at which the pandemic grows and the covered population. The authors suggested that early vaccination would be more relevant for rapid growth pandemics. The results assumed three sizes of the pandemic: R_0 values of 1.2, 1.5 and 1.8. The authors performed one-way uncertainty analyses on key parameters (including the pandemic-size), and a PSA but without including uncertainty in the contact parameters. Adverse events due to vaccination were considered, but productivity losses were not.

Finally, the article published by Sander et al., (2010) used an individual level simulation model estimating a mass vaccination campaign against the 2009 A(H1N1) pandemic in a city of 13 million individuals. Individuals were assigned (based on demographic data from the studied location), an age class, a community a household plus a day care, school or workplace depending on their age. The vaccination campaign began at the end of October 2009 (two weeks before the peak of the pandemic) with approximately 45% of the total population assumed to have been vaccinated within a period of 14 weeks. The base case scenario assumed a vaccine protection of 70% (altered to 80% for the sensitivity analysis). The estimated ICER of $9,388 CAN per QALY gained suggested a CE intervention. The analysis neither included adverse events due to vaccination nor productivity losses.

3.6 Summary

The initial literature review (with a cut-off date of the 31st of July 2010) identified 327 relevant articles. The update (from the 1st of August 2010 until the end of April 2017[39]) found an additional 257 relevant articles (making 584 in total). This search naturally found more relevant hits than the 276 found by Kim and Goldie, (2008b) who reviewed the literature between 1976 and 2007, however, consistent with their findings, most of the published articles found followed a static approach (83%). Most static papers followed a DTM or MM methodology. The SD or compartmental

[39] See Section 3.3.5 for details about the cut-off date

modelling technique was the preferred technique when using a dynamic model.

In contrast with the results found by Kim and Goldie, (2008b), the literature review identified some simulation models, both static and dynamic.

Chapter 4. ODE model

4.1 Overview of the Chapter

This Chapter details the model used to estimate the CE of the A(H1N1) vaccine during the 2009 pandemic in Mexico using an ordinary differential equation (ODE) method based on a susceptible-exposed-infectious-recovered (SEIR) approach. The model assumed a heterogeneous mixing pattern in a closed population and used a Markov chain Monte Carlo (MCMC) routine to generate probabilistic estimates.

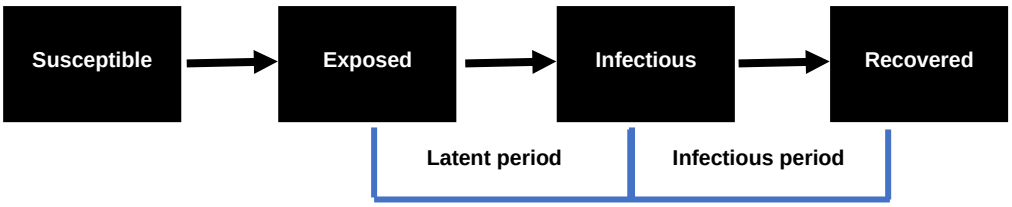
Section 4.2, defines the infectious disease model using ODE. Section 4.3 describes how the model was constructed, as well as the main assumptions and initial settings. Section 4.4 describes the calibration, parameterisation and results while 4.5 provides a summary of the Chapter.

4.2 Defining the infectious disease model using ODE

The ODE model was constructed using standard infectious disease modelling techniques with disease progression in individuals characterised by the latent period and the infectious period. A differential equation model was constructed that partitions individuals into four categories: susceptible; exposed; infectious; and recovered.

The latent period is defined as the time from infection to when the host is first able to transmit the disease to another individual (that is, becoming infectious). The infectious period comprises the period in which the individual can transmit the disease to others. Figure 4.1 represents this process in the context of a SEIR model.

Figure 4.1 graphical representation of the SEIR model approach



This type of model structure has been used previously to estimate the spread of the 2009 influenza pandemic. Eames et al. 2012 replicated the 2009 A(H1N1) pandemic in

the UK using an ODE, age-structured model. A brief theoretical background description of compartmental models that include ODE models can be found in Appendix II).

The ODE model constructed here considered the entire Mexican population and assumes a heterogeneous mixing structure, based on age group. The model assumes a closed population, assumption that was though reasonable since the duration of the pandemic was relatively short.

Death due to the illness or due to natural causes was not considered in the epidemiological model. However, the impact of any death due to an infection with the A(H1N1) virus, was taken into consideration when estimating the CE of the vaccine. This is discussed in further detail in Chapter 6. This assumption was made to simplify the modelling and adjustment process and due to limited data on A(H1N1) attributable deaths.

4.3 Model structure

4.3.1 Temporality, population and age groups

The first case of A(H1N1) influenza in Mexico was reported at the beginning of March 2009, while the end of the pandemic was declared by August 2010.

The National Council of Population or CONAPO (by its name in Spanish) records data on the population of Mexico by age and sex. CONAPO estimates the population at the beginning and middle of each the year. For the analyses undertaken in this thesis, the population in mid-2009 was used: 107,507,300 individuals (CONAPO, 2012).

The total population was categorised by age. In Mexico children between 3 or 4 and 15 years of age are obliged to attend school. In addition, children from 3 months until three years can attend nursery. Individuals aged 16 years or older can enter the labour market or continue with high school and undergraduate or postgraduate studies.[40] The 30 to 60-year-old age group mainly constitutes the core of the working population. The retirement age for most the population is between 60 and 65 years.

The following age groups were considered appropriate given the spread of the lab-confirmed cases and the general population distribution of activities (school age

[40] In 2011, a reform in the law made high school or superior level education mandatory, meaning that people would not be able to access the labour market until they are 18 years.

individuals, working class and retirement age): 0 to 15; 16 to 29; 30 to 59; and 60 years and over. Table 4.1 shows the distribution of cases and the total population in each age group.

Table 4.1 Distribution of infected cases and total population in the selected age groups

Age	Number of lab-confirmed cases* (%)	Total population (%)
0 to 15	29,414	33,034,807
	(47)	(31)
16 to 29	17,657	27,078,077
	(28)	(25)
30 to 60	14,616	38,306,904
	(23)	(36)
60 and over	1,273	9,087,542
	(2)	(8)
Total	62,960	107,507,330

**Total number of lab-confirmed cases from March (start of the pandemic) until November 2009 (last month of the daily recording of lab-confirmed cases).*

4.3.2 Contact matrix

The rate at which infection was spread throughout the defined age groups was dependent on the prevalence of infectious individuals within the population, the prevalence of susceptible individuals and the numbers of effective contacts made by a susceptible individual. The effective contact rate was determined based on the assumed number of contacts made by individuals and the rate of transmission of disease.

A 4 x 4 contact matrix was defined to determine the number of contacts made by individuals in each age group. No information on how individuals in Mexico enter into contact with each other exists. Therefore the entries were based on POLYMOD (Mossong et al., 2008). The contacts between the aimed age groups from the UK were adjusted by the size of the population in Mexico and reciprocity.

Table 4.2 Assumed contact Matrix for the Mexican population based on POLYMOD

	0-15	16-29	30-59	60+
0-15	11.83	2.54	4.19	0.83
16-29	2.81	8.51	4.48	0.99
30-59	3.64	3.51	5.59	1.03
60+	2.97	3.21	4.27	0.84

While the contacts between individuals in different age groups were fixed, the numbers of effective contacts were included within the MCMC process (described in Section 4.4 of this Chapter).

Based on the lab-confirmed dataset, the spread of the disease in Mexico showed three waves (described in Chapter 2). An initial rise in cases was followed by the first decline which was created by the implementation of several Government actions (between 27th April and 29th May). After the government measures, there was a subsequent increase in the number of confirmed cases. The second decline coincided with the end of the school term presumably due to the reduction in the numbers of contacts per child of school age. Towards the end of this second wave, on the 18th July, the Mexican government announced the decision to purchase the vaccine as they were expecting a third wave once the school resumed at the end of August 2009.

It was assumed that both Government actions and school holidays would result in fewer effective contacts per individual due to a reduction in contacts. To not overfit the model, it was assumed that the decrease in effective contacts was identical for both Government actions and school holidays. A “reduction in contacts” parameter was used to reduce the contacts during the periods described above. The parameter was included within the MCMC process (Section 4.4).

4.3.3 Under-reporting and pre-existing immunity

Under-reporting

The information on the total number of lab-confirmed cases provides insight on how the disease spread during the pandemic emergency. However, the actual number of infections within the population is unknown as the lack of virological evidence would have resulted in an underestimation of this number. It is also likely that a significant

number of individuals with A(H1N1) were asymptomatic or had sufficiently mild symptoms that they did not seek medical attention (Eames et al., 2012; Chowell et al., 2011; Elizondo-Montemayor et al., 2011). As such, it is thought that the available dataset containing only lab-confirmed cases could significantly underestimate the actual number of infections that occurred during the pandemic.

A total of four reporting rates (RR) were included into the model (one for each age group). These parameters were introduced to rescale the spread of the disease to match the available information, in this case, the number of lab-confirmed cases in the population. (more details on how these parameters were calibrated in Section 4.4).

Pre-existing immunity

Pre-existing immunity was likely, particularly in older age groups. Therefore, the model considers those individuals who could not contract the disease, based on prior immunity. Sensitivity analysis was performed assuming no prior immunity.

4.3.4 Vaccination

The reduced probability of acquiring the disease when a susceptible individual receives a vaccination depends on the degree of protection that the vaccine confers. Any protection, however, is not immediate and is related to the type of vaccine and individual characteristics.

Non-immunised individuals can benefit from a vaccination campaign. If the vaccination strategy is significant, they face a reduced probability of meeting an infectious individual and their probability of acquiring the disease decreases. This phenomenon is known as herd immunity (HI) and affects how the disease spreads in the population.

The Mexican Government purchased approximately 30 million vaccines. The vaccination campaign began on the 27th November 2009 and ended on the 21st of April 2010 lasting 145 days in total. Although the campaign was focused initially on vulnerable groups, for simplicity the CE of two vaccination strategies was tested: i) vaccinating groups in proportion to the size of each cluster (population strategy) and ii) vaccinating groups in proportion to the numbers of lab-confirmed cases at 18th of July 2009 (lab-confirmed strategy). Table 4.3 shows the estimated proportions vaccinated under each strategy.

Table 4.3 Proportion of vaccines applied under the two scenarios

Age groups	Population Strategy	Lab confirmed strategy
0-15	31%	51%
16-29	25%	28%
30-59	36%	20%
60 over	8%	1%

The model assumes that a proportion of the vaccinated individuals would become permanently immune to the infection while non-responders will remain susceptible to infection. This percentage was given by the effectiveness of the vaccine (details provided below).

A lag was introduced from the time of the vaccination to when protection was conferred. The lag was assumed fixed at 14 days (Córdova-Villalobos et al., 2010).[41] In accordance with the immunisation strategy of the Mexican government during the 2009 A(H1N1) pandemic, only one dose of the vaccine was modelled.

The model allows the possibility of considering several different strategies such as universal or targeted vaccination, and different vaccination schedules. However, the fact that the population was categorised by the age groups stated above, limits the possibility to test scenarios of targeted vaccination at subgroups such as pregnant women or alternative age groups such as 0 to 2-year-olds for example.

The model assumes that the vaccine was applied at a constant rate during the duration of the campaign. It is also assumed that although a proportion of already exposed or infectious individuals might have been vaccinated, this would not have an effect on their disease or on the probability of infecting other individuals. The following set of differential equations describes the model (Equation 4.1). Whilst people who have recovered may be vaccinated this would not affect the disease dynamics.

[41] According to Córdova-Villalobos et al. (2010) the maximum immunity could be achieved between two and four weeks. It was assumed that the average time was of two weeks, as this was also the mean value assumed in Baguelin et al. (2010)

Equation 4.1 Differential equation model including a vaccine intervention

$$dS_i/dt = -\beta\phi S_i \sum_j \mathrm{B}_{i,j} I_j/n_j - vS_i$$

$$dE_i/dt = \beta\phi S_i \sum_j \mathrm{B}_{i,j} I_j/n_j - r\,E_i$$

$$dI_i/dt = rE_i - gI_i$$

$$dR_i/dt = gI_i + vS_i$$

Where:
$S_i =$ *Suseptible population in age group i*
$E_i =$ *Exposed population in age group i*
$I_i =$ *Infectious population in age group i*
$R_i =$ *Recovered population in age group i*
$\beta =$ *rate of transmission*
$\phi =$ *Reduction in contacts parameter*
$\{\mathrm{B}_{i,j}\}$ = Contact Matrix: *number of contacts per unit time each individual in group i makes with individuals in group j*
$n_j =$ *Size of group j*
$r =$ *Infectious rate or*
$r = 1/_{latent\ period}$
$g =$ *Recovery rate or*
$g = 1/_{Duration\ of\ infectiousness\ or\ infectious\ period}$
$v =$ *rate of vaccinated individuals*
$i = 1, 2, 3, 4$ *for each age group*
$j = 1, 2, 3, 4$ *for each age group*

4.3.5 Software

The software used to construct the model was R. R allows an MCMC approach to be employed allowing probabilistic analysis to be conducted.

4.4 Calibration

The calibration process fitted the output of the ODE model to the lab-confirmed data when taking RRs into consideration. The model was calibrated up to the time at which the decision to purchase the vaccine was announced. Therefore, only data known or estimated up to this time point was used where available. If necessary, values from later periods were used and sensitivity analyses performed. From the data known at the date of the decision to purchase the vaccines, it was not possible to robustly estimate the number of susceptible individuals in the population at that time point. Therefore, it was necessary to make some assumptions regarding the RR. Three scenarios were considered using different reporting rates for the 0-15-year-old age group: 0.001 (one lab-confirmed per 1,000 infected), 0.01 (one lab-confirmed per 100

infected) and 0.75 (one lab-confirmed per 1.33 infected) RRs. The calibration, (which included the relative RRs for the remaining age groups) was undertaken for each of the three RRs.

An MCMC approach was used for the calibration. MCMC are algorithms used to generate a sample from the joint posterior distributions, which may not follow any standard parametric form and allow the correlations between the chosen parameters to change to be maintained.

The process was categorised into seven steps following Vanni et al. (2011). A summary of the main characteristics of the adjustment process are mentioned as follow:

1. Selection of the parameters to be varied in the calibration process

   Five parameters were adjusted: rate of transmission ($\boldsymbol{\beta}$); Three RRs with the RR in the 0-15 age group assumed to be fixed at three different values: (0.001, 0.01 and 0.75); three parameters providing the relative RRs in the 16-39 years, 40-59 years and 60 years and over groups; and a reduction in contact parameter (described in section 4.3).[42]

2. Selection of the calibration targets
   Data on lab-confirmed cases compiled by the MMH for each of the four age groups (0-15, 16-29, 30-59 and 60 & over)
3. Definition of the measure of goodness of fit (GOF) to be used
   A Poisson likelihood was used for the lab-confirmed counts where the rate parameters were determined by the ODE solution and the RR parameters.
4. Definition of the parameter searches strategy
   An MCMC method using an Automated Factor Slice Sampling method as described in Tibbits et al. (2014) implemented in R following code developed by Dr Peter Dodd (University of Sheffield). This method was thought to be more suitable than affine invariant approaches due to its ability to produce traditional diagnostic tests to ensure that there was good mixing within the MCMC chains.
5. Definition of what determines an acceptable GOF parameter set or convergence criteria
   Several convergence diagnostics were undertaken to assess the validity of the adjustment: trace and density plots; assessment of the correlation between the

[42] A model with only three variables was tested but the Akaike information criterion (AIC) applied to the maximum-likelihood fit showed that the 6 variables model was a better fit.

chosen parameters; autocorrelation between draws; visual overlay of chains and Gelman-Rubin multiple sequence diagnostic test (diagnostic graphs for the 0.01 RR are shown in section 4.4. The rest are shown in Appendix IV)

6. Determination of the termination rule of the calibration
   The calibration process was terminated when convergence was achieved, evaluated with the diagnostic tests described in point 5.
7. Integration of the model calibration results and economic parameters.
   Independent draws from a thinned chain were used to run the model with and without vaccine to estimate the CE of the vaccine using the data at the time the decision was made.

4.4.1 Calibration process

The model use data from the 12th April at which point the numbers of lab-confirmed infections rapidly increased, to the 18th of July 2009 the date at which the decision to purchase the vaccine was made public (day 98 in the model).

The ODE model in R, used the "DeSolve" package (to solve the differential equation model) followed by the "Optim" package, to obtain the "best fitting" answer given the data to use as starting point for the MCMC process.

The optimisation was performed using the Nelder-Mead method as it produced results more quickly than other methods tested. It was thought that using a different optimisation method would not have an impact on the end results of the adjustment provided that the MCMC chains mix appropriately after a burn-in period.

The "best fitting" answer was perturbed randomly using a multiplier of 1+ draw of a normal distribution function (0,1)/5 to establish different starting points for each chain in the MCMC routine.[43] Three perturbations were used in the MCMC routine.

The mixing of the chains was tested using trace and density plots, correlation, and autocorrelation test. The MCMC chains exhibited good mixing as shown in Section 4.4.3 and Appendix IV.

This process was undertaken for three reporting rates for the 0-15-year age group: 0.001; 0.01; 0.75. These three parameters were chosen to explore a broad range of RRs. A 0.75 RR was assumed to constrain the RR in the 15-29 group to be below

[43] The 95% CI of the multiplier was between 0.6-1.4

100% based on analysis of preliminary results. This RR was considered high enough to show the potential impact of the vaccine in a high reporting rate scenario.

4.4.2 Parameterisation of variables not included in the MCMC routine

Prior-immunity and recovered population at the start of the model: a literature search in OVID Medline attempting to identify on serological testing articles to estimate prior immunity to the 2009 pandemic virus found no specific papers relating to the Mexican context.[44] As such, data by Miller et al., (2010) on serum samples obtained in 2008 to assess the prevalence of antibodies to the 2009 A(H1N1) pandemic was used. This assumption imposes a limitation as the potential values used are specific to the UK context, and the Mexican Government did not know these data at the time of the decision although it is likely that it would have suspected some immunity. Pre-existing immunity was assumed per age group (Table 4.4) with such people assumed to be recovered. To explore the impact of the limitations in the prior immunity data used a sensitivity analysis was conducted assuming zero prior immunity.

Infected and exposed population at the beginning of the model: it was assumed that the number of infectious people in the model was the same as the number of exposed. These values were calculated based on the actual number of lab-confirmed cases at the beginning of the modelling process (12th April 2009) adjusted by the RR scenario.

Susceptible population at the start: total population in Mexico during 2009 (107,507,330) minus pre-existing immunity (recovered), infected and exposed population.

*Mean g*eneration time: This was set in the base case to 1.9 days, based on Fraser et al. (2009) and assuming a latent period of 1 day and an infectious period of 1.8 days. The Fraser et al. (2009) estimation, however, does not provide a breakdown for the latent and infectious period. To facilitate populating the model, a study published after the conclusion of the pandemic was used (Eames et al., 2012), which assumed a latent and infectious period of 1 and 1.8 respectively. These values were derived by a modelling work by Baguelin et al. (2010) using data from the UK between 1st June and 18th of October 2009. Using the definition of the generation time by Cummings and

[44] The Mesh terms used were: Seroepidemiologic Studies; Influenza Human; Influenza A Virus; H1N1 subtype; Influenza A virus; Influenza Vaccine; Pandemics; Antibodies Monoclonal; Cross Reaction; Antibodies, Viral; Pre-existing immunity AND Mexico

Lessler, (2014) [45], the Eames et al. (2012) values have a generation time of 1.90 days which is very similar to the value of 1.91 generation time estimated by Fraser et al. (2009). Given the costs associated with the purchase of the vaccine, it was likely that the MMH would have been attempting to estimate the relative size of the latent and infectious period, and it was assumed that this would be similar to the ratio provided in Eames et al. (2012).

To assess the sensitivity of the model to generation time, scenario analyses were also undertaken assuming the lower and upper CIs of generation times estimated by Fraser et al. (2009) (1.3 and 2.71) and the CE of the vaccine intervention estimated (Chapter 6).

Contact matrix: see details section 4.3.2

RRs: the RR for the 0-15 age group was set as reference and was fixed at 0.01, 0.001 and 0.75

Vaccine effectiveness: was not included as the epidemiological model was calibrated only up to the point where the decision was made.

Table 4.4 provides a summary of the different parameters used in the model, their assumed values and the acronym used in the text of the thesis.

[45] The following definition of mean generational time was used: *"If infectiousness is evenly distributed across the infectious period, then the mean generation time will be equal to the mean latent period plus one-half the mean infectious period"* from Cummings and Lessler, (2014).

Table 4.4 Parameters utilised in the model

Parameter	Acronym	Value	Source/Comment
Pre-infectious or latent period	-	1 day	Eames et al., (2012)
Infectious period	-	1.8 days	Eames et al., (2012)
Rate of recovery	g	1/1.8	
Rate of becoming infectious	r	1/1	
Rate of transmission of the disease	β	Calibrated	-
Reporting rates			
0-15	RR_1	0.001; 0,01; 0.75	Three models were run, one for each RR
16-29	RR_2	Calibrated	
30-59	RR_3		
60 and over	RR_4		
Pre-existing immunity*			
0-15	p_1	2.79%	Miller et al., (2010)
16-29	p_2	17.50%	
30-59	p_3	12.00%	
60 and over	p_4	23.32%	
Susceptible and recovered individuals at the start of the model			
0-15	S_1, R_1	-	Susceptible: total population minus pre-existing immune individuals, initial infected and exposed Recovered: pre-existing immune individuals
16-29	S_2, R_2	-	
30-59	S_3, R_3	-	
60 and over	S_4, R_4	-	
Values for both the initial infected and exposed at the start of the model			
0-15	I_1, E_1	$8/RR_1$	Derived from the actual number of lab-confirmed cases and adjusted according to the RR used
16-29	I_2, E_2	$6/RR_2$	
30-59	I_3, E_3	$6/RR_3$	
60 and over	I_4, E_4	$2/RR_4$	

*Based on Miller et al., (2010) who reported data for the 0-4; 5-14; 15-24; 25-49; 50-64; 65-74; 75-79 and 80 and over age groups. The data from 0-4 and 5-14 were used to estimate the 0-15 pre-existing immunity; the data of the 15-24 age group was assumed for the 16-29 age group. The data of the 25-49 and 50-64 age groups was used for the 30-60 while the 65-74; 75-79 and 80 for the 65 and over age group

4.4.3 Results from the MCMC routines

The diagnosis tests showed good mixing of the chains while correlation was observed between parameters. After a burn-in of 5,000 iterations followed by 5,000 further iterations, the chains were evaluated to determine if they had converged. The first diagnostic was performed by via a visual inspection of a trace plot. The trace plot aids in determining whether the chain is mixing well (moving around the parameter space).

The parameters were transformed to logarithmic form for the calibration and referred as in the diagnostic charts: reduction in contact parameter: logRedBeta; RR 60 and over:

logRR4Mult; RR 30-59: LogRR3Mult; RR 16-29: LogRR2Mult; rate of transmission: LogBeta. Figure 4.2 provides the results when assuming an RR of 0.01 for the 0-15-year age band.

Figure 4.2 pane a displays the results of the trace plot and shows that the chain has a good mixing around the parameter space for all the calibrated parameters.

Figure 4.2 pane b shows density and correlation plots. These plots aimed to determine the normality of chain and if correlation between the calibrated parameters existed. As observed, the density plot of all five parameters appears to follow a normal distribution. Furthermore, the correlation observed is consistent with what it is expected, for example, the rate of transmission (named as Beta in the graph) had a negative relationship with the reduction in Beta. This was anticipated, as for higher values of Beta, bigger reductions in Beta during Government closures and school holidays assist in fitting the fixed data better.

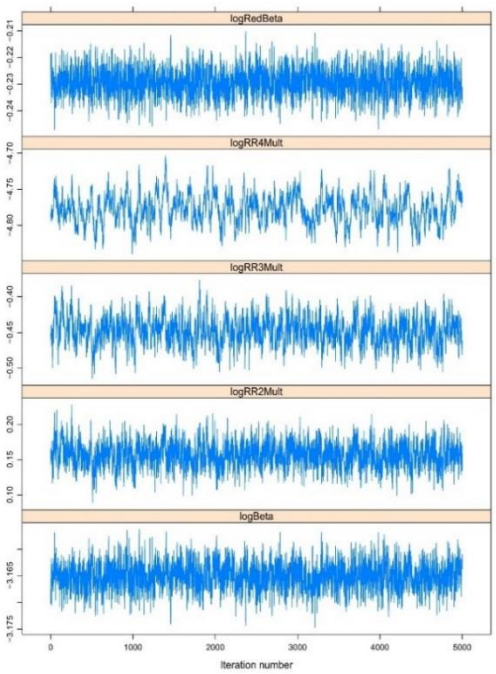
Figure 4.2 pane c provides a visual representation of the autocorrelations between draws. In a chain with a good mixing, it is expected to see that the *kth* lag autocorrelation becomes smaller as *k* increases. Autocorrelation was observed to be zero or near to zero at the 25^{th} lag. This value was therefore used to thin the chain, with 5,000 iterations after the burn-in period being reduced to 200 samples to use in the PSA.

Figure 4.2 pane d shows an overlaid trace plot. This test has an objective to test if different starting values will reach the same parameter space. As described in section 4.4.3, three different perturbations from the “best fitting” answer were evaluated. It can be observed the three chains overlap considerably.

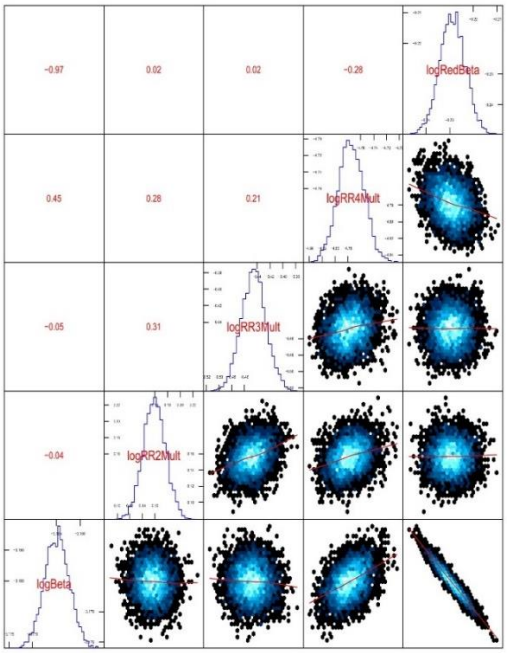
Additionally, the Gelman-Rubin test was performed on the chains used. This test uses the within-chain and between-chain variance to calculate the potential scale reduction factor. This factor should be below 1.1 for all parameter. Otherwise, the chain needs to be run further. Both Figure 4.2 pane e and pane f show that the potential scale reduction factor in all parameters reaches a number very close to 1 at 5,000 iterations after the burn-in period. The diagnostics plots of the 0.001 and 0.75 RR scenarios can be found in Appendix IV.

Figure 4.2 Trace plot, density plots and correlation for the 0.01 reporting rate scenario

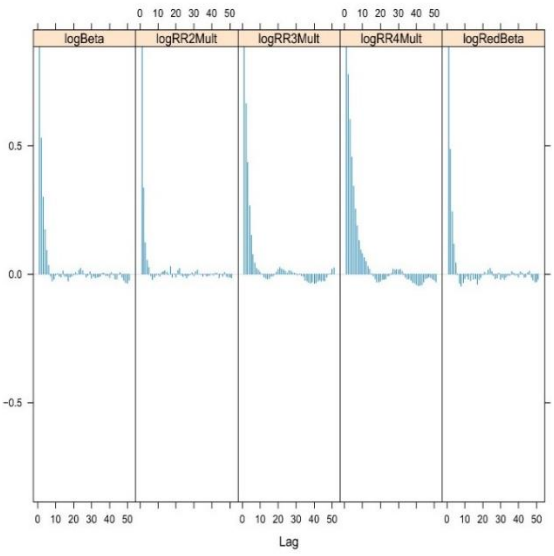
a) Trace plot



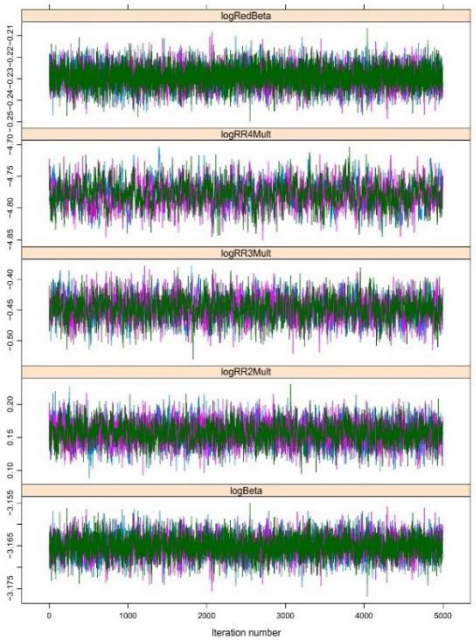
b) Density and correlation plots



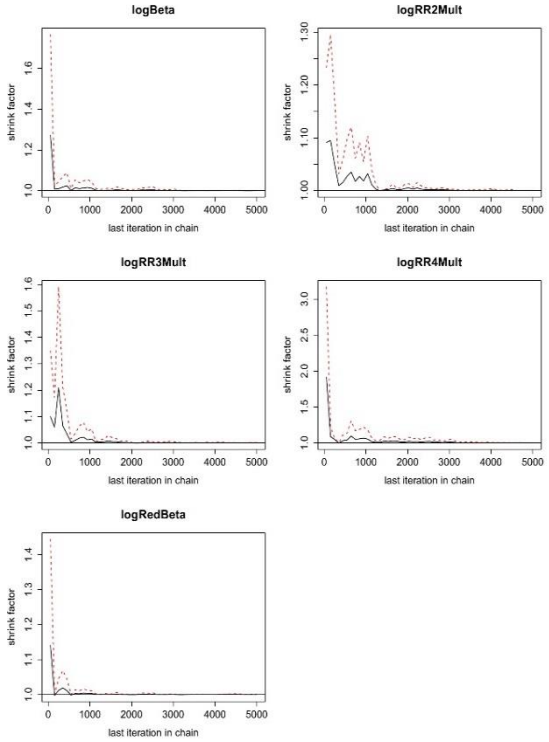
c) Autocorrelation plots



d) Overlayed trace plots



e) Gelman plots



f) Gelman diagnostics

```
> gelman.diag(allmc)
Potential scale reduction factors:

           Point est. Upper C.I.
logBeta             1          1
logRR2Mult          1          1
logRR3Mult          1          1
logRR4Mult          1          1
logRedBeta          1          1

Multivariate psrf
```

All outputs shown were obtained directly from R
Reduction in contact parameter: LogRedBeta; RR 60 and over: LogRR4Mult; RR 30-59: LogRR3Mult; RR 16-29: LogRR2Mult; rate of transmission: LogBeta.

4.4.4 Discussion of the estimated trends

When calibrating the model at the time the decision was made it was not possible to determine the number of susceptible individuals that remain in the population. That would have an impact on the overall trend of the pandemic as the natural depletion of the susceptible population will signal the end of the pandemic.

Lipsitch et al. (2009) have estimated that the RR for the A(H1N1) in Mexico by the 30th of April at a factor of 100 cases per one reported.

The three reporting rate scenarios were chosen to cover three possible scenarios: a low (0.001 or one reported case per 1,000 infections), medium (0.01 or one reported case per 100 infections) and high reporting rate (0.75 or one reported per 1.33 infections).

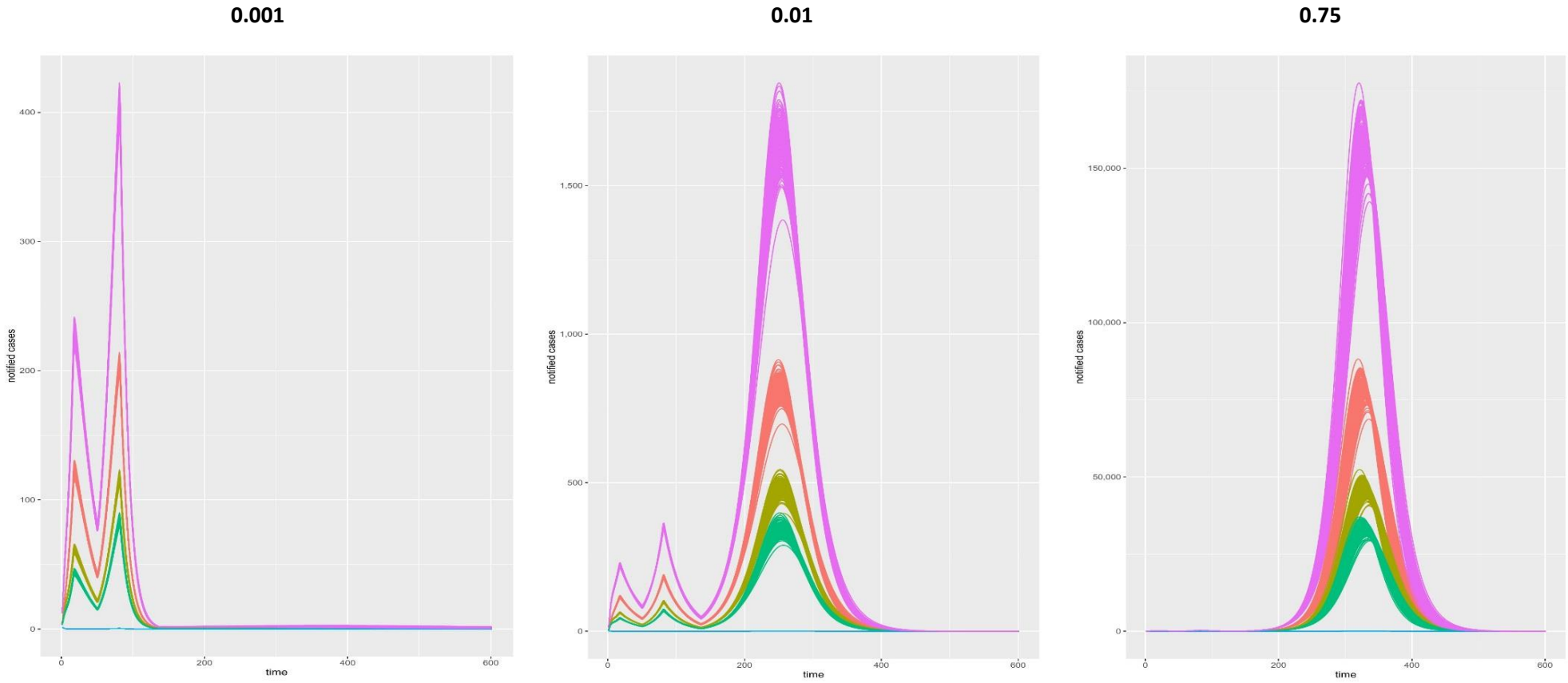
Figure 4.3 shows the estimated spread of the three reporting scenarios considered after thinning the chain. The figure indicates that given a 0.001 RR most notifications occurred during the first phase of the pandemic, in this case, the susceptible are

depleted early. In the case of the A(H1N1) pandemic in Mexico, it means that no third wave was observed. When the RR is 0.01, the spread of the pandemic shows three waves with the third wave having the largest number of notifications. Lastly, when an RR of 0.75 was assumed, the third wave dwarves the first two waves.

Irrespectively of the reporting RR, the model estimated between 19 and 22 million overall infections. When the generation times were changed, the model estimated between 14 and 19 million infections (generation time of 1.3) and between 26 and 28 million total cases (generation time of 2.7). Appendix IV Figure IV.3 shows the spread of the pandemic for the three mean generation times assumed.

Given the actual number of notifications at the end of the pandemic, 72,548 lab-confirmed cases were reported by the MMH, using this information and the average ODE model estimations (20.73 million total), the RR would be around 0.0035 (1 notification per 286 infections).

Figure 4.3 Estimated trends of the pandemic depending on reporting rate



x-axis represents time, y-axis total number of notifications;
Decision time occurred on the 18th July 2009 or day 98 in the model
Lines in pink correspond to the total number of estimated infections in all ages
Lines in orange correspond to the 0-15 age group; Lines in olive correspond to the 16-39 age group; Lines in green correspond to the 40-59 age group;
Lines in blue correspond to the 60 and over age group

4.5 Summary

This Chapter describes how the ODE model was constructed and calibrated using the data at the time the decision to purchase the vaccines was made public. The model is an ODE model for the entire Mexican population during the 2009 A(H1N1) pandemic. The Mexican population was divided into four age groups: 0-15 years; 16-29 years; 30-59 years and 60 years and over. It followed a SEIR structure and assumed a heterogeneous mixing pattern within a closed (and non-ageing) population. Under-reporting and pre-existing immunity were taken into consideration. The model was constructed in R and had a time horizon of 600 days.

The model was calibrated using an MCMC routine by maximising the likelihood of the model parameters given the lab-confirmed data. The method used was the Automated Factor Slice sampling method described in Tibbits et al. (2014) and was implemented in R using a package developed by Dr Peter Dodd (University of Sheffield).

The model was calibrated to the only available data: lab-confirmed cases. These data captured only confirmed cases of A(H1N1) from those with ILI disease who sought medical attention. A total of 5 variables were subject to calibration in the MCMC routine: the rate of transmission, three RRs and a reduction in contact parameter. The epidemiological model does not include mortality due to disease or natural caused.

Calibration was undertaken three times, once each for RR in the 0-15 years of 0.001, 0.01 and 0.75. Mixing of chains was observed to be good as assessed by trace and density plots, correlation between parameters visual overlay between chains and Gelman-Rubin test. A selected chain was thinned selecting every 25^{th} sample leaving 200 parameters sets to use in the PSA (described in Chapter 6).

Chapter 5. Discrete Event Simulation Model

5.1 Overview of the Chapter

This Chapter describes the discrete event simulation model built, in an iterative approach to estimate the CE of the 2009 A(H1N1) vaccine in Mexico. This DES model was constructed before the ODE model. However, ultimately, given the complexity of the pandemic along with the characteristics of modelling with DES, it was found not to be an appropriate approach. The ODE model (described in Chapter 4) was then constructed incorporating improvements that were not included in the DES model. Therefore, the two models are not identical. This Chapter describes the method, the calibration attempt and the reasons why it is believed it failed to achieve what was intended.

The Chapter is divided into five sections. Section 5.2 defines the conceptual infectious disease model developed using a DES approach. Section 5.3 focuses on the structure of the model, the main parameters, variables and the software in which the model was implemented. Section 5.4 describes the calibration method and the reasons why it was believed not to be successful. Lastly, the Chapter summary follows in Section 5.5

5.2 Conceptually defining the infectious disease model using DES

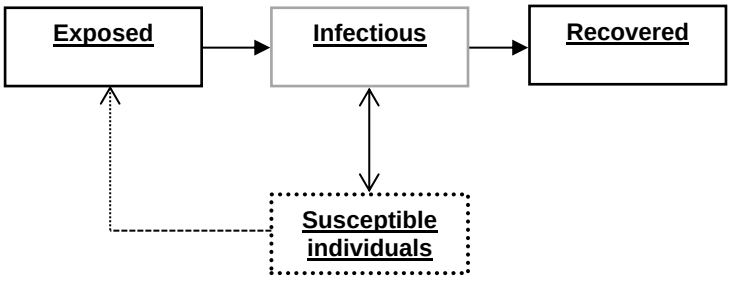
The DES model considered the entire Mexican population and assumed a heterogeneous mixing structure. The population was divided into four age groups: 0-15-years; 16-29-years; 30-59-years and 60-years and over.[46] The DES model assumes a non-ageing closed population. Death was not considered explicitly within the model.

The DES technique is stochastic and individual-based by nature (a brief theoretical background on the DES modelling technique can be found in Appendix III). One of the key elements to consider in attempting a modelling technique with those characteristics is the total population to be analysed. As previously stated, the population of Mexico during the A(H1N1) epidemic was approximately 107 million, a number too large to be explicitly modelled using an individual level approach. To allow a simulation of the pandemic, a decision was made to record only exposed and infectious individuals. The advantage of this method is in significantly reducing the computational burden, as susceptible and recovered patients are not modelled individually.

[46] The age groups were established following the same logic and proportions as in the ODE model (described in Chapter 4).

The transitions from exposed to infectious and from infectious to recovered were explicitly simulated. Whilst patients were in the infectious state, the model simulated the contacts made by the individual (and the status of the person encountered – susceptible, exposed, infectious, recovered/immune) and whether the disease was transmitted to those who were susceptible. The process of simulating the experiences of each infectious patient allows the model to capture the dynamic nature of the epidemic and to incorporate HI. Figure 5.1 shows the general structure of the DES model.

Figure 5.1 General Structure of the model



This is the simulated experience of an exposed patient. When the patient recovers gains immunity to further infection with the pandemic A(H1N1) virus

Contacts were assumed to occur daily to simulate the disease in accordance with the available data. The numbers of susceptible and exposed individuals were updated instantly following disease transmission which resulted in a changing force of infection. As described below, under-reporting was acknowledged when developing the model, but the model structure outlined in the sections below correspond to the model assuming 100% RR. Given the calibration results and the complexities found when using the DES method, which is detailed in this Chapter, any further attempts to run or calibrate this model were not attempted.

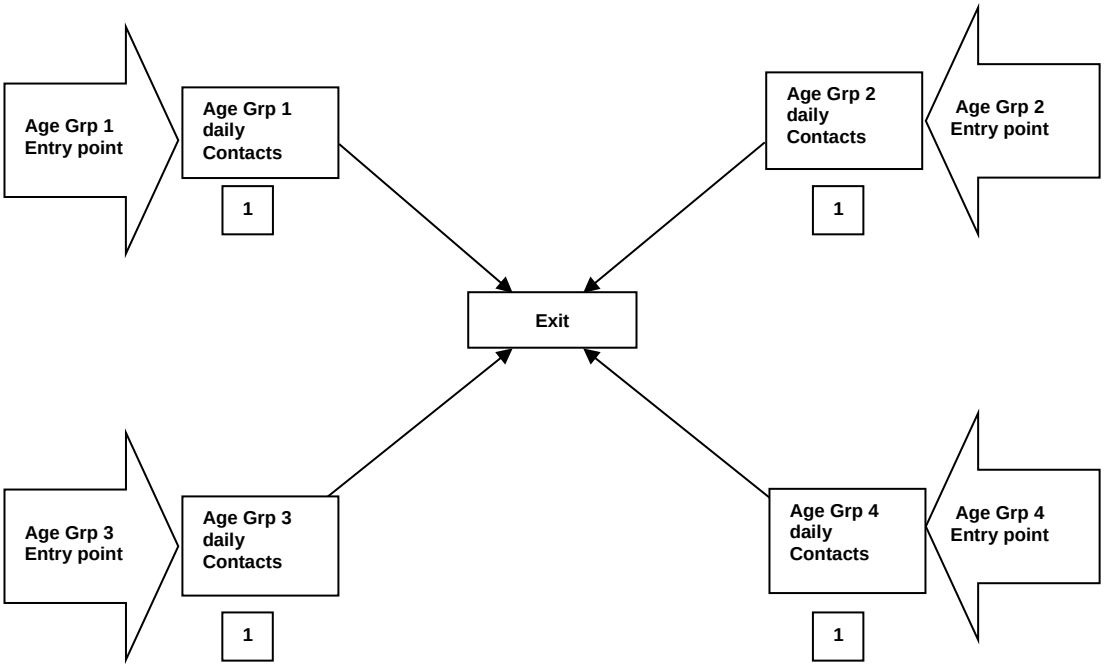
5.3 Model Structure

The model construction was an iterative process. Following the development of a model deemed conceptually appropriate and to have been coded correctly, amendments were made that decreased the computational time required whilst maintaining the same results. This approach was undertaken so that there was clarity within the initial model construction process.

The final model structure is shown in Figure 5.2. The infected enter the model via their corresponding age group entry point. Immediately after the patients travel to their

corresponding age group work centre where contacts are simulated (No. 1, Figure 5.2). After completing their daily contacts, people exit the model. This process continues until no more infectious individuals remain or the time horizon of the simulation is reached.

Figure 5.2 Final structure of the model



The simulation relies on a series of spreadsheets embedded in the software. These spreadsheets account for the simulated numbers of exposed, infectious and recovered for each age group. These were used to estimate the newly infectious individuals entering the simulation at day $k+1$ as the sum of exposed individuals who become infectious at the end of day k plus the infectious at the start of day k minus the infectious individuals at the start of day k who have recovered by the end of day k (Equation 5.1).

Equation 5.1 Infectious individuals introduce into the model at day k+1

$$\boldsymbol{DEntrants_{ik+1} = Ex\_Inf_{ik} + Inf_{ik} - R_{ik}}$$

$i = 1\ to\ 4\ \ for\ each\ age\ group$
$k = simulated\ day\text{: } 1\ to\ N\ depending\ on\ the\ current\ day\ of\ the\ model$

Where:

$DEntrants_{ik+1} = Daily\ infectious\ Entrants\ to\ the\ model\ on\ day\ k+1$

$Ex\_Inf_k = Exposed\ individuals\ who\ become\ infectious\ at\ the\ end\ of\ day\ k$
$Inf_k = Infectious\ individuals\ at\ the\ start\ of\ day\ k$
$R_k = Individuals\ who\ at\ the\ start\ of\ of\ day\ k\ who\ recoverd\ by\ the\ end\ of\ the\ day$

5.3.1 Temporality, population and age groups

The simulation was intended to run for 500 days. The total population was based on information reported by CONAPO: 107,503,300 individuals (CONAPO, 2012) and was divided into four age group: 0-15 years; 16-29 years; 30-59 years and 60 years and over.

5.3.2 Contacts between age groups and disease transmission

Infectious individuals enter into contact with individuals daily according to a contact matrix. Since four age groups were considered a 4x4 contact matrix was constructed.

The 4x4 matrix requires 16 parameters. However, logically the contacts between pairs of groups are dependent resulting in only ten parameters needing to be estimated. Since the size of the population in each of the chosen age groups was different an adjustment factor (f_{ij}) was introduced to maintain logical consistency. For illustration, consider that there are two groups: Group 1 (50 people) and Group 2 (200 people). If on average a person in Group 1 met one person from Group 2 each day, then there would be 50 contacts between the groups, and thus, on average each person from Group 2 would meet 0.25 people from Group 1. This would equate to an adjustment factor for Group 2 meeting group 1 compared with the contacts of group 1 meeting Group 2 of 50/200. The adjustment factors are shown in Table 5.1.

Table 5.1 Population adjustment factors or f_{ij}

Age	Population	Factor			
		0-15	**16-29**	**30-59**	**60 & Plus**
0-15	33,034,807 (A1)				
16-29	27,078,077 (A2)	$f_{21} = 1.22$ (A1/A2)			
30-59	38,306,904 (A3)	$f_{31} = 0.86$ (A1/A3)	$f_{32} = 0.71$ (A2/A3)		
60 & Plus	9,087,542 (A4)	$f_{41} = 3.64$ (A1/A4)	$f_{42} = 2.98$ (A2/A4)	$f_{43} = 4.22$ (A3/A4)	

The number of parameters to be estimated in the model was a concern (due to the calibration process required and the risk of overfitting the model). The number of

contact parameters to be estimated was reduced to 4, one for each age group. Only the sum of contacts per age group excluding contacts already calculated in younger age groups was considered as a parameter. These calculations are shown in Table 5.2.

Table 5.2 Contact matrix on the number of daily contacts per age group

Age	0-15	16-29	30-59	60 & over	Sum of total contacts
0-15	$C_{11} = TC_1 * Z_1$	$C_{12} = TC_1 * Z_2$	$C_{13} = TC_1 * Z_3$	$C_{14} = TC_1 * Z_4$	TC_1
16-29	$C_{21} = f_{21} * C_{12}$	$C_{22} = TC_2 * Y_2$	$C_{23} = TC_2 * Y_3$	$C_{24} = TC_2 * Y_4$	TC_2
30-59	$C_{31} = f_{31} * C_{13}$	$C_{33} = f_{32} * C_{23}$	$C_{33} = TC_3 * X_3$	$C_{34} = TC_3 * X_4$	TC_3
60 & over	$C_{41} = f_{41} * C_{14}$	$C_{42} = f_{42} * C_{24}$	$C_{43} = f_{43} * C_{34}$	$C_{44} = TC_4$	TC_4

Where:

$Z_i = {}^{n_i}/_{N} \; for \; i = 1,2,3,4$

$Y_i = {}^{n_i}/_{(N - n_1)} \; for \; i = 2,3,4$

$X_i = {}^{n_i}/_{(N - n_1 - n_2)} \; for \; i = 3,4$

$C_{ij} = daily \; contact \; parameters$

$f_{ij} = adjustment \; parameters \; based \; on \; populations$

$i = 1,2,3,4 \; for \; each \; age \; group$

$j = 1,2,3,4 \; for \; each \; age \; group$

$\boldsymbol{n_i = number \; in \; population \; i}$

$\boldsymbol{N = number \; in \; the \; entire \; population}$

Given the focus on infectious individuals, once a contact of an infectious individual was simulated it was necessary to determine if it was with a susceptible individual. On an individual basis this was assumed to occur if a draw from a uniform (0,1) distribution was lower than the prevalence of susceptibles within the relevant age group $({}^{S_j}/_{n_j})$ where S_j is the number of susceptibles in group j and n_j is the total population in group j.

If the contact was with a susceptible individual, then the model determined if an exposure occurred. The definition of the new exposure was based on the probability of transmission given a contact (PrT). If the value of a random number sampled from a uniform (0,1) distributionPrT was lower than then it was simulated that an infection would occur. The value of PrT was estimated when calibrating the model.

If the contact resulted in new exposure, the number of susceptibles and exposed individuals' updates resulting in a lower prevalence of susceptible individuals.

In contrast to the ODE model (Chapter 4), the possibility of differential probability of transmission for each age group was considered. This adjustment rate was used to modify the PrT. This is shown in Equation 5.2.

Equation 5.2 Transmission adjustment factor for each age group

$$PrT_j = Prt * A_j$$

Where:
$PrT = probability\ of\ transmission\ given\ a\ contact\ with\ a\ suceptible\ individual$
$A_j =$ transmission $adjustment$ factor $per\ age\ group\ j$
$j = 1,2,3,4$

The transmission adjustment factor was set by a calibration process (more details are provided on this in Section 5.4).

5.3.3 Disease incidence

As previously described the spread of the disease had three waves. To simulate these waves in the ODE model used a single reduction in contacts multiplier (Chapter 4 section 4.3.2). In the DES model, however, two parameters (termed multipliers) were included instead. These were used to alter the number of contacts during the general closure of activities and school holidays and were denoted *GCM* and *SHM* respectively.

As the pandemic began during school term times, it was assumed that the initial number of contacts per age group TC_i corresponds to this period. The use of the multipliers assumes that the total sum of contacts during the Governmental actions and the holiday period multipliers were lower than those that occurred during term time.

The GCM was applied to the contact matrix between the beginning of the governmental closure and its conclusion (24th April- 5th May 2009). Similarly, the SHM was applied at the end of and the beginning of the school term (15thJune-10th August): At any other time point the number of contacts per age group remained at TC_i. Figure 5.3 shows, for illustrative purposes only, the use of these multipliers, whilst Table 5.3 shows how the multipliers modify the contacts between age groups.

Figure 5.3 The inclusion of multipliers to simulate waves of infections

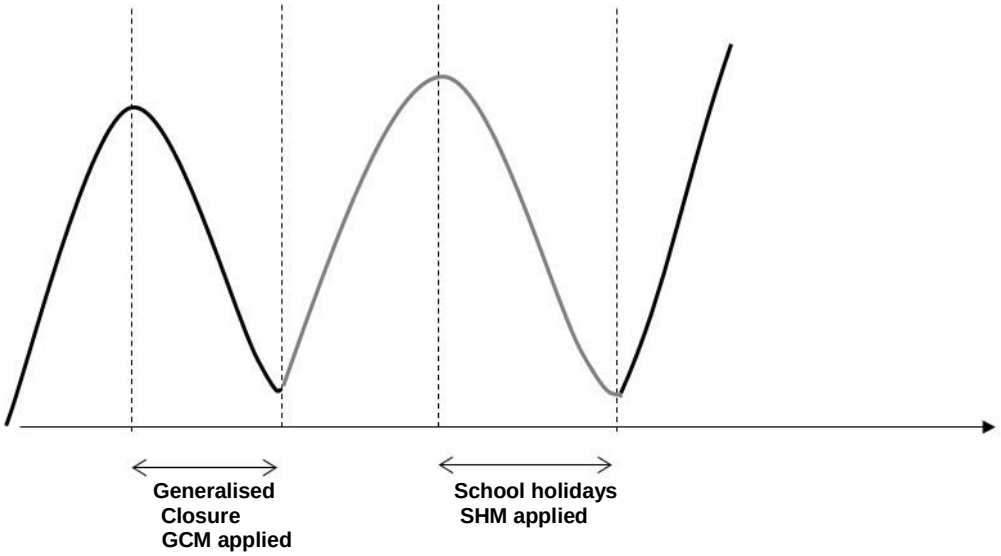


Table 5.3 Contact matrices and factors GCM and SHM

Age	0-15	16-29	30-59	60 & plus
0-15	$C_{11}{*}M$	$C_{12}{*}M$	$C_{13}{*}M$	$C_{14}{*}M$
16-29	$C_{21} * M$	$C_{22}{*}M$	$C_{23}{*}M$	$C_{24}{*}M$
30-59	$C_{31}{*}M$	$C_{33} * M$	$C_{33}{*}M$	$C_{34}{*}M$
60 & Plus	$C_{41}{*}M$	$C_{42} * M$	$C_{43} * M$	$C_{44}{*}M$

Where:

$$M = \begin{cases} GCM\ if\ t > t_{start\ of\ generalised\ closure} and\ t < t_{end\ generalised\ closure} \\ SHM\ if\ t > t_{end\ of\ schoo\ term}\ and\ t_{start\ of\ school\ term} \\ 1\ \ otherwise \end{cases}$$

5.3.4 Under-reporting and pre-existing immunity

Under-reporting was due to be considered in the DES model. The initial model and adjustment were made assuming a 100% reporting rate. Given that the development and calibration results found that the DES was not an appropriate approach, further analysis exploring different reporting was not pursued.

Pre-existing immunity was considered as in the ODE model. Both models used the same information on this regard obtained from Miller et al., (2010)

5.3.5 Vaccination

As with the ODE model, the DES model was constructed assuming that vaccination had protective effect only for susceptible individuals, and did not affect the disease progress of those exposed or infectious.

To account for the vaccination strategy, the simulation determines if the susceptible that meets an infectious individual had been vaccinated by comparing a draw from a Uniform [0,1] distribution with the ratio of the number of vaccinated susceptible individuals divided by the number of susceptible individuals in the corresponding age band.

If the susceptible person was vaccinated, then the individual faced a reduced probability of infection based on the protection conferred by the vaccine, with the risk of infection multiplied by (1- Vaccine Efficacy). Thus, if the effectiveness of the vaccine was assumed to be perfect, transmission could not take place. However, given that the model was only calibrated up to the moment the decision was made, these elements had no influence in the model. Box 5.1 shows a summary of the DES model.

Box 5.1 A summary of the infectious process in the DES model

Step 1: Model determines the number of contacts that an infectious individual would have in a day. The following steps are undertaken for each contact.

Step 2: Using S_j/n_j and a random number the model determines if the contact was with a susceptible individual. If the individual was susceptible the model moves to step 3, otherwise it is assumed that there is no transmission

$$if\ Rn\ < S_j/n_j\ \therefore\ An\ infectious\ person\ meets\ a\ suceptible\ person\ in\ group\ j$$

Step 3: The model determines if transmission would occur using Step 4 or 5 dependent on vaccination status.

If unvaccinated

Step 4: *A* random number determines if the susceptible individual becomes infected:

$$if\ Rn\ < PrT_j\ :\ an\ exposure\ occurs$$

$$Susceptible\ in\ group\ j\ reduced\ by\ 1$$
$$Exposed\ in\ group\ j\ increased\ by\ 1$$

$$otherwise:\ \ Individual\ remains\ susceptible$$

If vaccinated:

Step 5: *A random number determines if the vaccinated susceptible individual becomes infected:*

$$if\ Rn\ < PrT_j.(1-VE)\ :\ an\ exposure\ occurs$$

$$Susceptible\ in\ group\ j\ reduced\ by\ 1$$
$$Exposed\ in\ group\ j\ increased\ by\ 1$$

$$otherwise:\ \ Individual\ remains\ susceptible$$

Where:
$S_j\ = Number\ of\ susceptible\ individuals\ in\ group\ j$
$n_j\ = Number\ of\ individuals\ in\ group\ j$
$PrT = Probability\ of\ transmision\ given\ contact\ with\ a\ susceptible\ individual$
$VE = Assumed\ vaccine\ efficacy$
$Rn = Random\ number\ from\ a\ uniform\ [0,1]\ distribution$

When the above process concludes, the code stores the changes in suceptibles and exposed to populate the corresponding spread sheets at the end of the simulation day.

5.3.6 Software

Specialised software packages to run discrete event simulations are commercially available. These types of software are usually based on a visual interactive modelling system (VIMS). Software based on VIMS approaches combine a visual representation to construct a simulation with a programming language to specify complex events. By allowing a visual representation of the simulation, it provides a clear idea of the logic behind the model. It additionally allows easy and flexible experimentation, modification of model components and debugging (Pidd, 2004).

The selected VIMS software to construct the DES model was SIMUL8© (1993-2012 SIMUL8 Corporation ver. 19).[47] In SIMUL8© it is possible to set model components by placing icons and linking them with other structures or networks. Actions can be performed when an entity arrives or exits. Visual logic elements can also be included at the start of the model, at designated time periods or when completing a simulation (which is appropriate for calibration proposes). Partial results can be observed while the simulation is running or at the end of the process.

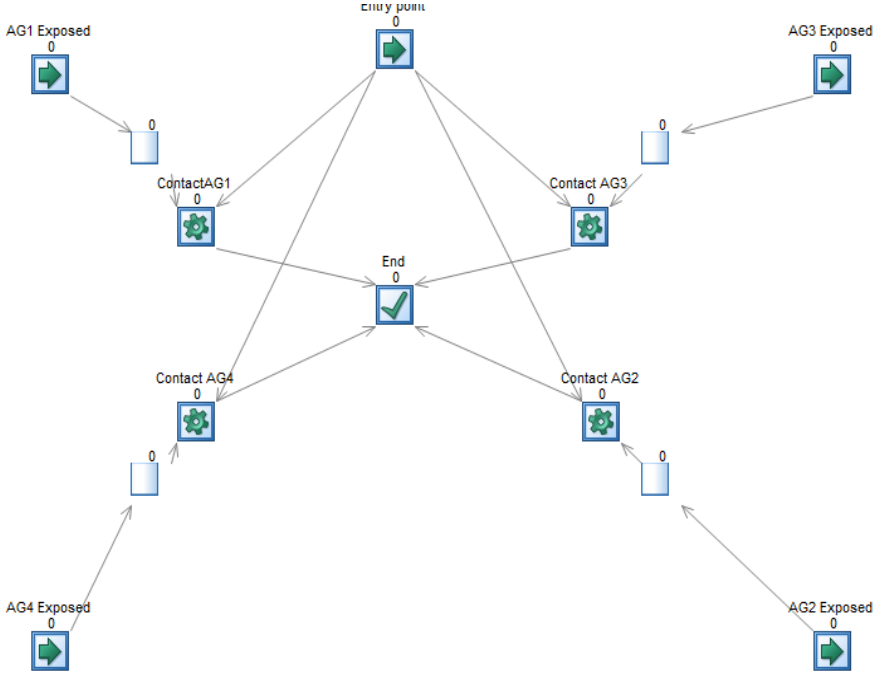
SIMUL8© has five main components: work entry points; storage bins; work centres; resources, and work exit points. Table 5.4 shows how these elements were used in the context of the infectious disease model described above. Figure 5.4 show a screen shot of the model.

[47] Several software packages in the market to perform DES simulations: Arena® (Arena Solutions Inc. 2013©, SIMUL8© 1993-2012 SIMUL8 Corporation ver. 19, Micro Saint (Copyright ©2011 Alion Science and Technology), AnyLogic (Copyright Anylogic corporation ©2013), etc. all with similar characteristics and programming languages. This type of software offer advantages and disadvantages. Compared with other software SIMUL8 offers a full student version for PhD students with no limitations in terms of the size and complexity of the model. It was also widely used within the Health Economics and Decision Science Unit (HEDS), where my PhD supervisors were based, which also offered an advance simulation course based on this platform. Those elements resulted in Simul8 being the chosen package.

Table 5.4 SIMUL8© elements and how are being used in the infectious disease model described above

Element	Definition	Final model structure
Work entry point	The entities or main objects of the simulation enter the simulation	Five entry points were used. At the beginning of the model, one entry point is used to distribute the initial infected population according to their age group. From day two onwards, the remaining four were used to introduce new infectious into the model based on their age group
Storage bins	Where entities wait before being processed	Only "dummy" storage bins were used for debugging of the model. No holding in queues was considered in this structure
Work centres	Where the processing of activities or work are modelled	Four work centres were used to process the daily contacts of the infectious individuals
Resources	Not used within the simulation. These represent tools, elements or people that can be used to process an activity or work process	Not applicable
Work exit points	Where entities leave the model	One exit point was used only.

Figure 5.4 Screen shot of the DES model in SIMUL8©



5.4 Calibration

As with the ODE model, the constructed model was adjusted to the available lab-confirmed reported data. The adjustment was attempted up to the moment the decision to purchase the vaccine was announced. The same challenges described in Chapter 4 Section 4.4 on the RR being uncertain remain. Although it was intended to adjust the model for several RR scenarios, it became apparent during this thesis that a DES approach was not applicable. Therefore only one run assuming an RR of 1 was attempted. A brief summary of the process that was categorised following (Vanni et al., 2011) is mentioned here.

1. Selection of the parameters to be varied in the calibration process:

   A total of 11 parameters were calibrated: Probability of transmission given contact ($\boldsymbol{PrT}$); general closure and school holidays multipliers ($\boldsymbol{GCM}$ & $\boldsymbol{SHM}$); sum of total contacts per age group ($\boldsymbol{TC_i}$) and four transmission adjustment factors ($\boldsymbol{A_j}$)

2. Selection of the calibration targets:
   Data on lab-confirmed cases compiled by the MMH for each of the intended age groups (0-15, 16-29, 30-59 and 60 & over)
3. Definition of the measure of goodness of fit (GOF) to be used:
   Maximum likelihood of the model parameters to the lab-confirmed data. As the lab-confirmed data is a positive integer, the log-likelihood of the Poisson function was used.
4. Definition of the parameter searches strategy
   An MCMC method using the Metropolis-Hastings (MH) algorithm. Based on the description of the process in Whyte et al. (2011)
5. Definition of what determines an acceptable GOF parameter set or convergence criteria
   Trace and density plots plus and a visual comparison between the spread of the lab-confirmed estimated outputs versus the observed lab-confirmed were used to assess the calibration.
6. Determination of the termination rule of the calibration:
   The calibration process was evaluated after 20,000 iterations to determine if convergence was achieved (as determined by the tests described in 5).
7. Integration of the model calibration results and economic parameters.

If the model converged, a set of Independent draws obtained by thinning of the chain was intended to be used to run the model with and without the vaccine.

5.4.1 Calibration process

The calibration process comprises used data from 19th April 2009 to the 18th July 2009 as target values. The start point was marginally later than in the ODE model to reduce the probability of stochasticity that can lead to the pandemic dying out.

Due to the complexity of the model, the number of variables to be calibrated and the number of infections a single run of the DES model took typically between 30 to 45 seconds. To aid the calibration process the starting values and prior distributions were based on findings from the literature search and from optimising a previously developed ODE.[48] Iterations were aborted if the daily number of confirmed cases reached 10,000 or if the total number of confirmed cases through a run reached 150,000, as these values were far in excess of those reported in Mexico, and if not aborted would result in substantial computational burdens for no gain.

The first 5,000 iterations were run using a relatively big jump sizes in the calibrated parameter, which were reduced progressively until small jumps were used at the end of the run. This was undertaken to explore potentially largely different parameter configurations relatively quickly as recommended by Whyte et al. (2011).

The number of parameters varying at the same time was also limited. This reduced the dimension of parameter search at each iteration and was aimed at increasing the rate of acceptance parameters. A random process determined the parameters being changed. At the start of the calibration process, each parameter in the current set had an 80% chance of being changed in the candidate set. This value was gradually reduced as the calibration progressed based on the accepted/rejected ratio. If the calibration process was not accepting at least 1% of the iterations, the percentage was reduced. The lowest value used was 20% towards the end of the calibration process.

Within the DES method, it was necessary to define a random number stream at the beginning of the model. The stream selected was based on previous work (contained in the initial thesis submission) which tested the applicability of multiple random number

[48] This ODE model was a previous version of the one described in Chapter 4. This model was deterministic model subject to an optimisation process using the Nelder-Mead method in Berkeley Madonna. This model was later replaced with the version described in Chapter 4 due to concerns with the robustness of the optimiser within Berkeley Madonna. The methods and results from the Berkeley Madonna model are not shown or discussed in this thesis.

streams, with stream 11 within the Simul8© software shown to produce a good fit. If a DES approach were deemed to be appropriate, the model would need to be run using several other random number streams to come up with a distribution of optimal parameter sets. This was not done as it became apparent that the DES approach was not as good as the ODE approach (developed in Chapter 4) adding significantly to the computational time for no gain.

5.4.2 Parameterisation of variables included and not included in the MCMC routine

The parameters included in the MCMC were (described in section 5.3):

- Probability of transmission given contact ($\boldsymbol{PrT}$);
- general closure and school holidays multipliers ($\boldsymbol{GCM}$ & $\boldsymbol{SHM}$);
- Four sums of total contacts per age group ($\boldsymbol{TC_i}$) (one for each age group)
- Four transmission adjustment factors ($\boldsymbol{A_j}$) (one for each age group)

The parameters not included in the MCMC were:

Prior-immunity and recovered population at the start of the model: prior-immunity assumed as the same as the described for the ODE model (Chapter 4). Recovered at the beginning of the model correspond to those with pre-existing immunity.

Infected and exposed population at the start of the model: These values were based on the actual number of lab-confirmed cases in the period before the beginning of the modelling process.

Suceptible population at the start of the model: total population in Mexico during 2009 (107,507,330) minus pre-existing immunity, initially exposed and infectious.

RR: fixed and set as 1 for all age groups.

Latent and infectious period: 1 and 2 respectively[49,50]

Vaccine effectiveness: not included as the model was calibrated only up to the point where the decision was made.

Table 5.5 provides a summary of the different parameters used in the model, their assumed values and acronyms.

[49] Note that the infectious period is 2 instead of the 1.8 assumed for the ODE model. This is because the coding of the DES model was simpler when this value was an integer.
[50] Refer to Chapter 4 Section 4.4.2 for more details on the source of these variables.

Table 5.5 Parameters used in the DES model

Parameter	Acronym	Value	Source/Comment
Pre-infectious or latent period	-	1 day	Eames et al. 2012
Infectious period	-	2 days	Eames et al. 2012 but set to 2 instead of 1.8
Probability of transmission given contact	PrT	Calibrated	-
General closure multiplier	GCM	Calibrated	-
School holidays multiplier	SHM		
Sum of total contacts			
0-15	TC_1	Calibrated	Initial value based on POLYMOD (Mossong et al., 2008)
16-29	TC_2		
30-59	TC_3		
60 and over	TC_4		
Reporting rates			
All age groups	RR	1	Fixed
Pre-existing immunity*			
0-15	p_1	2.79%	Miller et al., (2010)
16-29	p_2	17.5%	
30-59	p_3	12%	
60 and over	p_4	23.32%	
Transmission adjustment factors			
0-15	A_1	Calibrated	
16-29	A_2		
30-59	A_3		
60 and over	A_4		
Susceptible and recovered individuals at the start of the model			
0-15	S_1, R_1	-	Susceptible: total population minus pre-existing immune individuals, initial infected and exposed Recovered: pre-existing immune individuals
16-29	S_2, R_2	-	
30-59	S_3, R_3	-	
60 and over	S_4, R_4	-	
Initial infected and exposed individuals at the start of the model			
0-15	I_1, E_1	72	Derived from the actual number of lab-confirmed cases.
16-29	I_2, E_2	42	
30-59	I_3, E_3	35	
60 and over	I_4, E_4	3	

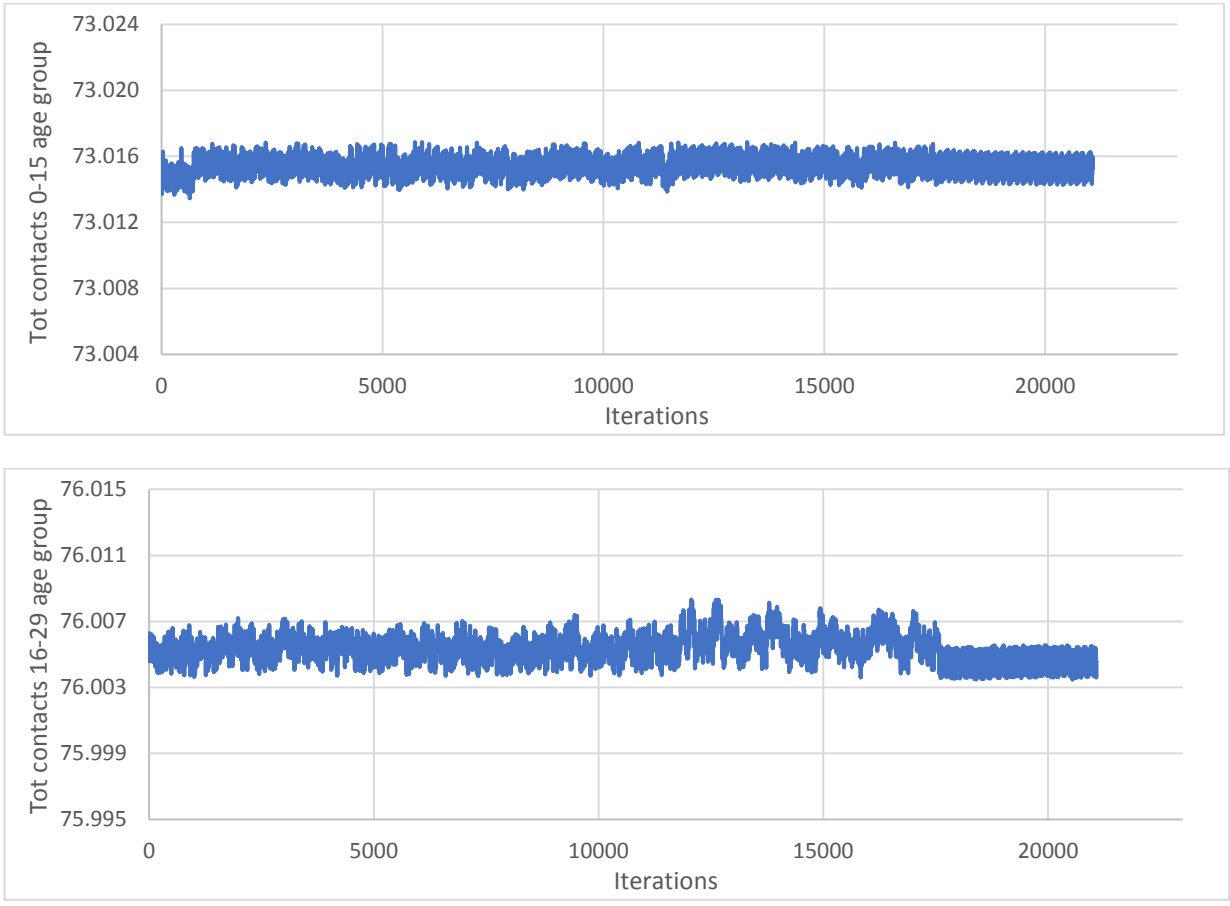
* Based on Miller et al., (2010) who reported data for the 0-4; 5-14; 15-24; 25-49; 50-64; 65-74; 75-79 and 80 and over age groups. The data from 0-4 and 5-14 were used to estimate the 0-15 pre-existing immunity; the data of the 15-24 age group was assumed for the 16-29 age group. The data of the 25-49 and 50-64 age groups was used for the 30-60 while the 65-74; 75-79 and 80 for the 65 and over age group

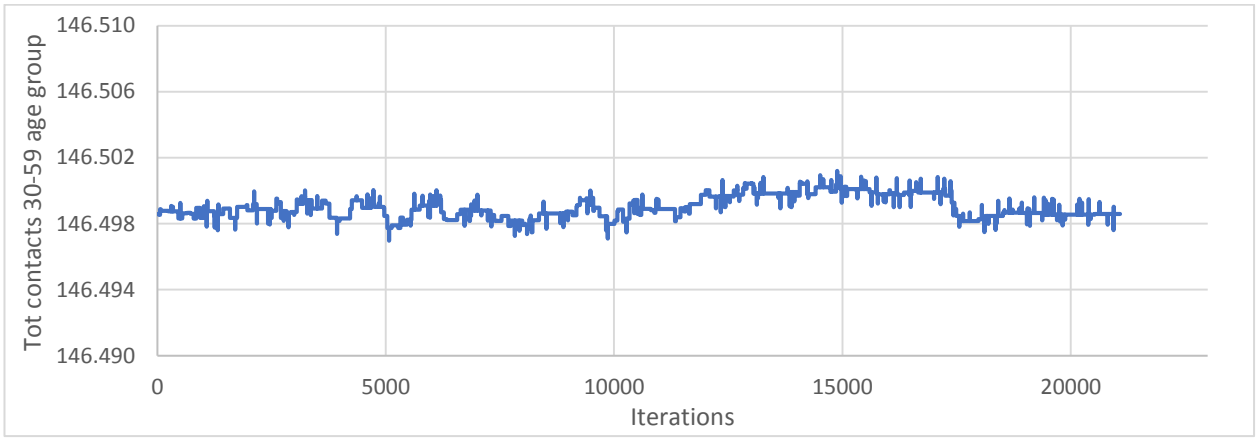
5.4.3 Convergence assessment outcome and use of the DES strategy

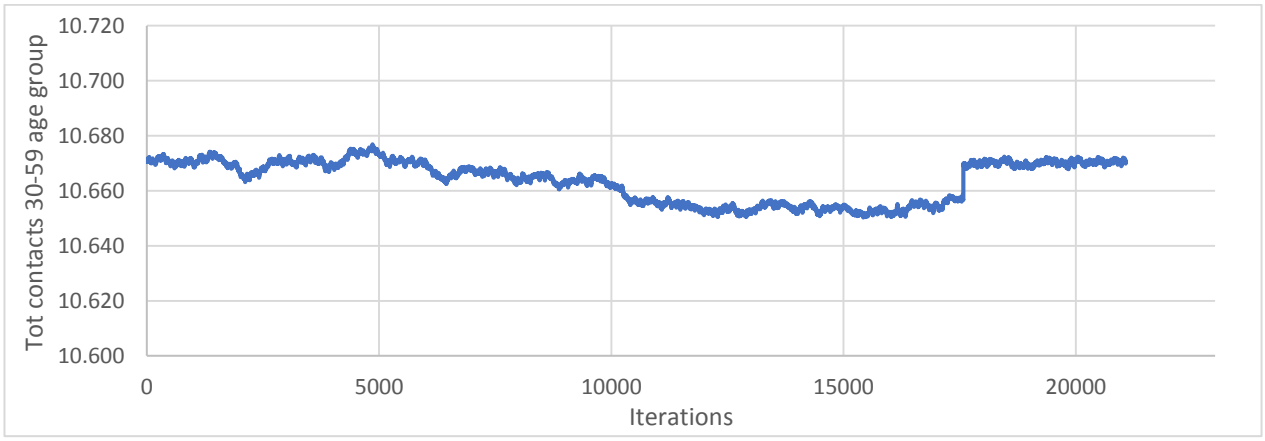
Despite running the chains for over 20,000 iterations the mixing of the chains was poor. This suggested that either it was necessary to run the chains for longer in an attempt to improve mixing and reach conversion or that the method was not flexible enough to allow full exploration of the parameter space. The trace plots in Figure 5.5 shows poor mixing. If compared with the plots produced by the ODE model under the RR rate (0.01), the trace plots generated by the DES model show little movement. None of the density plots (not shown) show normality in the chains.

Given the computational time needed to run one single random number stream to 20,000 iterations (over 200 computer hrs or over eight days on an Intel Core i5-2400 CPU @3.10 GHz) analysing multiple streams was not believed to be feasible.

Figure 5.5 Trace plots of adjusted total sum of contacts







5.5 Summary

This Chapter focused on describing the development and adjustment of the DES model that was constructed before the ODE model described in Chapter 4. The Chapter shows that the construction of an infectious disease model to simulate the A(H1N1) is a lengthy process. This alone can prove to be excessive in the context of the need of timely and robust advice to inform the decision to purchase the vaccine.

The construction of the model showed that the model struggled to simulate a large number of individuals going through the system as it either runs very slowly or crashes producing no outputs. This problem would be exacerbated if lower RRs were used.

The calibration approach used the Metropolis-Hastings algorithm. The mixing of the chains after 20,000 iterations was shown to be poor.

Although the aim of this thesis was not to make a direct comparison between the ODE and DES model, it was found that the ODE model offers a more practical approach. This work found no advantage in using DES over the ODE technique. Indeed the DES approach appeared to be considerably worse that the ODE method. Furthermore, the

DES method took significant longer to run. As such, this thesis showed that the DES technique is not suitable to model a pandemic with a large population such as the observed in Mexico in 2009. Having reached this conclusion, all analysis presented were undertaken using the ODE model.

Chapter 6. Cost effectiveness of the A(H1N1) vaccine

6.1 Overview of the Chapter

This Chapter focuses on the CE of the A(H1N1) vaccine in Mexico. It describes the assumptions, processes, and the parameter values used for the ODE model. The Chapter includes a description of the methods, assumptions and parameters used (costs, utility losses and vaccine effectiveness) (Section 6.2). Section 6.3 details the base case, primary, secondary and sensitivity analyses. Section 6.4 describes the results obtained. Lastly, a summary of the Chapter is presented (Section 6.5).

6.2 Methods

The focus of the analysis was to determine the potential CE of a general population-based vaccine strategy at the moment when the Mexican Government chose to purchase it. As such, this was assessed using only the knowledge that was available to the Mexican Government at the time of the decision.

As described in Chapter 1, Strategies targeting the at-risk population have been reported to be cost-effective (Baguelin et al., 2010). Such a scenario was not considered here as distinguishing between risk groups could have potentially generated more uncertainty and increase the difficulties of the calibration process, as no information about contacts was available for such groups. A sensitivity analysis exploring the impact of greater severity of consequences per infection was performed to explore the potential impact on the CE of the vaccine interventions.

The analyses within the thesis focus on exploring the CE of alternative vaccination scenarios based on general population by age groups. The strategies tested against the no vaccination alternative were: Strategy 1: vaccination of the entire population based on the proportion of individuals in each age group (henceforth denoted the population strategy); and Strategy 2: vaccination of the general population with vaccination based on the proportion of lab-confirmed individuals at the moment the decision to purchase the vaccine was made (henceforth denoted the lab-confirmed strategy).

The primary analysis assumed that the vaccine arrived as expected, however since it was thought that the timing of the vaccination could play a major role in the CE of the vaccination strategy an alternative scenario of the vaccine arriving late was also tested.

By assuming three different reporting rates for the 0-15 age group (0.001, 0.01 and 0.75), the calibration of the ODE model (described in Chapter 4) provided three different sets of probabilistic projections of the potential spread of the pandemic beyond the point at which the decision to purchase was made. These three projections were used to estimate the CE of the two strategies described above.

The CE analyses performed, assume the perspective of the MMH. The population under analysis was the entire Mexican population (as of 2009) which was divided into four age groups: 0-15; 16-29; 30-59; and 60 years and over. The time horizon was 600 days.

The outcome was measured in quality-adjusted life years (QALYs) losses for each strategy. These were estimated from the utility losses related to having or dying from the disease, as well as those incurred from experiencing an adverse event associated with the vaccine itself.

The costs considered included those incurred in the purchase and provision of the vaccine, costs of medical treatment (outpatient and inpatient care), costs of adverse events from the vaccination and those related to productivity losses due to sickness.

Incremental costs and QALYs in comparison to a no vaccination strategy were used to calculate the incremental CE ratio (ICER) of the vaccine intervention. The ICER was then compared against pre-defined thresholds. Since no official threshold value exists for Mexico, suitable cost per QALY threshold values have been defined by the WHO have been used. These suggest that a medium income country in North, Central and South America should have a threshold value between one and three times the Gross Domestic product (GDP) per capita (WHO, 2010a). If the cost per QALY falls below one GDP per capita, the intervention is considered to be very cost-effective; if it falls between one and three times the intervention is considered CE; whilst if it is above three times the GDP per capita, then the intervention would not be considered CE. Given the GDP per capita in Mexico during 2009, this would represent a value lower threshold value of $110,000 and an upper threshold value of $330,000 MXP. These thresholds are only guidelines. The MMH has stated that even though the intervention might fall into a suitable CE range, it is necessary to consider other elements, such as the potential to ensure fairness and equality in the distribution of the health benefits or the impact on the health care services and available resources (González-pier et al., 2007).

CE planes, CE acceptability curves (CEAC) and CE acceptability frontiers (CEAF) were provided to aid interpretation of the results.

6.2.1 Influenza-like infections (ILI)

A large number of individuals were asymptomatic or had mild symptoms, and therefore they did not seek medical attention (Eames et al., 2012; Chowell et al., 2011; Elizondo-Montemayor et al., 2011). Those who sought medical attention were initially classified as influenza-like infections (ILI).[51] The CE analyses performed here are based on the total number of cases of A(H1N1) and those with ILI who sought medical attention.

Statistics from the Pan-American Health Organisation (PHO) and the MMH from July 2009 indicated that 102,773 people with ILI had sought medical attention from which 20,502 had a A(H1N1) laboratory confirmed result. These data were used to estimate that for every 5.01 (102,773/20,502) ILI patients who sought medical attention one had a positive confirmatory test.[52] Since the model predictions provided an estimate of the lab-confirmed cases, the proportion of ILI cases who sought medical attention could be estimated for the middle and low reporting rate scenarios (0.01 and 0.001). For the high reporting rate scenario (0.75) it was assumed that all people with ILI who sought medical attention had a confirmatory test.[53]

6.2.2 Medical treatment

The first contact for individuals seeking medical attention was assumed to be a medical consultation with a general practitioner (GP). The GP would then decide if the patient required only palliative treatment (painkillers and rest), antiviral treatment (outpatient care) or hospitalisation (inpatient care). A proportion of patients requiring inpatient care were assumed to require intensive care unit (ICU) treatment. Deaths due to A(H1N1) were assumed only for those patients who sought medical attention.[54]

Outpatient care

[51] The symptoms to classify a patient as ILI were describe in Chapter 2 Section 2.2

[52] As described in Chapter 2, only a proportion of these ILI cases had a confirmatory test. The only data available to use in the model correspond to those ILI cases that had a positive lab-test (lab-confirmed cases). The underlying assumption here was that the confirmatory tests were maintained during the pandemic and therefore it was possible to assume that the actual spread of the disease followed the same pattern as the one observed in the lab-confirmed dataset. Chowell et al. (2011) suggested that the number of confirmatory tests remained constant during the pandemic.

[53] Assuming a 5.01 ratio between ILI and laboratory confirmed test would have meant that more ILI sought medical attention than the actual cases predicted by the model. A sensitivity analysis assuming this ratio showed that the CE results (described below) were not affected by this assumption.

[54] This assumes that no deaths occur in those with mild symptoms or who were asymptomatic. Furthermore, deaths for other causes different from an ILI case or vaccine adverse event were not considered

If palliative or antiviral treatment was given, a second consultation was provided. Palliative treatment was assumed not to generate any use of extra resources (apart from this consultation) as it required only painkillers and rest. For those requiring antivirals, a 5-day treatment course was offered (2 tablets per day of Oseltamivir at 75mg if older than three years of age or 45mg twice a day if younger). Estimations based on Echevarría-Zuno et al., (2009a) suggest that 75% of patients showing signs of ILI received antiviral treatment. It was assumed that none of these patients would later require hospital care.

Prophylaxis for family members of those patients requiring antiviral treatment was also included. A 10-day course of oseltamivir (at half the dose per day compared to the infected member) was offered to family members with a high risk of developing a complication (individuals with obesity, diabetes, asthma and pregnant women). Prophylaxis treatment with antivirals was only recommended for individuals over 36 months of age (CDC, 2009; WHO, 2010c; Mexican Ministry of Health, 2009b). The average family size of the Mexican population (4.8 members per family) and the total population at high risk of contracting or developing complications from an A(H1H1) infection (18.5%)[55] were used to estimate this proportion.[56]

Inpatient care

Only one GP consultation was assumed for these patients on the basis that the patient was immediately admitted to hospital. Depending on the progression of the hospitalised patient and the availability of ICU beds, critically ill patients might be admitted to ICU treatment.

The proportion of ILI patients requiring hospitalisation was obtained from Echevarría-Zuno et al., (2009a). This value comes from influenza surveillance data compiled by the Mexican Institute for Social Security (IMSS from its name in Spanish).[57] The data were collected from the 1st of April until the 31st of July 2009 (near the day the decision to purchase was made) and focussed on IMSS hospitals and health care units, which represents the biggest social health care providers in Mexico.

---

[55] This proportion was estimated by dividing the estimated population at risk (18,500,000) (estimations by the MMH Córdova-Villalobos et al., (2010) (includes medical personnel and in nurseries, pregnant women and those with an underlying condition such as diabetes, asthma, obesity, heart diseases among others) by the population above 36 months (99,859,336)

[56] The average family size minus the identified individual with the disease were multiplied by the proportion of identified individuals requiring antiviral treatment and the proportion of population at risk above 36 months.

[57] The IMSS is part of the Mexican health system that covers workers from the private sector and their families (accounting for approximately 40% of the population). The remaining population is covered by the public servants' scheme, the Ministry of Health and the private sector.

The information on the paper was presented in nine age groups (<1, 1-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69 and 70 years and over). However, since the authors provided information on the total number of ILI, ILI admitted to hospital and ILI mortality rate it was possible to combine some of the age groups to fit the proposed age groups. This was done as follows: <1, 1-9: assumed for the 0-15 age group; 10-19 and 20-29 were assumed for the 16-29 age group; 30-39, 40-49, 50-59 assumed for the 30-59 age group and; 60-69, 70 and over assumed for the 60 years and over age group. This assumption underestimates the hospitalisation rate slightly for the 0-15 age group and over-estimates this slightly for the 16-29 age group. Table 6.1, shows these values. These parameters were included in the PSA analysis of the model (section 6.3.1.1).

Table 6.1 Number of ILI patients requiring hospitalisation

Age	Total number of ILI cases who sought medical attention	ILI admitted to hospital care	Required age groups	Proportion of ILI requiring hospital care
<1	1,636	184	0-15	5.2%
1-9	11,452	495		
10-19	10,071	306	16-29	3.7%
20-29	11,502	483		
30-39	8,204	373	30-59	5.6%
40-49	5,550	326		
50-59	3,129	254		
60-69	1,319	182	60 and over	20.2%
70 and over	1,173	322		

The proportion of patients requiring ICU treatment in Mexico was obtained from Dominguez-Cherit et al., (2009). The study described the characteristics, treatment and outcomes of critically ill patients in several Mexican hospitals between March and June 2009. The data suggested that 6.5% of hospitalised patients required ICU treatment. However, the study does not disaggregate by age group. Therefore this rate was assumed for all ages. The parameter was included in the PSA analysis (Section 6.3.1.1).

Death

Information about deaths among ILI patients was obtained from Echevarría-Zuno et al., (2009a)[58] from data collected from the 1st of April until the 31st of July 2009. As with the data on ILI requiring hospitalisation, the information in the paper was presented in nine age groups. The same calculations made for that parameter were made here (see

[58] Death was only assumed possible in those ILI patients who sought medical attention

above). The mortality rates for people with ILI who sought medical attention are shown in Table 6.2.

Table 6.2 The mortality rates for patients with ILI seeking medical attention

Age	Total number of ILI cases who sought medical attention	ILI who died	Required age groups	Proportion of ILI who died
<1	1,636	184	0-15	0.06%
1-9	11,452	495		
10-19	10,071	306	16-29	0.07%
20-29	11,502	483		
30-39	8,204	373	30-59	0.20%
40-49	5,550	326		
50-59	3,129	254		
60-69	1,319	182	60 and over	0.28%
70 and over	1,173	322		

6.2.3 Vaccination

The expectations that the MMH had on the effectiveness of the vaccine at the time when the decision was made was used. The MMH estimate of the most likely effectiveness value was 50% effectiveness (Chapter 2) (Córdova-Villalobos et al., 2010). Within sensitivity analyses, 30% and 70% effectiveness values were tested.

Two different types of adverse events were considered: low/mild and severe. The low/mild category included local reactions (pain, tenderness or redness at the site of the injection) or systemic adverse events (fever, headaches, malaise and myalgia). Due to the transient nature of these episodes, no use of resources was assumed. Since the incidence of these adverse events was unknown when the decision to purchase was made, it was assumed that the rates for the rH5N1 vaccine prototypes reported in Leroux-Roels et al., (2007) were generalisable. The Sanofi-Pasteur vaccine was a 15μg dose with no co-adjuvant, as such the incidence of the 15μg rH5N1 vaccine with no co-adjuvant was assumed. The GSK vaccine was a 3.75μg dose with co-adjuvant, and therefore the incidence of the 3.8 μg rH5N1 vaccine with co-adjuvant was assumed.

If the patient had a severe adverse, however, it was assumed that hospitalisation (and potentially admission to ICU) was required. As described in Chapter 2, the MMH was mostly concern about GBS. When the decision to purchase the vaccine was made, the MMH expected 10 cases of GBS for every 1,000,000 vaccinated individuals. An overall rate of 0.001% was assumed alongside differential rates by age group based on data

reported by De Wals et al., (2012). Most cases of GBS linked to the A(H1N1) vaccine pertain to the 60 and over age group (56%) followed by the 30 to 59 years (36%) and 4% in the 0 to 29 years. Although these proportions are from a study post-decision time, the MMH expectations were that most of the cases would occur in the 25 and over age group which is in line with the distributions used for the analysis.

Whilst only 4 to 8% of patients with GBS would die (Carroll et al., 2003; CENETEC, 2016), a significant number can develop a long-term or permanent disability (mean 55%: range 25-85%) (CENETEC, 2016) and incur in long inpatient care (on average of 55.6 days, ranging from 21-94 days) (Carroll et al., 2003). Regarding the resources necessary for its treatment, according to the MMH guidelines (CENETEC, 2016), the recommended treatment therapy is via immunoglobulin therapy combined with anti-inflammatory medications to ease the pain.[59]

Table 6.3 summarises the proportions and length of stay for adverse events related to the vaccination.

Table 6.3 Adverse events due to the 2009 A(H1N1) vaccine

Parameter		Proportion/Mean (Min-Max)	Description
Sanofi-Pasteur	No adverse events	57.999%	Assumed as 1-(A)-(B)
	Low to mild adverse events* (A)	42% (28.2%-56.8%)	Leroux-Roels et al. (2007)
	Serious adverse events (B)	0.001%	MMH estimates based on Schonberger et al., (1979)
GSK	No adverse events	9.999%	Assumed as 1-(C)-(D)
	Low to mild adverse events* (C)	90% (78.6-96.7%)	Leroux-Roels et al. (2007)
	Serious adverse events (D)	0.001%	MMH estimates based on Schonberger et al., (1979)
Serious adverse events requiring hospitalisation (including ICU)**		96%	De Wals et al. (2012)
Serious adverse events requiring ICU		11%	Carroll et al. (2003)
Average days in hospital due to severe adverse events (ICU or Hospitalisation)		55.6 (21-94)	Carroll et al. (2003)
Death from Serious adverse events		6% (4-8%)	Carroll et al. (2003)
Recovered patients with long term disability		55% (25-85%)	Assumed from CENETEC (2016)

**Correspond to pain, whose incidence was the highest reported*
***Correspond to data after the decision was made, however, it was thought that this proportion would not have been different at the time of the decision.*

[59] Although the CENETEC (2016) guidelines are recent, this new version main updates are on prevention, diagnostic, treatment (the main treatment remains the same: immunoglobulin therapy combined with anti-inflammatory medications), referrals and follow-up

Several doses were lost in the process of application, transportation and storage; therefore, wastage was considered in the analysis. The MMH reported at the end of the campaign that a total of 28.5 million vaccines were applied. However, the MMH at decision time estimated a wastage of 12% based on previous influenza campaigns (Córdova-Villalobos et al., 2010). The base case scenario assumes this 12% wastage while a sensitivity analysis considers a 5% wastage (equivalent to 28.5 million vaccines being applied) (Cordova-Villalobos et al., 2017).

The actual vaccination campaign duration was 145 days (from 27th November 2009 to 21st of April 2010). However, the MMH made an assumption that it could take 90 days to apply 30 million vaccines based on previous influenza vaccination campaigns (Córdova-Villalobos et al., 2010).

6.2.4 Productivity losses

Productivity losses were considered as days absent from work for those individuals who required inpatient or outpatient care, or for those vaccinated that suffered a severe adverse event. The productivity losses were estimated using a weighted average of the daily income in 2009 in Mexico (126.20 MXN) (INEGI, 2009), the ratio between working and leisure days a month (0.714)[60], the proportion of labour force in the relevant age group (BIE, 2012) and the average days of treatment. Productivity losses were only accounted for the population over 14 years old. Table 6.4 shows the average wage loss per episode per age groups. Appendix V contains more details on how these calculations were performed.

[60] Calculation based on an average of 30.14 days, 4.35 weeks in a month and a working week of five days.

Table 6.4 Average wage loss per episode of A (H1N1)

Age group	Average wage loss per episode	Comment
Lost wages for those who receive outpatient care		
14-29	$198.84	An average of 5 days' treatment
30-59	$306.34	
60 and over	$171.71	
Lost wage for those hospitalised		
14-29	$210.77	An average of 5.30 days' treatment
30-59	$324.72	
60 and over	$182.01	
Lost wage for those who required ICU care		
14-29	$470.46	An average of 11.83 days' treatment
30-59	$724.82	
60 and over	$406.27	

6.2.5 QALY losses

QALY losses were estimated for individuals with the disease (including those who did not report the infection or were unidentified) and those who experienced an adverse event due to vaccination.

Although several papers have estimated the QALY losses related to the 2009 A(H1N1) pandemic (van Hoek et al., 2011; Lavelle et al., 2011) they were published after the decision to purchase the vaccine was made. As such, the information regarding QALY losses was taken from Siddiqui and Edmunds, (2008) which QALY loss estimates are based on O'Brien et al. (2003) and Melegaro and Edmunds, (2004), both papers were available at the time the decision to purchase was made.

The QALY lost for a symptomatic episode of A(H1N1) seeking for medical attention was assumed to be 0.0086 independent of age group. The QALY loss for those who did not seek medical attention or were unidentified, either because the disease was asymptomatic or mild, was assumed as 0.0046. Patients requiring inpatient care were assumed to have a QALY loss of 0.0106. It was assumed that patients requiring ICU treatment would have a QALY loss two times higher than those requiring inpatient care (0.0212).[61]

[61] The QALY loss estimates for symptomatic cases were assumed as the sum of an uncomplicated ILI and outpatient pneumococcal pneumonia: 0.0046+0.004. QALY loss for inpatient care were assumed as the sum of an uncomplicated ILI and an inpatient

The QALYs lost due to a fatal episode was estimated using the 2009 life expectancy of the Mexican population (74.5) (CONAPO, 2012) and the average utility values for the UK population by age estimated by Kind et al. (1999) as these data was not available for Mexico. These were discounted at a 5% rate which is used for Mexico (Consejo de Salubridad General and INSP, 2008). The average QALYs lost considered per fatality were: 16.5 for the 0-15 age group; 16.01 for the 16-29 age group; 13.30 for the 30-59 age group and 5.97 for the 60 and over.

Individuals who suffered from a low/mild adverse event were assumed to incur only a slight reduction in QALYs (0.00023)[62]. The QALYs lost for patients experiencing a serious adverse event (assumed as GBS) was assumed as four times the QALY loss for those patients requiring inpatient care (0.0424) per episode with complete recovery. For patients who recover but with a permanent disability, a utility reduction of 0.0424 per year was assumed. As the QALY loss estimated due to fatality (described above) data from the UK (Kind et al. 1999) were used, and a 74.5 life expectancy was assumed (CONAPO, 2012). The average QALY losses per age group, discounted at a 5% rate, for people with a permanent disability were: 0.86 for the 0-15 age group; 0.83 for the 16-29 age group; 0.70 for the 30-59 age group and 0.32 for the 60 and over age group. A scenario where no adverse events were considered was also evaluated. Table 6.5 summarises the QALY losses assumed in the model.

pneumococcal pneumonia: 0.0046+0.006 (Siddiqui and Edmunds, 2008; O'Brien et al., 2003; Melegaro and Edmunds, 2004)

[62] This was assumed to as 5% of the QALY loss of an uncomplicated ILI reported by (Siddiqui and Edmunds, 2008)

Table 6.5 Summary of the QALY losses assumed in the model

Variable	Value	Source/comment
Vaccine adverse events*		
Low/Mild	0.00023 (SE: 0.00003)	5% of a QALY loss uncomplicated ILI cases (Siddiqui & Edmunds 2008). SE adjusted proportionally
Severe	0.042 (SE 0.0024)	Assumed as four times, the QALYs lost for patients requiring inpatient care. SE from uncomplicated ILI infection adjusted proportionally
Permanent disability		
0-15 years	0.86	Estimated from average Mexican life expectancy and Kind et al. (1999)
16-29 years	0.83	
30-59 years	0.70	
60 and over years	0.32	
Influenza infection*		
Asymptomatic or mild (did not seek medical attention)		
All age groups	0.0046 (SE 0.0006)	Assumed as an uncomplicated ILI case (Siddiqui and Edmunds, 2008; O'Brien et al., 2003)
Symptomatic (sought medical attention)		
All age groups	0.0086	Assumed as the sum of QALYs loss of an uncomplicated ILI case (Siddiqui and Edmunds, 2008; O'Brien et al., 2003) and pneumococcal pneumonia for outpatient care (Melegaro and Edmunds, 2004)
Uncomplicated ILI case	0.0046 (SE 0.0006)	
Outpatient pneumococcal pneumonia	0.004 (0.0034-0.0046)	
Patients requiring inpatient care		
All age groups	0.0106	Assumed as the sum of QALYs loss of an uncomplicated ILI case (Siddiqui and Edmunds, 2008; O'Brien et al., 2003) and pneumococcal pneumonia for inpatient care (Melegaro and Edmunds, 2004)
Uncomplicated ILI case	0.0046 (SE 0.0006)	
Inpatient pneumococcal pneumonia	0.006 (0.0051-0.0069)	
Patients requiring ICU treatment		
All age groups	0.021 (SE: 0.0012)	Assumed as two times, the QALYs lost for patients requiring inpatient care. SE from uncomplicated case adjusted proportionally
Death		
0-15 years	16.50	Estimated from average Mexican life expectancy and Kind et al. (1999)
16-29 years	16.01	
30-59 years	13.30	
60 and over years	5.97	

* Siddiqui and Edmunds, (2008) *reported standard deviation*

6.2.6 Costs

The costs considered were those for people with ILI that sought medical attention and those related to providing the vaccination and treating serious adverse events.

Costs were obtained from the MMH internal registries (Mexican Ministry of Health, 2009b), and the IMSS (Costos Unitarios por Nivel de Atención Médica para el año

2009 IMSS). No discounting was applied to the costs as they only were considered for the relatively short duration of the model (600 days).

6.2.6.1 Outpatient care costs

The outpatient care resources used were described in Section 6.2.2. Table 6.6, shows the average cost per person of outpatient care. Detailed estimations of these costs can be found in Appendix V.

Table 6.6 Outpatient care costs

Item	Description	Unit cost (MXN)
Oseltamivir	Cost per adult	$297.83
	Cost per children	$27.20
	Prophylaxis	$171.61
Medical consultation	Two medical consultations	$1,034.00
Total cost per patient requiring outpatient care		$1,530.65

6.2.6.2 Inpatient care costs

The resources used for inpatient care were described in Section 6.2.2. The total costs of hospitalisation costs were estimated based on the average length of stay reported by Chowell et al. (2012) (5.3 days). Although this estimate is for the whole pandemic, the authors have indicated that this average did not change over time. For those patients requiring ICU treatment, the time from hospitalisation until admission to ICU (1 day on average) and the duration of stay in ICU (10.83 days on average) was obtained from Dominguez-Cherit et al. (2009) using data between March and June 2009 (Table 6.7).

General items, overheads, personal costs, equipment, are included in the cost provided by IMSS, but not the specific medication required for the treatment of A(H1N1). These were obtained from the MMH (Mexican Ministry of Health, 2009b) and were weighted averages of the medication and hospital costs for adults and children. Table 6.8 shows a summary of the cost per patient for each service.

Table 6.7 Variables used for inpatient care cost estimations

Variables	Mean	Description/source
Average length of stay for hospitalised patients	5.3	Chowell et al. (2012)
Average length of stay for patients requiring ICU	11.8	On average patients spend one day in the general ward before being transferred to ICU (Dominguez-Cherit et al. 2009)

Table 6.8 Summary of the average inpatient costs associated with A(H1N1)

Variables		Cost (MXN)	Description
Hospitalisation	First contact medical consultation	$517.00	-
	Bed day general ward	$25,275.00	5.3 days on average ($4,769 per day, excluding medication)
	Medication	$3,885.80	5.3 days on average Medication to treat an A(H1N1) such as *Oseltamivir, Metamizole, Salbutamol, Omeprazole, Ranitidine, Ceftriaxone, Amoxicillin, Clarithromycin, Ciprofloxacin, Meropenem, Imipenem, Ceftazidime, Vancomycin* (Mexican Ministry of Health, 2009b).
Total hospitalisation cost (MXN)		**$29,678.50**	
ICU	First contact medical consultation	$517.00	-
	Bed day general ward	$4,769	One day on average
	Medication in general ward	$1,051.26	Medication to treat A(H1N1) such as *Oseltamivir, Metamizole, Salbutamol, Omeprazole, Ranitidine, Ceftriaxone, Amoxicillin, Clarithromycin, Ciprofloxacin, Meropenem, Imipenem, Ceftazidime, Vancomycin* (Mexican Ministry of Health, 2009b)
	ICU bed day	$304,083	10.83 days on average
	Medication	$29,792.19	For the duration of ICU stay. Include medication specific to threat A(H1N1) plus others such as neuromuscular blocking drugs, Anaesthetics, Antibiotics, Antivirals, Neurotransmitters (Mexican Ministry of Health, 2009b).
Total ICU cost (MXN)		**$335,444.39**	

Based on deterministic average

6.2.6.3 Vaccine

The purchased vaccine was acquired from Sanofi-Pasteur and GSK. The cost per vaccine was $95.00 MXN on average, resulting in a total cost of $2,850 million MXN (without delivery, consumables, transport and cold chain). Delivery costs based on the conditions required to apply the vaccine were considered (CNV, 2009). The cold chain requirements (the temperature-controlled supply chain necessary to maintain vaccine vials in optimum conditions before its application) were also included. A cost per dose was estimated based on a weighted average of the cost and capacity (in litres) of the most representative units available in the cold chain elements. This information was retrieved from Biologics and Reagent Laboratories of Mexico (BIRMEX® from its name in Spanish). The costs of transportation in the process was taken from (Gutierrez and Bertozzi, 2005) and inflated to 2009 MXN using the National Price Index (INEGI, 2013). The cost of the vial, delivery, cold chain and transportation were added to produce a total cost per dose. Personnel costs were not considered in the base case scenario as they were assumed fixed since most of the patients would seek the vaccination in their medical centre with personnel that had permanent positions. However, a sensitivity analysis including the costs of hiring temporary personnel to apply the vaccines was analysed (Section 6.3.1.2). Table 6.9 describes the costs of the vaccine including transportation, storage and cold chain.

Table 6.9 Cost of the vaccine

Item	Cost (MXN)	Observations
Vial	$95.00	Average cost of the two brands of vaccines purchased
Consumables	$1.61	Includes syringes, torundas cotton, antiseptic soap, paper towels, paper sheets, disposal bags and containers
Cost of transport & storage	$0.38	Gutierrez & Bertozzi (2005)
Cold Chain	$0.09	Estimation based on the number of doses and the size of the vial
Total (MXN)	**$97.08**	**Cost of 30 million doses: $2,912 million**

Costs expressed in Mexican Pesos MXN

The average number of days in hospital care due to GBS from Carroll et al. (2003) (55.6 inpatient care on average) were used to estimate the costs of a serious adverse

event.[63] The MMH guidelines recommend intravenous immunoglobulin therapy as a treatment for GBS syndrome (CENETEC, 2016). The costs of this therapy were not available from Mexican data. Therefore the costs (US dollars, 2011 prices) published by Winters et al. (2011) were used as a reference. They include a treatment of five infusions for patients with an average weight of 70 kg and the infusion supplies at a reported cost of $9,855.25 USD. The exchange rate during 2011 was used ($11.52 MXN per 1 USD) along with the national price index (INEGI, 2013) to deflate the 2011 prices to 2009 prices. Table 6.3 provides details of the parameters used to estimate the proportion of vaccinated individuals who might experience an adverse event, while Table 6.10 details the cost of a serious adverse event.

Table 6.10 Adverse events treatment costs per patient

Variables		Cost (MXN)	Description
Hospitalisation	First contact	$517	-
	Bed day general ward	$265,156	55.6 days on average at $4,769. 89% of patients will only require hospitalisation in the general ward
	Immunoglobulin therapy	$84,245	For the duration of treatment
Total hospitalisation cost (MXN)		**$349,918**	
ICU	First contact	$517	
	Bed day in the ICU unit	$1,561,081	55.6 days on average at $28,077 per day in ICU 11% of patients will require ICU treatment
	Immunoglobulin therapy	$84,245	For the duration of treatment
Total ICU cost (MXN)		**$1,645,843**	

[63] Serious adverse events were assumed as an episode of GBS. This assumption was made on the bases that the GBS requires more resources and potentially carries a bigger QALY loss than other serious adverse events. The risk of narcolepsy was considered significant in the GSK vaccine, as a causal association was found in Finland and England (Miller et al., 2013; Partinen et al., 2012). This adverse event, however, was not observed in an influenza vaccine before the 2009 pandemic.

.

6.3 Base case scenario, secondary and sensitivity analysis

Two different vaccination alternatives were analysed: strategy 1: population strategy and 2: lab-confirmed strategy. Both strategies were analysed assuming three RR for the 0-15 age group: 0.001, 0.01 and 0.75 and were compared to no vaccination. The base case scenario assumed that the vaccine arrived as expected, a wastage of 12%, a vaccine effectiveness of 50%, a vaccination campaign lasting 90 days, and that the adverse events of the vaccination and productivity losses were incorporated. A secondary analysis evaluated these vaccination strategies assuming that the vaccine arrived 31 days later than anticipated. Table 6.11 summarises the base case scenario. PSA and one way and scenario sensitivity analysis were also performed.

Table 6.11 Base case scenario

Parameters	No vaccination strategy	Population strategy	Lab-confirmed strategy
Duration	600 days	600 days	600 days
Vaccination strategy*	No	Yes	Yes
Wastage	NA	12% (26.4 million vaccines applied)	12% (26.4 million vaccines applied)
Vaccinated population	NA	Based on the proportion of individuals in each age group: 0-15: 31% 16-29: 25% 30-59: 36% 60 and over: 8%	Based on the proportion of lab-confirmed cases at decision time 0-15: 51% 16-29: 28% 30-59: 20% 60 and over: 1%
Vaccine effectiveness	NA	50%	50%
Vaccine arrival	NA	As anticipated	As anticipated
Vaccination campaign duration	NA	90 days	90 days
Adverse events	NA	Included	Included
Productivity losses	NA	Included	Included

For details on the parameter values, please see section 6.2 methods.

6.3.1 Sensitivity analysis

6.3.1.1 Probabilistic sensitivity analyses (PSA)

The CE of the vaccine was determined via PSA. The 200 thinned draws from the calibration process detailed in Chapter 4 were used and provided 200 different outputs regarding number of infections. These figures were used to estimate the number of deaths, hospitalisations, ICU, adverse events and productivity losses. Input values for

parameters related to costs, QALYs and the proportion of hospitalisations, ICU stays, and adverse events were sampled from distributions to allow a probabilistic estimate of incremental costs and QALYs. This allowed the estimation of the ICER, CEAC, CEAF. Table 6.12 summarises the deterministic value and the distributions and their parameters used.

Table 6.12 Deterministic and probabilistic values for the PSA analysis

Variable			Deterministic value Proportion/Mean /Mode	Distribution	Parameters	Source
Medical care						
Out- patients requiring antiviral treatment			75%	Beta	α: 466 β: 157	Echevarría-Zuno et al., (2009)
Proportion of patients requiring hospitalisations (only those ILI who seek medical attention)	**0-15**		5.2%	Beta	α: 679 β: 12,409	Echevarría-Zuno et al., (2009)
	16-29		3.7%	Beta	α:789 β:20,784	
	30-59		5.6%	Beta	α: 953 β:15,930	
	60 and over		20.2%	Beta	α: 504 β:1,988	
Mortality rate (only those ILI who seek medical attention)	**0-15**		0.06%	Beta	α: 7 β: 13,081	Echevarría-Zuno et al., (2009)
	16-29		0.07%	Beta	α: 15 β: 21,558	
	30-59		0.20%	Beta	α: 33 β: 16,850	
	60 and over		0.28%	Beta	α: 7 β: 2,485	
Average length of stay for hospitalised patients			5.3	Normal	SE: 0.13	Chowell et al. (2012)
Hospitalised patients requiring ICU treatment			6.5%	Beta	α: 58 β: 841	Dominguez-Cherit et al. (2009)
Length of stay in ICU			10.83	Gamma	α: 1 β: 12	Dominguez-Cherit et al. (2009). These patients had one day in the general ward first
Vaccination and Adverse Events						
Vaccine effectiveness			50%	-	Fixed	Córdova-Villalobos et al. (2010)
Vaccine adverse events	**Sanofi**	**No adverse events (A)**	57.999%	-	1-(B)-(E)	-
		Low to mild adverse events (B)	42%	Beta	α: 19 β: 26	Leroux-Roels et al. (2007)
	GSK	**No adverse events (C)**	9.999%	-	1-(D)-(E)	-
		Low to mild adverse events (D)	90%	Beta	α: 37 β: 4	Leroux-Roels et al. (2007)
	Serious adverse events (E)		0.001%	-	Fixed	Estimations made by the MMH based on (Schonberger et al., 1979)
Serious adverse events requiring hospitalisation (F)			96%	-	Fixed	De Wals et al. (2012)
Serious adverse events requiring ICU (G)			11%	-	Fixed	Carroll et al. (2003)
Average days in hospital due to severe adverse events (ICU or Hospitalisation) (H)			55.6	Gamma	α: 1 β: 53	Carroll e al. (2003)
Death from Serious adverse events (I)			6%	Beta	α: 32 β: 508	Carroll et al. (2003)
Recovered from hospitalisation or ICU treatment (J)			94%	-	1-(I)	CENETEC (2016)
Recovered patients with long-term disability (K)			55%	Beta	α:5 β:4	CENETEC (2016)
Recovered patients gaining full health (L)			45%	-	1-(K)	CENETEC (2016)

Table 6.12 Deterministic and probabilistic values for the PSA analysis (cont…)

QALYs lost						
QALYs lost due to ILI	**Asymptomatic or mild (did not seek medical attention; all ages)**		0.0046		Beta	α: 59 β: 12,659	See Table 6.5 for more details (Siddiqui and Edmunds, 2008; O'Brien et al., 2003)
	Symptomatic (sought medical attention	Uncomplicated ILI case	0.0086	*0.0046*	Beta	α: 59 β: 12,659	Uncomplicated ILI and outpatient pneumococcal pneumonia sampled independently and then added together. See Table 6.5 for more details Triangular distribution assumed in Siddiqui & Edmunds (2008)
		Outpatient pneumococcal pneumonia		*0.0040*	Triangular	a: 0.0034 b: 0.0046	
	Hospitalised	Uncomplicated ILI case	0.0106	*0.0046*	Beta	α: 59 β: 12,659	Uncomplicated ILI and inpatient pneumococcal pneumonia sampled independently and then add together. See Table 6.5 for more details Triangular distribution assumed in Siddiqui & Edmunds (2008)
		Inpatient pneumococcal pneumonia		*0.0060*	Triangular	a: 0.0051 b: 0.0069	
	Patients requiring ICU treatment (all age groups)		0.021		Beta	α: 300 β: 13,976	See Table 6.5 for more details
QALYs lost due to vaccine adverse events	**Low/Mild**		**0.00023**		Beta	α: 59 β: 255,437	Based on Siddiqui & Edmunds (2008) See Table 6.5 for more information.
	Severe (including hospitalisation or ICU)		0.042		Beta	α: 293 β: 6691	See Table 6.5 for details
Utility lost per year in disability	**0-15**		0.86		-	Fixed	Over the lifetime of the patient discounted at a 5% rate. See Section 6.2.5 for more details on estimation
	16-29		0.83				
	30-59		0.70				
	60 and over		0.32				
Utility lost per year in lost due to premature death	**0-15**		16.50		-	Fixed	Over lifetime discounted at a 5% rate. See section 6.2.5 for more details on estimation
	16-29		16.01				
	30-59		13.30				
	60 and over		5.97				

Parameters with no defined distribution were assumed as fixed
For the Beta distribution α was defined as the number of cases for each event while β was estimated as the total number of individuals at risk minus α.

A limitation of these analyses was that the average daily wage and utility loss due to premature death were assumed as fixed. Neither is likely to affect the results heavily, particularly when discounting is considered.

6.3.1.2 One way and scenario analyses

Apart from the secondary analysis exploring the impact on the CE of the vaccine arriving 31 days later than expected, sensitivity analyses were performed to evaluate the impact of several of the key parameters on the CE results. The scenarios were only tested in the strategies where an impact on the conclusion of the CE of the vaccine was deemed possible. These were decided once the CE results were produced and analysed and are listed in Table 6.13

Table 6.13 The sensitivity analyses performed

Base case scenario	Sensitivity analysis scenario
Adverse events as in Table 6.3	No adverse events
Prior immunity based on previous H1N1 epidemics (Chapter 4 Table 4.4) 0-15 y: 2.79% 16-29 y: 17.50% 30-59 y 12.00% 60 and over y: 23.32%	No prior immunity
12% based on expectations by MMH	5% Vaccine wastage (based on actual occurrences)
50% based on most likely effectiveness according to MMH expectations	70% Vaccine effectiveness (based on the maximum vaccine effectiveness expected by the MMH)
50% based on most likely effectiveness according to MMH expectations	30% Vaccine effectiveness (based on the minimum vaccine effectiveness expected by the MMH)
90 days, based on MMH previous experiences of applying the influenza vaccine	145 days' vaccination campaign duration (based on the actual duration)
Productivity losses as described in Section 7.2.4	No productivity loss
No additional medical personnel costs to apply the vaccines	Assumed as 10,000 medical assistants hired at the average wage in Mexico $126.20 per day for 90 days for a total of $113.58 million MXN
A QALY loss of 0.0046 for asymptomatic or mild cases as described in Table 6.5	0.0023 QALY loss for asymptomatic or mild cases (50% reduction vs. base case)
A QALY loss of 0.0046 for asymptomatic or mild cases as described in Table 6.5	No QALY loss for asymptomatic or mild cases
5.01 to 1 ratio between ILI who seek medical attention and lab-confirmed cases	10 to 1 ratio between ILI who seek medical attention and lab-confirmed cases
1 to 1 ratio between ILI who seek medical attention and lab-confirmed cases for the 0.75 RR scenario	5.01 to 1 ratio between ILI who seek medical attention and lab-confirmed cases

Optimistic and pessimistic scenarios were also tested. The optimistic scenario assumes a vaccine effectiveness of 70%; no adverse events included; a 5% wastage and a 90 days' vaccine campaign duration. The pessimistic scenario assumes a vaccine effectiveness of 30%, assumes adverse reactions (as described in Table 6.3), 12% vaccine wastage and 145 days' vaccination campaign duration.

An extreme scenario was tested for the 0.001 RR where it was assumed that the additional hospitalisations generated within the no vaccination strategy were

associated with the loss of life of a patient who could not be admitted to hospital. This was termed the opportunity cost scenario.

To explore the potential impact of vaccinating high-risk individuals, a scenario assuming an increased risk of the consequences of an influenza infection (in the form of hospitalisations, ICU treatment and deaths) was assumed. Although this cannot replace the actual impact of a vaccine strategy targeting risk groups it can provide an insight of its possible implications.

Additionally, two alternatives mean generation times were analysed: 1.3 days and 2.71 days based on the CIs reported by Fraser et al., (2009). The ratio of the latent period to infectious period in the base case was assumed generalisable to the different generation times.

6.4 Results

The results correspond to three RR for the 0-15 age group (0.001, 0.01 and 0.75). The RR was set fixed for the 0-15 age group and used as a reference to adjust the RR for the 16-29, 30-59 and 60 and over age groups via the MCMC routine described in Chapter 4. For brevity, these will be termed RR of 0.001, 0.01 and 0.75 omitting the 0-15 years of age band.

The no vaccine strategy predicted on average 19.9 million infections with around 13.2 million lab-confirmed cases when an RR of 0.75 for was assumed. When the RR was assumed to be 0.01, the model predicted 19.8 million cases but with only 175,000 lab-confirmed cases. Lastly, the 0.001 RR scenario, predicted on average 22.4 million cases with only 19,000 lab-confirmed cases.

The numbers of ILI who sought medical attention for the 0.01 and 0.001 RRs, were assumed to be 5.01 per 1 lab-confirmed case, based on data from the PHO (see section 6.1.2 for more details). In contrast to the 0.75 RR scenario, this was assumed as 1 ILI who sought medical attention per 1 lab-confirmed case.[64] As shown in sensitivity analyses this assumption did not have an impact in the CE of the vaccine.

19.9 million ILI sought medical attention using an RR of 0.75, compared with 878,000 for the 0.01 RR scenario and 95,000 for the 0.001 scenarios.

[64] Assuming the same rate as for the 0.01 and 0.001 would mean that more patients with an ILI sought medical attention than the actual number of total cases predicted.

The estimated number of ILI seeking medical attention requiring hospitalisations, ICU and deaths are shown in Table 6.14.

Table 6.14 Estimated number of ILI who sought medical attention, required hospitalisation, ICU and died assuming no vaccination

Patient distribution	Reporting scenario		
	0.75	**0.01**	**0.001**
ILI who sought medical attention	19,912,953	878,147	95,413
Hospitalisations	1,143,784	42,668	4,661
ICU	74,046	2,762	302
Deaths	21,771	769	83

6.4.1 Base case scenario

The vaccine was more beneficial when the lab-confirmed strategy was employed. Table 6.15 contains the number of predicted infections, ILI who sought medical attention, hospitalisations, ICU and deaths for the three RR assumed for both strategies population and lab-confirmed.

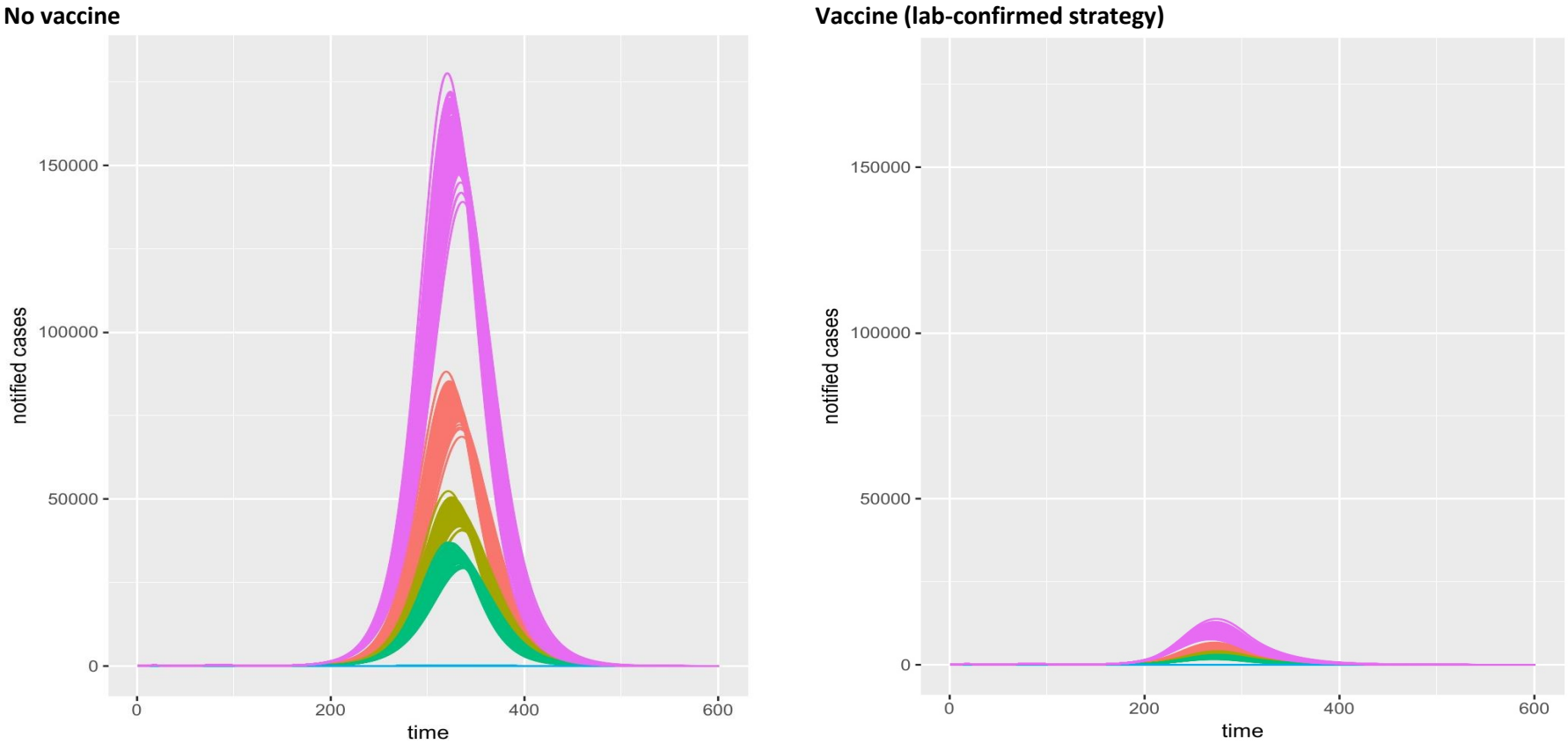
Table 6.15 Estimated infections, ILI who sought medical attention, hospitalisations, ICU and deaths for the three RR assumed

Reporting rate For the 0-15 age group	Vaccine Strategy		
	No-vaccine	**Population**	**Lab-confirmed**
0.75			
Total infections*	19,912,953	3,081,313	1,531,096
ILI	19,912,953	3,081,313	1,531,096
Hospitalisations	1,143,784	176,143	88,838
ICU	74,046	11,401	5,750
Deaths	21,771	3,306	1,713
0.01			
Total infections	19,856,040	13,736,851	12,698,004
ILI	878,147	608,059	559,467
Hospitalisations	42,668	29,574	27,194
ICU	2,762	1,915	1,761
Deaths	769	530	492
0.001			
Total infections	22,433,898	21,770,565	21,754,701
ILI	95,413	92,553	92,481
Hospitalisations	4,661	4,522	4,518
ICU	302	293	293
Deaths	83	80	80

The impact of the vaccine can be observed graphically. Figure 6.1 shows the impact of lab-confirmed vaccination strategy compared with the no vaccination strategy for each of the three RR scenarios. The highest drop in the number of cases can be observed when the 0.75 RR scenario was assumed, as there was a greater number of susceptible in the population when the vaccines arrived.

Figure 6.1 Trend of the pandemic with and without vaccination

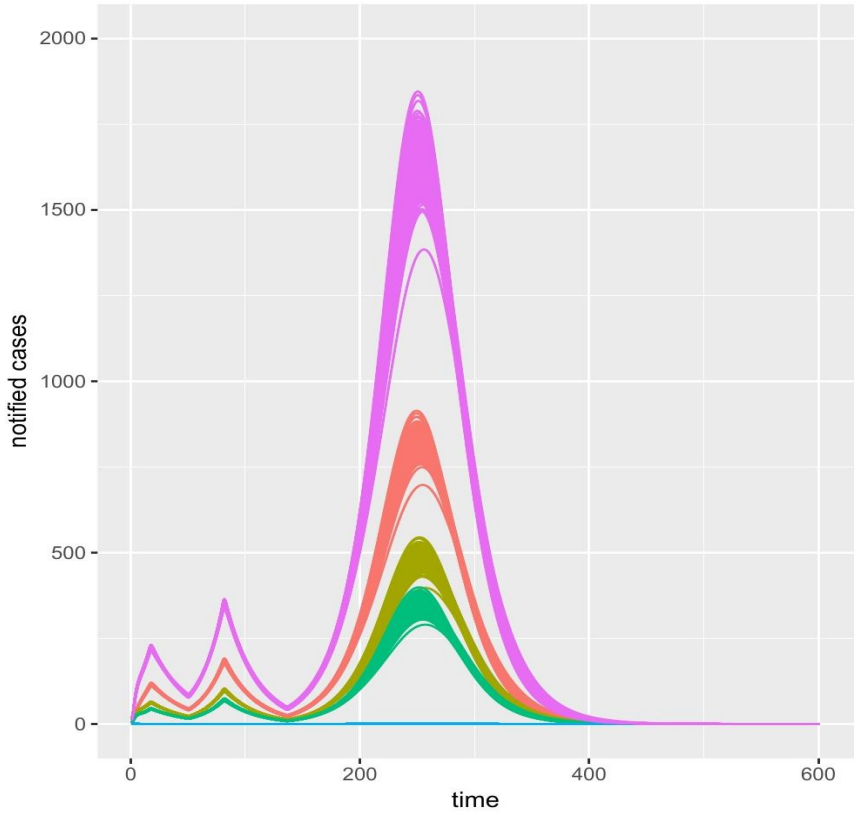
a) 0.75 reporting rate scenario



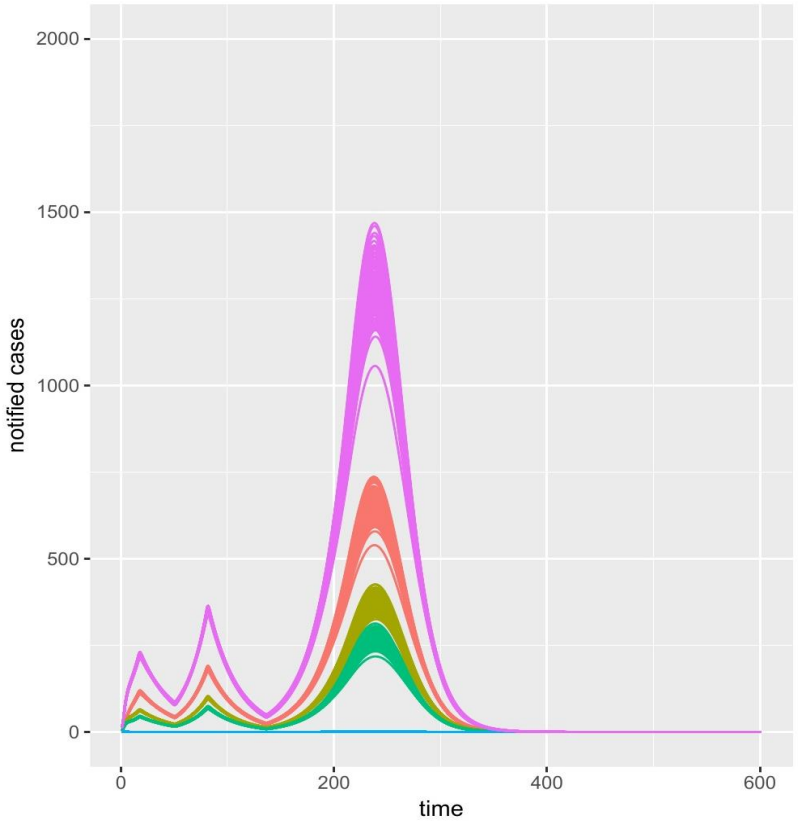
Lines in pink correspond to all age groups
Lines in orange correspond to the 0-15 age group
Lines in green olive correspond to the 16-39 age group
Lines in green correspond to the 40-59 age group
Lines in blue correspond to the 60 and over age group
the x-axis represents time, y-axis total number of notified cases;

b) 0.01 reporting rate scenario

No vaccine



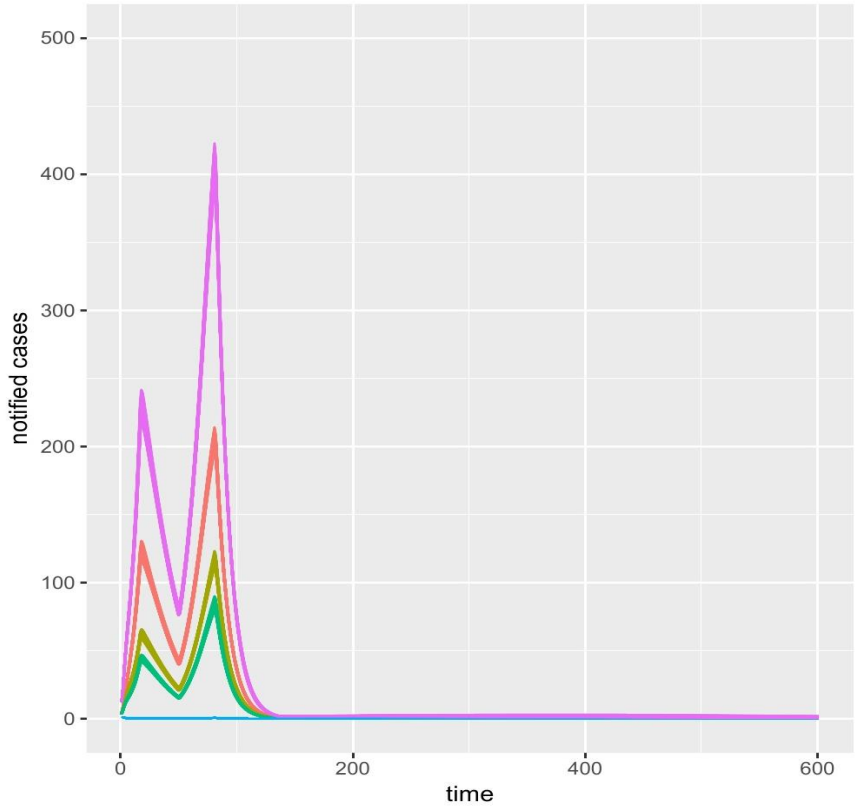
Vaccine (lab-confirmed strategy)



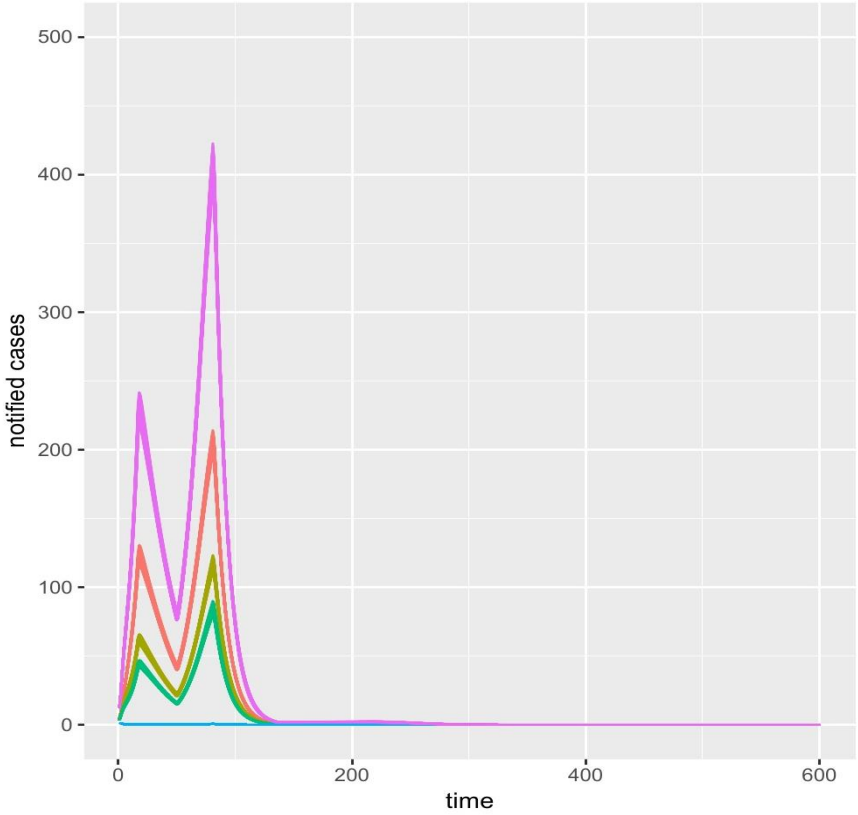
Lines in pink correspond to all age groups
Lines in orange correspond to the 0-15 age group
Lines in green olive correspond to the 16-39 age group
Lines in green correspond to the 40-59 age group
Lines in blue correspond to the 60 and over age group
the x-axis represents time, y-axis total number of notified cases

c) 0.001 reporting rate scenario

No vaccine



Vaccine (lab-confirmed strategy)



Lines in pink correspond to all age groups
Lines in orange correspond to the 0-15 age group
Lines in green olive correspond to the 16-39 age group
Lines in green correspond to the 40-59 age group
Lines in blue correspond to the 60 and over age group
the x-axis represents time, y-axis total number of notified cases

6.4.1.1 Cost-effectiveness results

The results presented here are from the PSA using the 200 thinned parameters from the MCMC routine. A jackknife 95% confidence interval for ICER was estimated to provide confidence levels on the ICER given that only 200 iterations were performed.

Since the costs and QALY loss estimates were based on the number of patients with ILI who sought medical attention,[65] the no vaccination strategy estimates were highest for the 0.75 RR scenario followed by the 0.01 and 0.001 (0.75: over $83.6 billion MXN; 0.01: over $3.3 billion MXN and 0.001: over $360 million MXN). The QALY losses were estimated to be 468,967; 106,140 and 104,414 QALY respectively.

In the 0.75 RR scenario, the net cost of vaccination was less costly than no vaccination, saving between $67 and $74 billion MXN. The vaccination strategies also estimated less QALY losses than the no vaccine by a large margin (between 393,000 and 429,000). Therefore, in both vaccination scenarios (population and lab-confirmed strategies) when a 0.75 RR was assumed vaccination dominates the no vaccination alternative.

When the RR was assumed to be 0.01, the vaccine strategies were more costly than the no vaccine (between $1.7 and $1.9 billion). However, in both vaccination strategies, the estimated QALY losses avoided were more than in the no vaccine scenarios (between 29,000 and 34,700 QALYs). The estimated ICERs for both vaccination strategies (population and lab-confirmed) were below the lower assumed threshold value ($110,000)

For the 0.001 RR analysis, the costs associated with the vaccination strategies were greater than no vaccination. Vaccination was associated with a slightly more number of QALY lost, therefore in both vaccination scenarios, the no vaccine dominated the vaccine strategies.

Results for all RR scenarios in the base case analysis are provided in Table 6.16.

[65] This assumes that those who did not seek medical attention were either asymptomatic or mild to low severity infections and would treat themselves. This assumes no costs incurred by the MMH but assumes a QALY loss due to sickness as 50% of those who seek medical treatment. This assumption was tested in the sensitivity analysis.

Table 6.16 Cost-effectiveness results for vaccine arriving as expected

a) RR 0.75

Intervention	Costs*	QALYs Lost	ICER	Results
No vaccination strategy	$83,622	468,967		
Population	$15,809	75,438	-	Dominates
Lab-confirmed	$9,406	39,937	-	Dominates

b) RR 0.01

Intervention	Costs*	QALYs Lost	ICER	Result	Jackknife	
					Lower bound	Upper bound
No vaccination strategy	$3,318	106,140	-	-	-	-
Population	$5,253	76,912	$66,189	Cost-effective	$64,708	$67,663
Lab-confirmed	$5,061	71,386	$50,142	Cost-effective	$48,807	$51,471

c) RR 0.001

Intervention	Costs*	QALYs Lost	ICER*	Result
No vaccination strategy	$361	104,414	-	-
Population	$3,305	104,794	-	Dominated
Lab-confirmed	$3,296	104,721	-	Dominated

Notes for all tables:
**Figures in millions of MXN*
Comparison was made against the no vaccine strategy
Jackknife only present if one of the interventions was not dominated
Cost-effective at a $110,000 or $330,000 threshold
- Not applicable

The probability of a vaccine having a cost-per-QALY below $110,000 was 100% for the 0.75 and 0.01 RR scenarios. The probability of a vaccine having a cost per QALY below $330,000 when the RR was 0.001 was 0%.

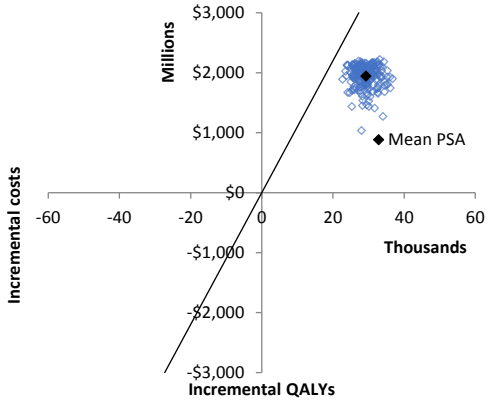
Figure 6.2 and Figure 6.3, show the scatter plot, CEAC and CEAF of the no vaccine vs. the vaccine strategy for the 0.01 RR scenario.[66] The Figures show that the scenario in which the vaccine intervention has a higher NMB is when the vaccine was targeted based on the proportion of lab-confirmed cases.

[66] The scatter plot for the 0.75 and 0.001 can be found in Appendix V. The CEAC and CEAF are not shown as in both RR scenarios the CEAC and CEAF the vaccine and no-vaccine intervention for the 0.75 and 0.001 respectively, have a probability of being CE of 1 for all threshold values analysed ($0-$500,000)

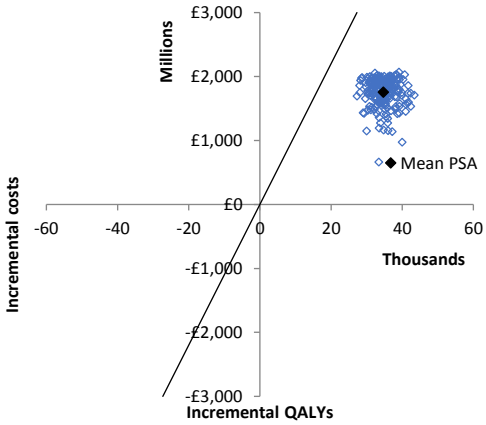
Figure 6.2 Scatter plot and CEAC: No vaccine vs. vaccine interventions for a reporting rate of 0.01

Scatter plot

a) Population strategy



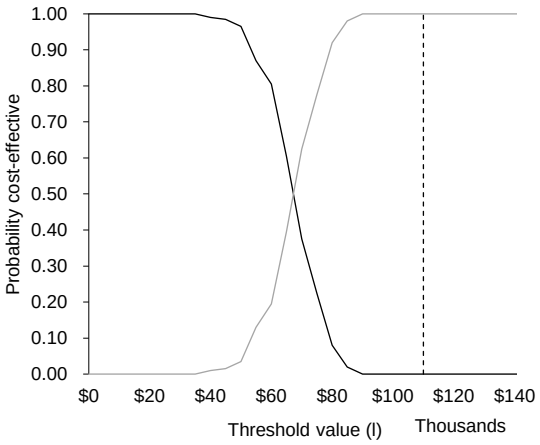
b) Lab-confirmed strategy



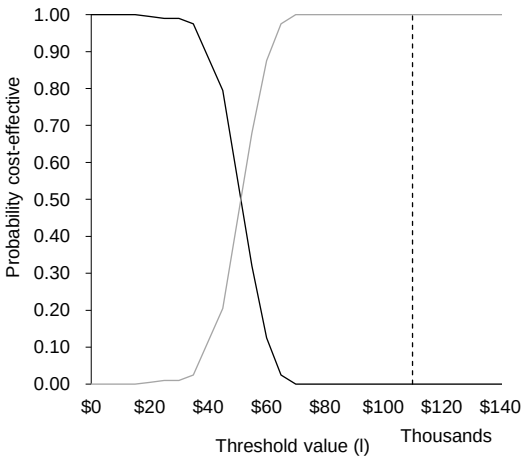
The black straight line represents the $110,000 threshold. Iterations to the right of the threshold line represents those where the vaccine intervention is cost-effective

Cost-effectiveness plane

c) Population strategy

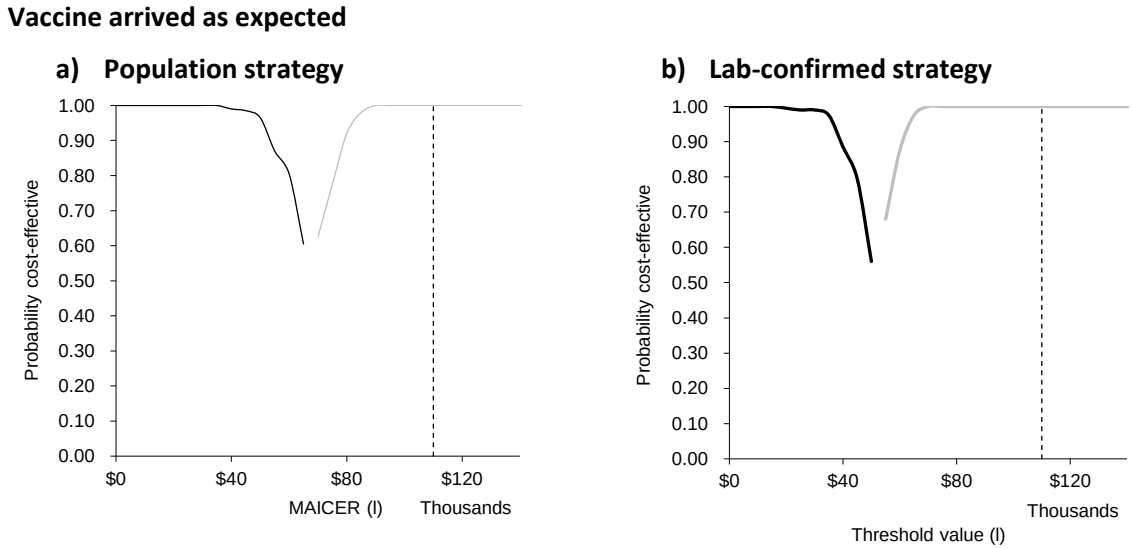


d) Lab-confirmed strategy



Black line: No vaccine strategy; Grey line: Vaccine strategy; Dashes line: $110,000 threshold

Figure 6.3 Cost-effectiveness frontier: No vaccine vs. vaccine interventions for a reporting rate of 0.01



Black line: No vaccine strategy; Grey line: Vaccine strategy; Dashes line: $110,000 threshold;

6.4.2 Sensitivity analysis

6.4.2.1 Secondary analysis

The analysis has the same assumptions described in Table 6.11 (and uses the same parameters values and distributions described in Table 6.12), except for when the vaccine arrived which was assumed to arrive 31 days later. Table 6.17 shows the estimated infections, ILI who sought medical attention, hospitalisations, ICU and deaths for the three RR. As expected, a late arrival of the vaccine prevents fewer cases (Appendix V contains a graph comparing the spread of the disease of the secondary versus the primary analysis).

Despite these results, the broad conclusions regarding the CE of the vaccine interventions did not change for RR of 0.75 and 0.001 (when the RR was assumed to be 0.75 the vaccine interventions dominate; with an RR of 0.001 the no vaccine intervention dominates). An impact was observed, however when the RR was assumed to be 0.01 as the ICER for both vaccination strategies lay between $110,000 and $330,000 instead of below the $110,000 threshold. In this scenario, the probability of a vaccine having CE below $110,000 was 0%, while when a $330,000 threshold was assumed the probability was 100%. The scatter plots, CEACs can be found in Appendix V.

Table 6.17 Estimated infections, ILI who sought medical attention, hospitalisations, ICU and deaths due to the vaccination campaign arriving one month later than expected for the three RR assumed

Reporting rate For the 0-15 age group	Vaccine Strategy		
	No-vaccine	**Population**	**Lab-confirmed**
0.75			
Total infections*	19,912,953	6,515,808	4,556,767
ILI	19,912,953	6,515,808	4,556,767
Hospitalisations	1,143,784	372,758	263,826
ICU	74,046	24,127	17,076
Deaths	21,771	7,017	5,078
0.01			
Total infections	19,856,040	17,039,452	16,543,352
ILI	878,147	753,987	730,422
Hospitalisations	42,668	36,652	35,497
ICU	2,762	2,373	2,298
Deaths	769	659	641
0.001			
Total infections	22,433,898	21,845,151	21,829,368
ILI	95,413	92,870	92,799
Hospitalisations	4,661	4,537	4,534
ICU	302	294	294
Deaths	83	80	80

Table 6.18 Cost-effectiveness results for vaccine arrival late

a) RR 0.75

Intervention	Costs*	QALYs Lost	ICER	Results
No vaccination strategy	$83,622	468,967		
Population size	$30,173	155,885	-	Dominates
Lab-confirmed	$22,149	111,728	-	Dominates

b) RR 0.01

Intervention	Costs*	QALYs Lost	ICER	Result	Jackknife	
					Lower bound	Upper bound
No vaccination strategy	$3,318	106,140	-	-	-	-
Population size	$5,804	94,582	$215,081	Cost-effective~	$210,930	$219,196
Lab-confirmed	$5,706	91,946	$168,269	Cost-effective~	$165,108	$171,404

c) RR 0.001

Intervention	Costs*	QALYs Lost	ICER	Result
No vaccination strategy	$361	104,414	-	-
Population size	$3,307	105,142	-	Dominated
Proportion of Infected	$3,297	105,069	-	Dominated

Notes for all tables:
**Figures are in millions of MXN*
Comparison was made against the no vaccine strategy
Jackknife only present if the vaccine intervention was not dominated
~ Cost-effective at $110,000 or $330,000
- Not applicable

6.4.2.2 One way and scenario analysis

Table 6.13 described the sensitivity and scenario analyses performed. The analyses show that the CE results are robust to changes in most the parameters of interest. None of the sensitivity analysis performed on the 0.75 RR showed any relevant change in the conclusion: vaccine intervention dominates no vaccine.

When the RR was assumed to be 0.01 however, vaccination was CE in all but two scenarios. These were when no QALYs lost were assumed for asymptomatic or mild cases (patient who did not seek medical treatment) and the “pessimistic scenario” where the following parameters were changed: vaccine effectiveness was set at 30%; the vaccination campaign lasted 145 days; 12% wastage and arrived later than expected (Table 6.19).

For analyses assuming an RR of 0.001, the vaccines were not CE in all but one scenario analyses. This was when a generation times of 2.71 days was assumed (Table 6.20)

Table 6.19 Sensitivity analysis tested scenarios

Sensitivity analysis scenario	Vaccine strategy tested			Base case results		Sensitivity analysis result		Comment
	RR	Vaccine arrival	Vaccine strategy	ICER	Pr. of CE $110,000/$330,000	ICER	Pr. of CE $110,000/$330,000	
No adverse events	**0.01**	**late**	**Population**	$215,081	0.00/1.00	$162,827	0.00/1.00	Lower ICER, no change in the decision
			Lab-confirmed	$168,269	0.00/1.00	$133,428	0.04/1.00	
	0.001	**Expected**	**Lab-confirmed**	Dominated	0.00/0.00	$902,666	0.00/0.00	Lower ICER but no change in the decision
No prior immunity	**0.001**	**Expected**	**Lab-confirmed**	Dominated	0.00/0.00	$3.1 mill	0.00/0.00	Lower ICER but not change in the decision
5% Vaccine wastage	**0.01**	**Late**	**Population**	$215,081	0.00/1.00	$202,078	0.00/1.00	Lower ICER, no change in the decision
			Lab-confirmed	$168,269	0.00/1.00	$158,314	0.01/1.00	
	0.001	**Expected**	**Lab-confirmed**	Dominated	0.00/0.00	Dominated	0.00/0.00	The vaccines remained dominated
70% Vaccine effectiveness	**0.01**	**late**	**Population**	$215,081	0.00/1.00	$160,040	0.01/1.00	Lower ICER, no change in the decision
			Lab-confirmed	$168,269	0.00/1.00	$129,266	0.12/1.00	
	0.001	**Expected**	**Lab-confirmed**	Dominated	0.00/0.00	Dominated	0.00/0.00	The vaccines remained dominated
30% Vaccine effectiveness	**0.01**	**Expected**	**Population**	$66,189	1.00/1.00	$112,966	0.40/1.00	Higher ICER but no change in the decision
			Lab-confirmed	$50,142	1.00/1.00	$82,517	1.00/1.00	
145 days' vaccination campaign duration	**0.01**	**Expected**	**Population**	$66,189	1.00/1.00	$106,891	0.57/1.00	Higher ICER but no change in the decision
			Lab-confirmed	$50,142	1.00/1.00	$73,183	1.00/1.00	
No productivity loss included	**0.01**	**Late**	**Population**	$215,081	0.00/1.00	$216,439	0.00/1.00	Higher ICER but no change in the decision
			Lab-confirmed	$168,269	0.00/1.00	$203,998	0.00/1.00	

Medical personnel cost to apply the vaccine	**0.01**	**Expected**	**Population**	$66,189	1.00/1.00	$70,456	1.00/1.00	Higher ICER but no change in the decision
			Lab-confirmed	$50,142	1.00/1.00	$53,787	1.00/1.00	
		Late	**Population**	$215,081	0.00/1.00	$225,364	0.00/1.00	Higher ICER but no change in the decision
			Lab-confirmed	$168,269	0.00/1.00	$176,712	0.00/1.00	
50% reduction in the QALY loss for asymptomatic or mild cases	**0.01**	**Expected**	**Population**	$66,189	1.00/1.00	$122,189	0.21/1.00	Higher ICER but no change in the decision
			Lab-confirmed	$50,142	1.00/1.00	$91,256	0.90/1.00	
No QALY loss for asymptomatic or mild cases	**0.01**	**Expected**	**Population**	$66,189	1.00/1.00	$793,730	0.00/0.00	**Decision changed to not cost-effective**
			Lab-confirmed	$50,142	1.00/1.00	$506,852	0.00/0.01	
10 to 1 ratio between ILI who seek medical attention and lab-confirmed cases	**0.001**	**Expected**	**Lab-confirmed**	Dominated	0.00/0.00	Dominated	0.00/0.00	No significant change observed
5.01 to 1 ration between ILI who seek medical attention and lab-confirmed	**0.75**	**Late**	**Population**	Dominates	1.00/1.00	Dominates	1.00/1.00	No significant change observed
Three times risk of hospitalisation, ICU and Death	**0.001**	**Expected**	**Lab-confirmed**	Dominated	0.00/0.00	Dominates	0.00/0.00	No significant change observed
Opportunity cost	**0.001**	**Expected**	**Lab-confirmed**	Dominated	0.00/0.00	$954,465	0.00/0.00	Lower ICER but no change in the decision
Optimistic scenario	**0.01**	**Late**	**Population**	$215,081	0.00/1.00	$120,234	0.18/1.00	Lower ICER, no change in the decision
			Lab-confirmed	$168,269	0.00/1.00	$100,391	0.77/1.00	
	0.001	**Expected**	**Lab-confirmed**	Dominated	0.00/0.00	$876,495	0.00/0.00	Lower ICER but no change in the decision
Pessimistic scenario	**0.01**	**Expected**	**Population**	$66,189	1.00/1.00	$190,949	0.00/1.00	Higher ICER but no change in the decision
			Lab-confirmed	$50,142	1.00/1.00	$136,025	0.05/1.00	
		Late	**Population**	$215,081	0.00/1.00	$697,973	0.00/0.00	**Decision changed to not cost-effective**
			Lab-confirmed	$168,269	0.00/1.00	$467,098	0.00/0.01	

Table 6.20. Sensitivity analysis: alternative generation intervals

Sensitivity analysis scenario	Vaccine strategy tested			Base case results		Sensitivity analysis result		Comment
	RR	Vaccine arrival	Vaccine strategy	ICER	Pr. of CE $110,000/$330,000	ICER	Pr. of CE $110,000/$330,000	
1.3 generation time	0.75	Expected	Population	Dominates	1.00/1.00	Dominates	1.00/1.00	No significant change observed
			Lab-confirmed	Dominates	1.00/1.00	Dominates	1.00/1.00	
		Late	Population	Dominates	1.00/1.00	Dominates	1.00/1.00	No significant change observed
			Lab-confirmed	Dominates	1.00/1.00	Dominates	1.00/1.00	
	0.01	Expected	Population	$66,189	1.00/1.00	$92,743	0.92/1.00	Higher ICER but no change in the decision
			Lab-confirmed	$50,142	1.00/1.00	$75,344	1.00/1.00	
		Late	Population	$215,081	0.00/1.00	$293,963	0.00/0.74	Higher ICER but no change in the decision
			Lab-confirmed	$168,269	0.00/1.00	$234,600	0.00/0.99	
	0.001	Expected	Population	Dominated	0.00/0.00	Dominated	0.00/0.00	No significant change observed
			Lab-confirmed	Dominated	0.00/0.00	Dominated	0.00/0.00	
		Late	Population	Dominated	0.00/0.00	Dominated	0.00/0.00	No significant change observed
			Lab-confirmed	Dominated	0.00/0.00	Dominated	0.00/0.00	
2.71 generation time	0.75	Expected	Population	Dominates	1.00/1.00	Dominates	1.00/1.00	No significant change observed
			Lab-confirmed	Dominates	1.00/1.00	Dominates	1.00/1.00	
		Late	Population	Dominates	1.00/1.00	Dominates	1.00/1.00	No significant change observed
			Lab-confirmed	Dominates	1.00/1.00	Dominates	1.00/1.00	
	0.01	Expected	Population	$66,189	1.00/1.00	$47,760	1.00/1.00	Lower ICER, no change in the decision
			Lab-confirmed	$50,142	1.00/1.00	$33,656	1.00/1.00	
		Late	Population	$215,081	0.00/1.00	$152,282	0.01/1.00	Lower ICER, no change in the decision
			Lab-confirmed	$168,269	0.00/1.00	$118,297	0.30/1.00	
	0.001	Expected	Population	Dominated	0.00/0.00	$203,857	0.00/0.99	**Decision change to cost-effective.**
			Lab-confirmed	Dominated	0.00/0.00	$193,895	0.00/0.99	
		Late	Population	Dominated	0.00/0.00	$250,753	0.00/0.93	**Decision change to cost-effective.**
			Lab-confirmed	Dominated	0.00/0.00	£235,667	0.00/0.98	

6.5 Summary

This Chapter detailed the CE analysis of the A(H1N1) vaccine in Mexico. The analysis was based on the moment the decision to purchase the vaccine was made, using the ODE model detailed in Chapter 4, which was calibrated to the lab-confirmed data. Analysing the CE of the vaccine at the time the MMH decided to make the purchase has relevance as it provides an estimation of whether this was a good use of money given the information available. However, the analysis was complicated given that the number of susceptibles in the population at the time the decision was made was unknown. This uncertainty had implications regarding calibration and in estimating the CE of the vaccine. Three RR scenarios were assumed for the 0-15 year of age group (Chapter 4). A high RR of 0.75 (one reported case per 1.33 cases); a medium to low RR of 0.01 (one reported per 100 cases) and a low RR of 0.001 (one reported per 1,000 cases). The performed analysis explores the CE of the vaccine in these three RR scenarios.

The CE model assumes the perspective of the MMH and aims to compare different strategies where the vaccine was available against non-purchase of the vaccine. The population was divided into four age groups 0-15; 16-29; 30 to 59 and 60 years and over. The main outcomes were the total number of predicted cases, asymptomatic or mild infections, patients with ILI seeking medical attention, hospitalisations, ICU treatment and deaths. Additionally, vaccine adverse events and productivity losses were considered. These outputs are used to estimate the QALYs and costs of each strategy.

Most of the information used to populate the models comes from the MMH, the INEGI or National Institute of Statistics and Geography or other published articles related to the 2009 A(H1N1) pandemic in Mexico that were available to the MMH at the time the decision was made.

Treatment guidelines and official documents on the resources required for the treatment of the patients with the 2009 A(H1N1) pandemic and their family members were used to estimate the resources necessary for their treatment. The QALYs losses were based on the results of a literature search. The cost of the vaccination, including delivery costs, cold chain and transportation were also included along with those related to potential adverse events of the vaccination.

The CE was determined via PSA. The parameter sets used were those obtained from the MCMC process described in Chapter 4. A total of 200 parameter sets were used providing 200 different outputs regarding number infections (and when combined with

the RRs the number of lab-confirmed cases). These numbers were used to estimate the number of deaths, hospitalisations, ICU, adverse events and productivity losses. Input values for parameters related to costs, QALYs and the proportion of hospitalisations, ICU, adverse events were sampled from distributions to allow a probabilistic estimate of incremental costs and QALYs. Those draws were sampled from appropriate distributions. This process allowed the estimation of ICERs, CEACs and CEAFs.

Two different vaccination strategies were tested: Strategy 1: vaccination of the entire population based on the proportion of individuals in each age group (population strategy) and strategy 2: vaccination of the general population with vaccination based on the proportion of lab-confirmed individuals at decision time (lab-confirmed strategy). The primary analysis assumed that the vaccine arrived as expected, while a secondary analysis assumed the vaccine arriving 31 days later. The base case scenario was based on the information available or the assumptions made by the MMH at the moment the decision to purchase was made. This assumed a 12% wastage, a vaccine effectiveness of 50%, a 90 days' vaccination campaign duration, adverse events of the vaccine and expected productivity losses.

The result of the PSA analysis estimated that the vaccine intervention dominated the no vaccine alternative when the RR was assumed at 0.75. When the RR was assumed at 0.001 however, the vaccine was dominated. When the RR was assumed at 0.01, the vaccine was cost-effective at the lower threshold £110,000 MXN.

The results were robust with the decision unchanging for the 0.75. The results for the 0.001 scenario mostly remain unchanged as the vaccine only became CE when a 2.71 mean generational interval was assumed. Otherwise, the vaccines strategies were dominated or not CE.

When the RR was assumed to be 0.01 however, vaccination was CE in all but two scenarios. These were when no QALYs lost were assumed for asymptomatic or mild cases (patient who did not seek medical treatment) and the "pessimistic scenario" where the following parameters were changed: vaccine effectiveness was set at 30%; the vaccination campaign lasted 145 days; 12% wastage and arrived later than expected.

For analyses assuming an RR of 0.001, the vaccines were not CE in all but one scenario analyses. This was when a generation times of 2.71 days was assumed.

The results suggest that the main factor in determining the CE of the vaccine intervention is the assumed RR. The higher the RR, the more CE the vaccine strategy.

The results show that assuming an RR of 0.01 (or higher) showed that the vaccine was CE. The MMH expectation was that for everyone identified case there would be ten asymptomatic. If assuming this to be an RR (0.09), the vaccine would have been CE. To determine the “threshold“ RR at which the vaccine intervention would switch between being cost-effective and not cost-effective a series of different RR would have been required. Given the time requirements of the MCMC routine, this was not carried out.

Chapter 7. Summary, contribution, discussion, and areas of future research

7.1 Overview of the Chapter

This Chapter provides a summary of the thesis including the main contributions to the knowledge base, discussion, limitations and areas of future research. Section 7.2 provides an overview of the thesis; Section 7.3 summarises the key findings whilst Section 7.4 compares these findings with other published work. Section 7.5 considers the limitations of the work. Section 7.6 provides a reflection on the use of DES in the context of this thesis. Section 7.7 details the main contribution of the thesis to the knowledge base, and Section 7.8 highlights areas of future research.

7.2 Overview of the Thesis

During 2009 Mexico experienced the A(H1N1) pandemic. Mexico was one of the earliest countries to be affected by this virus and displayed a marked increase (162%) in the number ILI and ARI between April and May compared with the same period in the previous year. Given these figures, the MMH feared an outbreak of 2 million cases that would result in one million deaths within a three month period (El Universal Online, 2010).

Initially, the MMH implemented actions in an attempt to contain the outbreak. These included school closures and a cessation of non-essential activates (24th of April-5th May 2009). At the end of these strategies, another wave arose (between May and August 2009). By the end of May 2009, the number of lab-confirmed cases reported by the MMH reached almost 7,000 with 97 deaths.

The MMH anticipated a bigger third wave would occur due to the beginning of the 2009-2010 school term and the Autumn and Winter months. Estimations made by the MMH suggested that the number of deaths could range between 9,000 to 49,000, while outpatient care and hospitalisations could range between 3 to 14 million and 50,000 and 250,000 respectively (Córdova-Villalobos et al., 2010).

Based on these estimations the MMH began negotiations to acquire vaccines under development by international pharmaceutical companies. The decision to purchase was announced on the 18th July 2009 (towards the end of the second wave). The MMH bought 30 million doses of the A(H1N1) vaccine from Sanofi-Pasteur (67%) and GSK (33%) for a value of 2,850 million Mexican pesos (MXN) (approximately 130 million GBP) (El Universal Online, 2009a).

A technical consultation group (TCG) was constituted in August 2009 to manage the vaccination program effectively. Based on the characteristics of the disease observed to that date the group concluded that the vaccination strategy should have as objectives reducing both the probabilities of fatalities and transmission of the disease. According to MMH calculations, the first batch of vaccines was due to arrive at the end of October 2009 when a third wave of the vaccine was expected.[67]

The value for money of the vaccines purchased was uncertain as little information about the effectiveness or availability of the vaccines was known at the time of the

[67] The vaccine arrived towards the end of November 2009 (Expansion, 2009)

decision, and additionally, the size of the future pandemic was unknown. The work undertaken in this thesis estimated the CE of a population-based vaccine strategy of the 2009 A(H1N1) pandemic in Mexico using the information available at the time the decision to purchase the vaccine was made.

To obtain accurate results, this required the model to be dynamic. An ODE model following a SEIR approach was used. Additionally, a model using a DES approach was constructed to assess whether such an approach was appropriate.

Six milestones were set within the thesis. The first, following a literature review, aimed to document the different models, and relative frequency used to estimate the CE of an infectious disease vaccine intervention.

The second and third milestone were to construct the ODE and the DES models. The ODE model was built in R, while the DES model built in Simul8©.

The fourth milestone was the calibration of these models so that the number of lab-confirmed cases in Mexico could be approximately replicated. The calibration of the ODE model used an MCMC chain using an Automated Factor Slice Sampling method as described in Tibbits et al. (2014), while the DES used the Metropolis-Hastings algorithm. The calibration used lab-confirmed data up to the moment the decision to purchase the vaccine was made (18th July 2009). Given the poor results and the difficulties found calibrating the DES model, this was deemed as a not appropriate approach to estimate the CE of the A(H1N1) vaccine intervention was not explored further.

The data available on lab-confirmed cases could significantly underestimate the actual number of infections if patients were asymptomatic or did not seek medical attention, and thus at the time of the decision to purchase the vaccines, it was not possible to robustly estimate the number of susceptible individuals in the population. To consider this, the model made assumptions regarding the RR. Three RR scenarios were considered using different reporting rates for the 0-15-year-old age group: 0.001 (one lab-confirmed case per 1,000 infected), 0.01 (one lab-confirmed case per 100 infected) and 0.75 (one lab-confirmed case per 1.33 infected).

The fifth milestone was to determine the CE of population-based vaccination strategies for A(H1N1) during the 2009 pandemic in Mexico. Three strategies were tested: Strategy 1: vaccination based on the entire population based on proportion of individuals in each age group (population strategy); Strategy 2: vaccination of the general population with vaccination based on the proportion of lab-confirmed individuals at the moment the decision to purchase was announced (lab-confirmed

strategy); and Strategy 3 no vaccination. The analysis was performed using the perspective of the MMH and included productivity losses due to sickness. Vaccine wastage and adverse events due to vaccination were included in the base case.

Lastly, the sixth milestone was to comment on the use of the DES methodology to predict the 2009 A(H1N1) pandemic in Mexico.

7.3 Summary of key findings

The results from this thesis have produced the following key outcomes listed in order of perceived importance.

1. In the base case, the analysed vaccine strategies were CE when an RR of 0.75 and RR of 0.01 was assumed. When a low RR (0.001) was assumed the no vaccine intervention dominated the vaccine strategies
2. These results were robust to most of the sensitivity analyses performed. The exceptions were:
    I. For the 0.001 RR scenario when a mean generational time of 2.71 was assumed where the vaccine strategies became CE
    II. For the 0.01 RR scenario when a pessimistic scenario (vaccine effectiveness of 30%, 145 days' vaccination campaign duration, 12% vaccine wastage and adverse events considered) where the vaccine strategies became not CE and
    III. For the 0.01 RR scenario where no QALY loss for asymptomatic or mild infection was assumed, the vaccine strategies became not CE.
3. The use DES methodology was deemed not to be suitable for simulating a pandemic. It was concluded that an ODE had clear advantages compared with a DES approach in such a setting.
4. Most articles produced to estimate the CE of a vaccine intervention of an infectious disease are predominantly based on a static approach. The use of dynamic models has increased over the years, but the static approach remains the preferred method for researchers. It was shown that the date of publication had a statistically significant influence on the probability of using a dynamic methodology. Latin America countries (clustered as medium GDP per capita) do not compare unfavourably with high GDP per-capita regions in the used of dynamic models.

7.4 Comparison of the cost-effectiveness methods and results with other published studies.

Eleven dynamic studies were found estimating the CE of pandemic influenza: Halder et al., (2014); Kelso et al., (2013); Lugner et al., (2012); Newall et al., (2010); Baguelin et al., (2010); Lee et al., (2010); Sander et al., (2010, 2009); Khazeni et al., (2009[a]); Lee et al., (2009); Khazeni et al., (2009b). Of these only three were related to the 2009 A(H1N1) pandemic Baguelin et al., (2010); Sander et al., (2010); Khazeni et al., (2009b).

As in the analysis done in this thesis, in Baguelin et al., (2010) at the time the analysis was made it was not possible to determine the actual number of susceptible individuals still available in the population. To account for this, Baguelin et al., (2010) tested three different rescaling factors to predict the Autumn wave. This is comparable to the approach taken in the thesis of using three RRs

In both models, the RR assumed had an impact on the predicted pandemic, with higher reporting values resulting in most of the predicted cases being concentrated in the third wave, while with lower reporting values (0.001) more of the cases occurred during the first two waves of the pandemic. This thesis found that the main factor in determining the CE of the vaccine interventions was the assumed RR, as the higher the RR and associated higher numbers of infections, the more CE the vaccine intervention is. The conclusion that the size of the epidemic was the biggest driver of CE was also stated in Baguelin et al., (2010)

In contrast with Baguelin et al., (2010) this work did not explore a vaccination strategy targeting high-risk individuals, although the results found in the thesis suggest that when high and middle RR (0.75 and 0.01) are assumed, the vaccine is CE even in a population-based strategy.[68,69]

Some studies such as Lugner et al., (2012), Sander et al., (2009), Newall et al., (2010), Baguelin et al., (2010), Sander et al., (2010) and Khazeni et al. (2009) found that the CE of vaccination is heavily dependent on the timing. Newall et al., (2010) suggested that a vaccination strategy before the start of the pandemic combined with antiviral

[68] Baguelin et al., (2010) found that the most CE strategy was vaccinating the high-risk group population while extending the vaccine to the 5-14 years' group being the more likely extension to be CE
[69] A sensitive analysis increasing the risk of the consequences of those infected was also included. The results did not change the overall conclusions in any of the RR scenarios explored.

treatment would be a CE strategy. Baguelin et al., (2010) found that delays in the program by a few weeks causes most of the benefits of the vaccination to be lost. Sander et al., (2010) concluded that a mass vaccination campaign two weeks before the peak of the pandemic would be highly CE. However, it was sensitive to the timing of the immunisation program. Khazeni et al. (2009) analysed the 2009 A(H1N1) pandemic and reported that vaccination in October was more cost-effective than in November. The results produced in this thesis showed that whilst the CE of the vaccines became worse as the initiation time was assumed to arrive 31 days later than expected, the overall CE recommendations remained unaltered.

In contrast with Baguelin et al., (2010), the costs of the vaccines were considered as part of the analysis (not sunk) as the MMH have not yet spent the money to purchase the vaccine. Although the high cost of the vaccine (over $2.8 million MXN), the vaccine interventions was CE for two of the three RR scenarios considered.

The results found in this work are in line with the early findings obtained by the TCG CE analysis which concluded that the vaccine intervention was only CE if the total numbers of infections and deaths were 15 times greater than the lab-confirmed cases and deaths reported at the date of the analysis (August 2009; approximately 20,000 infections).[70] Based on the results from the ODE model, it is seen that in all scenarios there were more than 300,000 infections and thus the TCG would have estimated the vaccination programme to be CE. However, it was estimated in the thesis that the vaccines were not cost-effective when the RR was low (0.001).

Three mean generation time were used to estimate the spread of the disease; base case 1.9; 1.3 and 2.71. Based on the range of average estimated cases (20.7 million to 26.9 million total infections), the proportion of the population infected was expected to be between 15 and 25% of the population. This proportions are similar to those estimated in other countries or regions: 21% in Pittsburg, 13% in Singapore, 26.7% in New Zealand, 13.8% in Beijing and 20-30% in Ontario (DENG et al., 2011; Zimmer et al., 2010; Achonu et al., 2011; ESR, 2010; Chen et al., 2010). Elizondo-Montemayor et al. (2012) estimated a higher number for a Mexican population (between 37 and 41%) however this study was based on a specific locality that accounts for only 2.5% of the entire Mexican population. Furthermore, selection bias might have been present, as

[70] Details on this analysis described were scarce - no published or unpublished information about this analysis was found. Uncertainty existed regarding the type of model developed; the method used, and the total numbers vaccinated in each group or in the universal vaccination scenario. It is likely, however, that this analysis came after the decision to purchase the vaccine was made as the TCG was formed after the announcement.

participants might have volunteered to participate given that they have experienced A(H1N1).

The estimates presented here also include productivity losses due to sick days for those patients who required medical attention in contrast with Khazeni et al., (2009b) whose analysis did not include these estimates. However, the impact of productivity losses was modest as the sensitivity analysis only show a slight increase in the ICER when these were not included.

7.5 Limitations of the analyses undertaken

The model constructed in the thesis has several limitations. The model only considered four age groups. It made no distinction between high-risk groups such as individuals with obesity, overweight, asthma, diabetes, pregnant women, with chronic obstructive pulmonary disease, chronic renal failure, diabetes, or cardiovascular conditions which could face a higher risk of complications due to an A(H1N1) infection. A sensitivity analysis increasing the risks of the consequences for those infected was performed with the aim of exploring the impact of infections in high-risk patients.[71] This analysis was only carried out in the 0.001 RR scenario as this was the only scenario in which the vaccine was not CE. The results showed that the vaccine intervention was no longer dominated although the estimated ICER remained above the upper assumed threshold ($330,000).

Disruption of health services due to the increase in the number of patients seeking medical attention was not explicitly modelled. However, a sensitivity analysis was performed where it was assumed that the additional hospitalisations generated within the no vaccination strategy were associated with the loss of life of a patient who could not be admitted to hospital. This extreme analysis was performed for the 0.001 RR scenario with no significant change in the decision: although the vaccine intervention was no longer dominated, its ICER was above the upper threshold value.

Only two vaccine strategies were tested: population and lab-confirmed. However, it is believed that potentially more efficient vaccination strategies would not alter the conclusion regarding CE. In the 0.001 RR scenario, the difference between the estimated number of cases prevented between the population and lab-confirmed

[71] This scenario assumes three times more risk of hospitalisations, ICU care and deaths compared to the base case assumptions

interventions was 15,800 cases compared with over a million when the 0.01 RR scenario was assumed. This relatively small difference was due to the number of a low number of susceptible available in the population in the 0.001 RR strategy, suggesting that alternative vaccination strategies would not have a significantly large impact to make the vaccines CE.

Medical personnel costs to apply the vaccines were included as a sensitivity analysis, as there was no information on whether these costs were considered sunk by the MMH. This sensitivity analysis assumed that an extra 10,000 temporary medical assistants were hired for the duration of the campaign (90 days) and were paid the average daily wage in Mexico ($126.20 MXN). The analysis was performed for the 0.01 RR for the population and lab-confirmed strategies when the vaccine arrived as expected and 31 days later, with no impact on the CE decision.

The study was based on the whole population of Mexico without differentiation by state or region, and thus pockets of infection were not modelled. No reduction in infectivity and the likelihood or transmitting disease was considered for those with mild or asymptomatic infection.

The QALY loss values used are not specific to the Mexican population as no utility data specific for the country exists.

It has been assumed that the data on confirmed cases are accurate. This assumption may be incorrect if people were more likely to report to clinics on weekdays rather than weekends or if there were errors introduced when the data were reported or compiled.

Whilst these limitations exist this is also true for other models, and it is not believed that these would strongly effect the conclusions within the thesis.

7.6 Use of the DES technique

The DES model was deemed unsuitable to simulate the A(H1N1) pandemic in Mexico. As shown in Chapter 5, the calibration of the model was not successful as the diagnostic trace plots showed that the chain was not properly exploring the parameter space after 20,000 iterations. A key reason for this is the use of a fixed number stream in each run of the DES model, which hinders movement away from a parameter set that fits the data well. If the DES model had been deemed to be an appropriate method, the output would need to have used multiple random number streams to

obtain a distribution of parameter sets that fit the data. Given the computational time requirements, (particularly if low RRs were used) the DES approach was not pursued further.

Since the ODE model had a much lower running time and could be successfully calibrated using an MCMC approach, this thesis concluded that the DES approach was not suitable for modelling a pandemic.

7.7 Contribution of the thesis to the knowledge base

The thesis classified published CE models within infectious disease settings by type (static and dynamic) and by type of method use. Analyses were undertaken to see if it were possible to predict factors that were associated with the use of a dynamic model. Year of publication was the only significant independent variable identified.

The thesis compared two different types of modelling approaches: ODE and DES. The conclusion was that the DES approach was unsuitable and provided no benefits compared with the ODE method which had multiple advantages over the DES method.

The results suggest that the MMH decision to purchase the vaccine was understandable as in only one of the three RR scenarios (0.001) the vaccine was not CE and the MMH estimate of RR was 0.09. In this scenario, the vaccines were estimated to be cost-effective if the generation time was at the 95% confidence interval of that anticipated. Whilst the decision ultimately was not shown to be cost-effective in hindsight, given the rapid depletion of the susceptible population and the delay in the vaccines arriving, the decision made given only the information available at that time point appears correct.

7.8 Areas of future research

In the thesis, the CE of the vaccines purchased by the Mexican Government using the information known at the time of purchase was estimated. There is little additional work on this that can be conducted given that the answer is known using hindsight, although it has been shown that the decision taken was understandable.

Whilst using an ODE model and calibrating this with an MCMC is not novel it has been shown that the CE of potential vaccination strategies could be calculated relatively quickly once probabilistic parameter sets have been generated. Future research could

involve simulation studies to ascertain whether pre-vaccination strategies or vaccinating certain age groups would be the optimal use of vaccines.

A key uncertainty in the work was the RR which determined the size of the pandemic regarding cases requiring medical attention and in the number of deaths and hospitalisations. Research analysing previous epidemics to see if any commonalities can be determined regarding the numbers of infections that are reported to medical attention, and latent and infectious periods would aid future researchers.

Analyses of the CE of other vaccine purchases within a pandemic setting would be of interest to establish whether the fear associated with the possibility of a very large number of cases has resulted in decisions to purchase vaccines that were not expected to be CE given the estimates of mean costs and QALY.

References

Aballea, S., Chancellor, J., Martin, M., et al. **(2007a)** The cost-effectiveness of influenza vaccination for people aged 50 to 64 years: An international model**. Value in Health, (of Publication: Mar 2007): 10 (2) (pp 98-116), 2007**

Aballea, S., De Juanes, J.R., Barbieri, M., et al. **(2007b)** The cost effectiveness of influenza vaccination for adults aged 50 to 64 years: A model-based analysis for Spain**. Vaccine, 25: 6900–6910**

Achonu, C., Rosella, L., Gubbay, J., et al. **(2011)** Seroprevalence of Pandemic Influenza H1N1 in Ontario from January 2009–May 2010 **Cowling, B.J. (ed.). PLoS ONE, 6 (11): e26427**

Aguilar, I.B.M., Mendoza, L.O., Garcia, O., et al. **(2015)** Cost-effectiveness analysis of the introduction of the human papillomavirus vaccine in Honduras. **Vaccine, 33 Suppl 1: A167-73**

Akumu, A.O., English, M., Scott, J.A.G., et al. **(2007)** Economic evaluation of delivering Haemophilus influenzae type b vaccine in routine immunization services in Kenya**. Bulletin of the World Health Organization, 85 (7): 511–518**

Baguelin, M., Van Hoek, A., Jit, M., et al. **(2010)** Vaccination against pandemic influenza A/H1N1v in England: A real-time economic evaluation**. Vaccine, 28 (12): 2370–2384**

Baltussen, R., Ament, A., Leidl, R.M., et al. **(1997)** Cost-effectiveness of vaccination against pneumococcal pneumonia in the Netherlands**. European Journal of Public Health, 7 (2): 153–161**

Banz, K., Iseli, A., Aebi, C., et al. **(2009)** Economic evaluation of varicella vaccination in Swiss children and adolescents**. Human Vaccines, 5 (12): 847–857**

Banz, K., Neiss, A., Goertz, A., et al. **(2002)** Routine varicella vaccination of children is effective and cost-beneficial in Germany. **Eur J Health Econom, Suppl 1: S64**

Banz, K., Wagenpfeil, S., Neiss, A., et al. **(2003)** The cost-effectiveness of routine childhood varicella vaccination in Germany**. Vaccine, 21 (11–12): 1256–1267**

Bauch, C.T., Anonychuk, A.M., Pham, B.Z., et al. **(2007)** Cost-utility of universal hepatitis A vaccination in Canada**. Vaccine, 25 (51): 8536–8548**

Beutels, P., Bonanni, P., Tormans, G., et al. **(1999)** An economic evaluation of universal pertussis vaccination in Italy**. Vaccine, 17 (19): 2400–2409**

Beutels, P., Clara, R., Tormans, G., et al. **(1996)** Costs and benefits of routine varicella

vaccination in German children**. Journal of Infectious Diseases, 174 Suppl: S335-41**

BIE **(2012) Tasa de ocupación, desocupación y subocupación (resultados mensuales ENOE) [online]. Available from: http://www.inegi.org.mx/sistemas/bie/ [Accessed 19 May 2013]**

BIRMEX **(2009) MEMORIA DE GESTIÓN VACUNA PANDÉMICA AH1N1. Mexico City**

Bonanni, P., Boccalini, S., Bechini, A., et al. **(2008)** Economic evaluation of varicella vaccination in Italian children and adolescents according to different intervention strategies: the burden of uncomplicated hospitalised cases**. Vaccine, 26 (44): 5619–5626**

Brisson, M. and Edmunds, W. **(2002)** The cost-effectiveness of varicella vaccination in Canada**. Vaccine, 20 (7–8): 1113–1125**

Brisson, M. and Edmunds, W. **(2003)** Varicella vaccination in England and Wales: cost-utility analysis**. Archives of Disease in Childhood, 88 (10): 862–869**

Brisson, M., Laprise, J.-F., Chesson, H.W., et al. **(2016)** Health and Economic Impact of Switching from a 4-Valent to a 9-Valent HPV Vaccination Program in the United States. **Journal of the National Cancer Institute, 108 (1): no pagination**

Burger, E.A., Sy, S., Nygard, M., et al. **(2015)** Too late to vaccinate? The incremental benefits and cost-effectiveness of a delayed catch-up program using the 4-valent human papillomavirus vaccine in Norway. **The Journal of infectious diseases, 211 (2): 206–215**

Carducci, A., Avio, C.M. and Bendinelli, M. **(1989)** Cost-benefit analysis of tetanus prophylaxis by a mathematical model**. Epidemiology and Infection, 102 (3): 473–483**

Caro, J.J., Getsios, D., El-Hadi, W., et al. **(2005)** Pertussis immunization of adolescents in the United States: an economic evaluation**. Pediatric Infectious Disease Journal, 24 (5 Suppl): S75-82**

Carroll, A., McDonnell, G. and Barnes, M. **(2003)** A review of the management of Guillain-Barré syndrome in a regional neurological rehabilitation unit. **International journal of rehabilitation research. Internationale Zeitschrift für Rehabilitationsforschung. Revue internationale de recherches de réadaptation, 26 (4): 297–302**

Cauchemez, S., Ferguson, N.M., Wachtel, C., et al. **(2009)** Closure of schools during an influenza pandemic. **The Lancet infectious diseases, 9 (8): 473–81**

CDC **(2009) Recommendations for the Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009-2010 Season [online]. Available from: http://www.cdc.gov/h1n1flu/recommendations.htm [Accessed 6 June 2013]**

CENETEC **(2016) Diagnóstico y tratamiento del Síndrome de Guillain-Barré. En el Segundo y Tercer Nivel de atención.**

Centre for Reviews and Dissemination **(2011) CRD Database [online] [online]. Available from: http://www.crd.york.ac.uk/crdweb/ [Accessed 5 August 2011]**

Chao, D., Elizabeth, H. and Longini, I. **(2010)** School opening dates predict pandemic influenza A (H1N1) epidemics in the USA**. J Infect Dis, 202 (6): 877–880**

Chen, M.I.C., Lee, V.J.M., Lim, W.-Y., et al. **(2010)** 2009 Influenza A(H1N1) Seroconversion Rates and Risk Factors Among Distinct Adult Cohorts in Singapore**. JAMA, 303 (14): 1383**

Chesson, H.W., Ekwueme, D.U., Saraiya, M., et al. **(2008)** Cost-effectiveness of human papillomavirus vaccination in the United States**. Emerging Infectious Diseases, 14 (2): 244–251**

Cho, B.-H., Clark, T., Messonnier, N., et al. **(2010)** MCV vaccination in the presence of vaccine-associated Guillain-Barré Syndrome risk: a decision analysis approach. **Vaccine, 28 (3): 817–22**

Chodick, G., Ashkenazi, S., Livni, G., et al. **(2005)** Cost-effectiveness of varicella vaccination of healthcare workers**. Vaccine, 23 (43): 5064–5072**

Chowell, G., Echevarría-Zuno, S., Viboud, C., et al. **(2011)** Characterizing the epidemiology of the 2009 influenza A/H1N1 pandemic in Mexico. **PLoS medicine, 8 (5): e1000436**

Chowell, G., Viboud, C., Simonsen, L., et al. **(2012)** Impact of antiviral treatment and hospital admission delay on risk of death associated with 2009 A/H1N1 pandemic influenza in Mexico. **BMC infectious diseases, 12 (1): 97**

Claes, C., Reinert, R.R. and von der Schulenburg, J.-M.G. **(2009)** Cost effectiveness analysis of heptavalent pneumococcal conjugate vaccine in Germany considering herd immunity effects**. European Journal of Health Economics, 10 (1): 25–38**

Clark, A.D., Walker, D.G., Rocio Mosqueira, N., et al. **(2009)** Cost-effectiveness of rotavirus vaccination in Peru**. Journal of Infectious Diseases, 200 (SUPPL. 1)**

CNV **(2009) Lineamientos Técnicos para la Vacunación contra el Virus de la**

Influenza Pandémica

CONAPO **(2012) Proyecciones de la Poblacion de Mexico 2010-2050 [online]. Available from: http://www.conapo.gob.mx/es/CONAPO/Proyecciones [Accessed 5 June 2013]**

Consejo de Salubridad General and INSP **(2008) Guía para la conducción de Estudios de evaluación económica para la actualización del Cuadro Básico de Insumos del Sector Salud en México**

Cordova-Villalobos, J.A., Macias, A.E., Hernandez-Avila, M., et al. **(2017)** The 2009 pandemic in Mexico: Experience and lessons regarding national preparedness policies for seasonal and epidemic influenza**. Gac Med Mex, 153153: 102–10**

Córdova-Villalobos, J., Valdsepino-Gómez, J. and Ponce-de-León, S. **(2010) La epidemia de infleunza A/H1N1 en México. Mexico, DF: Editorial Médica Panamericana**

Costos Unitarios por Nivel de Atención Médica para el año 2009 IMSS**.**

Couch, R.B., Atmar, R.L., Franco, L.M., et al. **(2012)** Prior infections with seasonal influenza A/H1N1 virus reduced the illness severity and epidemic intensity of pandemic H1N1 influenza in healthy adults. **Clinical infectious diseases, 54 (3): 311–317**

Coudeville, L., Paree, F., Lebrun, T., et al. **(1999)** The value of varicella vaccination in healthy children: cost-benefit analysis of the situation in France**. Vaccine, 17 (2): 142–151**

Coupe, V.M.H., Bogaards, J.A., Meijer, C.J.L.M., et al. **(2012)** Impact of vaccine protection against multiple HPV types on the cost-effectiveness of cervical screening. Vaccine**. 30 (10) pp. 1813–1822**

Cummings, D. and Lessler, J. **(2014) "Mathematical Modeling: The Dynamics of Infection." In Nelson, K. and Williams, C. (eds.)** Infectious Disease Epidemiology. Theory and Practice**. Third Edit. Burlington, MA: Jones & Bartlett Learning. pp. 131–166**

DENG, Y., PANG, X.H., YANG, P., et al. **(2011)** Serological survey of 2009 H1N1 influenza in residents of Beijing, China**. Epidemiology and Infection, 139 (1): 52–58**

Diaz, M., Kim, J., Albero, G., et al. **(2008)** Health and economic impact of HPV 16 and 18 vaccination and cervical cancer screening in India**. British Journal of Cancer, 99 (2): 230–238**

Diaz, M., de Sanjose, S., Ortendahl, J., et al. **(2010)** Cost-effectiveness of human

papillomavirus vaccination and screening in Spain**. European Journal of Cancer, 46 (16): 2973–85**

Dominguez-Cherit, G., S.E., L., A.E., M., et al. **(2009)** Critically Ill patients with 2009 influenza A(H1N1) in Mexico. JAMA : the journal of the American Medical Association**. 302 (17) pp. 1880–1887**

Doroshenko, A. and Qian, W. **(2016)** Evaluation of outbreak response immunization in the control of pertussis using agent-based modeling**.** PeerJ**. 2016 (8) p. no pagination**

Drolet, M., Laprise, J.-F., Boily, M.-C., et al. **(2014)** Potential cost-effectiveness of the nonavalent human papillomavirus (HPV) vaccine. **International journal of cancer, 134 (9): 2264–2268**

Drummond, Sculpher, Torrance, et al. **(2015) Methods for Economic Evaluation of Health Care programmes. Fourth. Oxford University Press**

Eames, K., Tilston, N., Brooks-Pollock, E., et al. **(2012)** Measured dynamic social contact patterns explain the spread of H1N1v influenza. **PLoS computational biology, 8 (3): e1002425**

ECDC **(2016) Influenza case definitions [online]. Available from: http://ecdc.europa.eu/en/healthtopics/influenza/surveillance/Pages/influenza_case_definitions.aspx [Accessed 26 May 2016]**

Echevarría-Zuno, S., Mejía-Aranguré, J., Mar-Obeso, A., et al. **(2009)** Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis. **Lancet, 374 (9707): 2072–9**

Elizondo-Montemayor, L., Alvarez, M., Hernandez-Torre, M., et al. **(2011)** Seroprevalence of antibodies to influenza A/H1N1/2009 among transmission risk groups after the second wave in Mexico, by a virus-free ELISA method. **International journal of infectious diseases, 15 (11): e781-6**

Elizondo-Montemayor, L., Hernandez-Torre, M., Ugalde-Casas, P., et al. **(2012)** Clinical and epidemiological features of 2009 pandemic H1N1 influenza differ slightly according to seroprevalence status during the second wave in the general population in Mexico. **Respiratory care, 57 (10): 1586–1593**

Ellis, A., Ruttimann, R.W., Jacobs, R.J., et al. **(2007)** Cost-effectiveness of childhood hepatitis A vaccination in Argentina: a second dose is warranted**. Pan American Journal of Public Health, 21 (6): 345–356**

Embase **(2010) What is Embase? [online] [online]. Available from:**

http://embase.com/info/what-embase [Accessed 5 August 2011]

ESR **(2010) Seroprevalence of the 2009 influenza A (H1N1) pandemic in New Zealand. New Zealand**

Expansion, C. **(2009) Sanofi dara a Mexico vacuna para A/H1N1 (Octubre 2009) [online]. Available from: ww.cnnexpansion.com/actualidad/2009/10/22sanofi-producira-vacuna-para-mexico**

FDA **(2013) Influenza A (H1N1) 2009 Monovalent Vaccines Descriptions and Ingredients [online]. Available from: https://www.fda.gov/biologicsbloodvaccines/vaccines/questionsaboutvaccines/ucm186102.htm [Accessed 24 April 2017]**

Fedson, D.S., Wajda, A., Nicol, J.P., et al. **(1993)** Clinical effectiveness of influenza vaccination in Manitoba**. JAMA: Journal of the American Medical Association, 270 (16): 1956–1961**

Fiore, A.E., Shay, D.K., Broder, K., et al. **(2009)** Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. **Morbidity & Mortality Weekly Report Recommendations & Reports, 58: 1–52**

Fleming, D.M., Watson, J.M., Nicholas, S., et al. **(1995)** Study of the effectiveness of influenza vaccination in the elderly in the epidemic of 1989-90 using a general practice database. **Epidemiology and infection, 115 (3): 581–9**

Folkenberg, M., Callréus, T., Svanström, H., et al. **(2011)** Spontaneous reporting of adverse events following immunisation against pandemic influenza in Denmark November 2009-March 2010. **Vaccine, 29 (6): 1180–4**

Foster, D., Talsma, A., Furumoto-Dawson, A., et al. **(1992)** Influenza vaccine effectiveness in preventing hospitalization for pneumonia in the elderly. **American journal of epidemiology, 136 (3): 296–307**

Fraser, C., Donnelly, C., Cauchemez, S., et al. **(2009)** Pandemic potential of a strain of influenza A (H1N1): early findings. **Science, 324 (5934): 1557–61**

Garten, R., Davis, C., Russell, C., et al. **(2009)** Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. **Science, 325 (5937): 197–201**

Gerlier, L., Lamotte, M., Greneche, S., et al. **(2017)** Assessment of Public Health and Economic Impact of Intranasal Live-Attenuated Influenza Vaccination of Children in

France Using a Dynamic Transmission Model. **Applied health economics and health policy, 15 (2): 261–276**

Getsios, D., Caro, J.J., Caro, G., et al. **(2002)** Instituting a routine varicella vaccination program in Canada: an economic evaluation**. Pediatric Infectious Disease Journal, 21 (6): 542–547**

Giglio, N.D., Cane, A.D., Micone, P., et al. **(2010)** Cost-effectiveness of the CRM-based 7-valent pneumococcal conjugated vaccine (PCV7) in Argentina**. Vaccine, 28 (11): 2302–2310**

Ginsberg, G.M., Berger, S. and Shouval, D. **(1992)** Cost-benefit analysis of a nationwide inoculation programme against viral hepatitis B in an area of intermediate endemicity**. Bulletin of the World Health Organization, 70 (6): 757–767**

Glanville, J., Kaunelis, D. and Mensinkai, S. **(2009)** How well do search filters perform in identifying economic evaluations in MEDLINE and EMBASE. **International journal of technology assessment in health care, 25 (4): 522–9**

Goldhaber-Fiebert, J.D., Stout, N.K., Salomon, J.A., et al. **(2008)** Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16,18 vaccination**. Journal of the National Cancer Institute, 100 (5): 308–320**

Goldie, S., Kim, J., Kobus, K., et al. **(2007)** Cost-effectiveness of HPV 16, 18 vaccination in Brazil**. Vaccine, 25 (33): 6257–6270**

Goldie, S., Levin, C., Mosqueira-Lovon, N., et al. **(2012)** Health and economic impact of human papillomavirus 16 and 18 vaccination of preadolescent girls and cervical cancer screening of adult women in Peru**. Revista Panamericana de Salud Publica, 32 (6): 426–434**

Goldie, S., O'Shea, M., Campos, N., et al. **(2008)** Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries**. Vaccine, 26 (32): 4080–4093**

González-pier, E., Gutiérrez-delgado, C., Stevens, G., et al. **(2007)** Definición de prioridades para las intervenciones de salud en el Sistema de Protección Social en Salud de México**. Salud pública de México, 49 (supl 1): S37–S52**

Govaert, T.M., Thijs, C.T., Masurel, N., et al. **(1994)** The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. **JAMA : the journal of the American Medical Association, 272 (21): 1661–5**

Grenfell, B.T. and Anderson, R.M. **(1985)** The estimation of age-related rates of infection from case notifications and serological data. **The Journal of hygiene, 95 (2):**

419–36

Griffiths, D.A. **(1974)** A Catalytic Model of Infection for Measles**. Journal of the Royal Statistical Society, 23 (3): 330–339**

GSK **(2010) AREPANRIX™ H1N1**

Gutierrez, J. and Bertozzi, S. **(2005)** Influenza vaccination in the elderly population in Mexico: Economic considerations. [Spanish]**. Salud Publica de Mexico, (of Publication: May 2005): 47 (3) (pp 234-239), 2005**

Hak, E., Buskens, E., van Essen, G.A., et al. **(2005)** Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. **Archives of internal medicine, 165 (3): 274–80**

Halder, N., Kelso, J.K., Milne, G.J., et al. **(2014)** A model-based economic analysis of pre-pandemic influenza vaccination cost-effectiveness. **BMC infectious diseases, 14 (1): 266**

Halloran, M.E., Cochl, S.L., Lieu, T.A., et al. **(1994)** Theoretical Epidemlologic and Morbidity Effects of Routine Varicella Immunization of Preschool Children in the United States**. American journal of medical genetics., 140 (2): C1**

Hammerschmidt, T., Bisanz, H. and Wutzler, P. **(2007)** Universal mass vaccination against varicella in Germany using an MMRV combination vaccine with a two-dose schedule: an economic analysis. **Vaccine, 25 (42): 7307–7312**

Hammerschmidt, T., Goertz, A., Wagenpfeil, S., et al. **(2003)** Validation of health economic models: the example of EVITA. **Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, 6 (5): 551–9**

Hardelid, P., Fleming, D., McMenamin, J., et al. **(2011)** Effectiveness of pandemic and seasonal influenza vaccine in preventing pandemic influenza A(H1N1)2009 infection in England and Scotland 2009-2010**. Euro Surveill, 16 (2)**

Hibbert, C.L., Piedra, P.A., McLaurin, K.K., et al. **(2007)** Cost-effectiveness of live-attenuated influenza vaccine, trivalent in preventing influenza in young children attending day-care centres**. Vaccine, 25 (47): 8010–8020**

van Hoek, A., Underwood, A., Jit, M., et al. **(2011)** The Impact of Pandemic Influenza H1N1 on Health-Related Quality of Life: A Prospective Population-Based Study**. PloS one, 6 (3): e17030**

Hontelez, J.A.C., Nagelkerke, N., Barnighausen, T., et al. **(2011)** The potential impact

of RV144-like vaccines in rural South Africa: a study using the STDSIM microsimulation model. Vaccine**. 29 (36) pp. 6100–6106**

Hsu, H.C., Lin, R.S., Tung, T.H., et al. **(2003)** Cost-benefit analysis of routine childhood vaccination against chickenpox in Taiwan: Decision from different perspectives**. Vaccine, (of Publication: Aug 2003): 21 (25-26) (pp 3982-3987), 2003**

Hubben, G., J.M. Bos, Ende, A. van der, et al. **(2007)** Enhanced decision support for policy makers using a web interface to health-economic models—Illustrated with a cost-effectiveness analysis of nation-wide infant vaccination with the 7-valent pneumococcal conjugate vaccine in the Netherlands**. Vaccine, 25: 3669–3678**

Hughes, R., Swan, A. and Van Doorn, P. **(2012)** Intravenous immunoglobulin for Guillain-Barré syndrome (Review)**. The Cochrane Collaboration, (7)**

IMSS **(2008) Guía de Práctica Clínica Diagnóstico y Tratamiento del Síndrome de Guillain-Barré En el Segundo y Tercer Nivel de Atención**

INEGI **(2009) México de un vistazo 2009**

INEGI **(2013) National Price Index [online]. Available from: http://www.inegi.org.mx/est/contenidos/proyectos/inp/inpc.aspx [Accessed 3 June 2013]**

INSP **(2009) Guía de Referencia Rápida Prevención, Diagnóstico y Tratamiento de la Influenza A (H1N1)**

Intercollegiate, S.G.N. **(2012) ISSG Search Filters Resource - Economic evaluations [online]. Available from: http://www.york.ac.uk/inst/crd/intertasc/econ.htm [Accessed 9 August 2012]**

Jefferson, T., Rivetti, D., Di Pietrantonj, C., et al. **(2007)** Vaccines for preventing influenza in healthy adults. **Cochrane database of systematic reviews (Online), (2): CD001269**

Jefferson, T., Smith, S., Demicheli, V., et al. **(2005)** Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review**. Lancet, 365 (9461): 773–780**

Kelso, J., Halde, N. and Milne, G. **(2013)** Vaccination strategies for future influenza pandemics: a severity-based cost effectiveness analysis**. BMC infectious diseases, 13 (81)**

Khazeni, N., Hutton, D.W., Garber, A.M., et al. **(2009a)** Effectiveness and cost-effectiveness of expanded antiviral prophylaxis and adjuvanted vaccination strategies

for an influenza A (H5N1) pandemic**. Annals of Internal Medicine, 151 (12): 840–853**

Khazeni, N., Hutton, D.W., Garber, A.M., et al. **(2009b)** Effectiveness and Cost-Effectiveness of Vaccination Against Pandemic Influenza (H1N1) 2009**. Annals of Internal Medicine, 151 (12): 829-U2**

Kiatpongsan, S. and Kim, J.J. **(2014)** Costs and cost-effectiveness of 9-valent human papillomavirus (HPV) vaccination in two East African countries. **PloS one, 9 (9): e106836**

Kim, J., Andres-Beck, B. and Goldie, S. **(2007a)** The value of including boys in an HPV vaccination programme: a cost-effectiveness analysis in a low-resource setting. **British journal of cancer, 97 (9): 1322–8**

Kim, J. and Goldie, S. **(2008a)** Health and economic implications of HPV vaccination in the United States**. New England Journal of Medicine, 359 (8): 821–832**

Kim, J. and Goldie, S. **(2009)** Cost effectiveness analysis of including boys in a human papillomavirus vaccination programme in the United States**. Bmj, 339: b3884**

Kim, J., Kobus, K., Diaz, M., et al. **(2008)** Exploring the cost-effectiveness of HPV vaccination in Vietnam: insights for evidence-based cervical cancer prevention policy**. Vaccine, 26 (32): 4015–4024**

Kim, J., Kuntz, K., Stout, N., et al. **(2007b)** Multiparameter calibration of a natural history model of cervical cancer. **American journal of epidemiology, 166 (2): 137–50**

Kim, J., Ortendahl, J. and Goldie, S. **(2009)** Cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in women older than 30 years in the United States. **Annals of Internal Medicine, 151 (8): 538–545**

Kim, S. and Goldie, S. **(2008b)** Cost-effectiveness analyses of vaccination programmes: A focused review of modelling approaches**. PharmacoEconomics, 26 (3): 191–215**

Kind, P., Hardman, G. and Macran, S. **(1999) UK population norms for EQ-5D. 172. York**

Knight, G., Griffiths, U., Sumner, T., et al. **(2014)** Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries. **Proceedings of the National Academy of Sciences of the United States of America, 111 (43): 15520–15525**

Laprise, J.-F., Drolet, M., Boily, M.-C., et al. **(2014)** Comparing the cost-effectiveness of two- and three-dose schedules of human papillomavirus vaccination: a transmission-

dynamic modelling study. **Vaccine, 32 (44): 5845–5853**

Laprise, J.-F., Markowitz, L.E., Chesson, H.W., et al. **(2016)** Comparison of 2-dose and 3-dose 9-valent human papillomavirus vaccine schedules in the United States: A cost-effectiveness analysis**.** Journal of Infectious Diseases**. 214 (5) pp. 685–688**

Lavelle, T.A., Meltzer, M.I., Gebremariam, A., et al. **(2011)** Community-based values for 2009 pandemic influenza A H1N1 illnesses and vaccination-related adverse events**.** PLoS ONE**. 6 (12)**

Lee, B., Bailey, R., Wiringa, A., et al. **(2010a)** Economics of employer-sponsored workplace vaccination to prevent pandemic and seasonal influenza**. Vaccine, 28 (37): 5952–5959**

Lee, B., Tai, J., Bailey, R., et al. **(2010b)** Economics of influenza vaccine administration timing for children**. The American journal of managed care, 16 (3): pp e75-e85**

Lee, G.M., Murphy, T. V, Lett, S., et al. **(2007)** Cost Effectiveness of Pertussis Vaccination in Adults**. American Journal of Preventive Medicine, 32 (3)**

Lee, G.M., Riffelmann, M. and Wirsing von Konig, C.H. **(2008)** Cost-effectiveness of adult pertussis vaccination in Germany**. Vaccine, 26 (29–30): 3673–3679**

Lee, V., Tok, M., Chow, V., et al. **(2009)** Economic Analysis of Pandemic Influenza Vaccination Strategies in Singapore**. PLoS ONE [Electronic Resource], 4 (9): Article No.: e7108**

Lenne, X., Domingo, J.D., Gil, A., et al. **(2006)** Economic evaluation of varicella vaccination in Spain - Results from a dynamic model**. Vaccine, 24 (47–48): 6980–6989**

Leroux-Roels, I., Borkowski, A., Vanwolleghem, T., et al. **(2007)** Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial**. Lancet, 370 (9587): 580–589**

Lipsitch, M., Lajous, M., O'Hagan, J., et al. **(2009)** Use of cumulative incidence of novel influenza A/H1N1 in foreign travelers to estimate lower bounds on cumulative incidence in Mexico**. PLoS ONE, 4 (9): 9–13**

Lloyd, A., Patel, N., Scott, D.A., et al. **(2008)** Cost-effectiveness of heptavalent conjugate pneumococcal vaccine (Prevenar) in Germany: considering a high-risk population and herd immunity effects**. European Journal of Health Economics, 9 (1): 7–15**

Lugner, A., Van Boven, M., De Vries, R., et al. **(2012)** Cost effectiveness of vaccination against pandemic influenza in European countries: Mathematical modelling analysis**.**

BMJ (Online), 345 (7868)

Mamma, M. and Spandidos, D.A. **(2013)** Economic evaluation of the vaccination program against seasonal and pandemic A/H1N1 influenza among customs officers in Greece**. Health policy, 109 (1): 71–77**

McGrogan, A., Madle, G.C., Seaman, H.E., et al. **(2009)** The epidemiology of Guillain-Barré syndrome worldwide. A systematic literature review. **Neuroepidemiology, 32 (2): 150–63**

McIntosh, E.D.G., Conway, P., Willingham, J., et al. **(2005)** Pneumococcal pneumonia in the UK-how herd immunity affects the cost-effectiveness of 7-valent pneumococcal conjugate vaccine (PCV)**. Vaccine, 23 (14): 1739–1745**

McKinlay, R.J., Wilczynski, N.L. and Haynes, R.B. **(2006)** Optimal search strategies for detecting cost and economic studies in EMBASE. **BMC health services research, 6: 67**

Medline Plus **(2013) Oseltamivir: MedlinePlus Drug Information [online]. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699040.html [Accessed 6 June 2013]**

Meeyai, A., Praditsitthikorn, N., Kotirum, S., et al. **(2015)** Seasonal influenza vaccination for children in Thailand: a cost-effectiveness analysis. **PLoS medicine, 12 (5): e1001829–e1001829**

Melegaro, A. and Edmunds, W. **(2004)** Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales**. Vaccine, 22 (31–32): 4203–4214**

Mexican Ministry of Health **(2009a) Estimacion del impacto potencial de las medidas de control de la influenza AH1N1 en Mexico (Mayo 2009) [online]. Available from: http://portal.salud.gob.mx/redirector?tipo=0&n_seccion=Boletines&seccion=2009-05-08_3961.html**

Mexican Ministry of Health **(2009b) Guía de Manejo Clínico de Influenza A(H1N1). Temporada Otoño-Invierno 2009**

Miller, E., Andrews, N., Stellitano, L., et al. **(2013)** Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis. **BMJ (Clinical research ed.), 346 (feb26_2): f794**

Miller, E., Hoschler, K., Hardelid, P., et al. **(2010)** Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study**. The Lancet, 375**

(9720): 1100–1108

MMH (Censia) **(2010) EVENTOS TEMPORALMENTE ASOCIADOS A VACUNACIÓN POR INFLUENZA A H1N1 ABRIL 2010**

Molinari, N.-A.M., Ortega-Sanchez, I.R., Messonnier, M.L., et al. **(2007)** The annual impact of seasonal influenza in the US: measuring disease burden and costs. **Vaccine, 25 (27): 5086–96**

Morens, D., Taubenberger, J., Harvey, H., et al. **(2010)** The 1918 influenza pandemic: Lessons for 2009 and the future**. Critical Care Medicine, 38 (SUPPL. 4)**

Mossong, J., Hens, N., Jit, M., et al. **(2008)** Social contacts and mixing patterns relevant to the spread of infectious diseases. **PLoS medicine, 5 (3): e74**

Mullooly, J.P., Bennett, M.D., Hornbrook, M.C., et al. **(1994)** Influenza vaccination programs for elderly persons: Cost-effectiveness in a health maintenance organization**. Annals of Internal Medicine, 121 (12): 947–952**

Najafzadeh, M., Marra, C.A., Galanis, E., et al. **(2009)** Cost effectiveness of herpes zoster vaccine in Canada**. PharmacoEconomics, 27 (12): 991–1004**

Newall, A., Wood, J., Oudin, N., et al. **(2010)** Cost-effectiveness of pharmaceutical-based pandemic influenza mitigation strategies. **Emerging infectious diseases, 16 (2): 224–30**

NHS Choices **(2013a) Bell's palsy - NHS Choices [online]. Available from: http://www.nhs.uk/conditions/Bells-palsy/Pages/Introduction.aspx [Accessed 9 June 2013]**

NHS Choices **(2013b) Chronic fatigue syndrome - NHS Choices [online]. Available from: http://www.nhs.uk/Conditions/Chronic-fatigue-syndrome/Pages/Introduction.aspx [Accessed 9 June 2013]**

NHS Choices **(2013c) Swine flu - Symptoms - NHS Choices [online]. Available from: http://www.nhs.uk/Conditions/Pandemic-flu/Pages/Symptoms.aspx [Accessed 6 June 2013]**

Nordin, J., Mullooly, J., Poblete, S., et al. **(2001)** Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. **The Journal of infectious diseases, 184 (6): 665–70**

Novaes, H.M.D., de Soarez, P.C., Silva, G.A., et al. **(2015)** Cost-effectiveness analysis of introducing universal human papillomavirus vaccination of girls aged 11 years into

the National Immunization Program in Brazil. **Vaccine, 33 Suppl 1 (S1): A135-42**

O'Brien, B., Goeree, R., Blackhouse, G., et al. **(2003)** Oseltamivir for Treatment of Influenza in Healthy Adults: Pooled Trial Evidence and Cost-Effectiveness Model for Canada**. Value in Health, 6: 116–125**

Olsen, J. and Jepsen, M.R. **(2010)** Human papillomavirus transmission and cost-effectiveness of introducing quadrivalent HPV vaccination in Denmark**. International Journal of Technology Assessment in Health Care, 26 (2): 183–191**

Osterholm, M., Kelley, S., Sommer, A., et al. **(2012)** Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. **The Lancet infectious diseases, 12 (1): 36–44**

Partinen, M., Saarenpää-Heikkilä, O., Ilveskoski, I., et al. **(2012)** Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. **Cowling, B.J. (ed.). PloS one, 7 (3): e33723**

Patrick, K.M. and Woolley, F.R. **(1981)** A cost-benefit analysis of immunization for pneumococcal pneumonia**. JAMA, 245 (5): 473–477**

Pechevis, M., Khoshnood, B., Buteau, L., et al. **(2003)** Cost-effectiveness of hepatitis A vaccine in prevention of secondary hepatitis A infection**. Vaccine, 21 (25–26): 3556–3564**

Pelletier, L., Chung, P., Duclos, P., et al. **(1998)** A benefit-cost analysis of two-dose measles immunization in Canada**. Vaccine, 16 (9–10): 989–996**

Pham, B., Chen, M., Tricco, A., et al. **(2012)** Use of a catalytic model to estimate hepatitis A incidence in a low-endemicity country: implications for modeling immunization policies**.** Medical decision making**. 32 (1) pp. 167–175**

Pidd, M. **(2004) Computer simulation in Managment Science. 5th ed. John Wiley & Sons, Ltd**

Poirier, B., De Wals, P., Petit, G., et al. **(2009)** Cost-effectiveness of a 3-dose pneumococcal conjugate vaccine program in the province of Quebec, Canada**. Vaccine, 27 (50): 7105–7109**

Porta, M. **(2008) A dictionary of epidemiology. Fifth ed. Oxford University Press**

Prosser, L.A., Lavelle, T.A., Fiore, A.E., et al. **(2011)** Cost-effectiveness of 2009 pandemic influenza A(H1N1) vaccination in the United States. PloS one**. 6 (7) p. e22308**

Puig-Barberà, J., Arnedo-Pena, A., Pardo-Serrano, F., et al. **(2010)** Effectiveness of seasonal 2008-2009, 2009-2010 and pandemic vaccines, to prevent influenza hospitalizations during the autumn 2009 influenza pandemic wave in Castellón, Spain. A test-negative, hospital-based, case-control study. **Vaccine, 28 (47): 7460–7**

Purdy, K.W., Hay, J.W., Botteman, M.F., et al. **(2004)** Evaluation of strategies for use of acellular pertussis vaccine in adolescents and adults: A cost-benefit analysis**. Clinical Infectious Diseases, 39 (1): 20–28**

Ray, G.T., Pelton, S.I., Klugman, K.P., et al. **(2009)** Cost-effectiveness of pneumococcal conjugate vaccine: an update after 7 years of use in the United States**. Vaccine, 27 (47): 6483–6494**

Ray, G.T., Whitney, C.G., Fireman, B.H., et al. **(2006)** Cost-effectiveness of pneumococcal conjugate vaccine: evidence from the first 5 years of use in the United States incorporating herd effects**. Pediatric Infectious Disease Journal, 25 (6): 494–501**

Reuters **(2010) WHO says H1N1 flu pandemic continues [online]. Available from: http://www.reuters.com/article/idUSTRE6521WF20100603 [Accessed 5 June 2013]**

Robin de Vries, Mirjam Kretzschmar, P., J.F.S., et al. **(2010)** Cost-Effectiveness of Adolescent Pertussis Vaccination for The Netherlands: Using an Individual-Based Dynamic Model**. PLoS One, 5 (10)**

Royle, P. and Waugh, N. **(2003)** Literature searching for studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system**. Health Technology Assessment, 7 (34)**

Rubin, J.L., McGarry, L.J., Klugman, K.P., et al. **(2010)** Public health and economic impact of vaccination with 7-valent pneumococcal vaccine (PCV7) in the context of the annual influenza epidemic and a severe influenza pandemic**. BMC Infectious Diseases, 10: 14**

Sander, B., Bauch, C., Fisman, D., et al. **(2010)** Is a mass immunization program for pandemic (H1N1) 2009 good value for money? Evidence from the Canadian Experience**. Vaccine, 28 (38): 6210–6220**

Sander, Bauch, C., Fisman, D., et al. **(2009a)** Is a Mass Immunization Program for Pandemic (H1N1) 2009 Good Value for Money? Early Evidence from the Canadian Experience**. PLoS currents Influenza, 17 (1): RRN1137**

Sander, Nizam, A., Garrison, L., et al. **(2009b)** Economic evaluation of influenza pandemic mitigation strategies in the United States using a stochastic microsimulation transmission model**. Value in health, 12 (2): 226–33**

Sassi, F., Archard, L. and McDaid, D. **(2002)** Searching literature databases for health care economic evaluations: how systematic can we afford to be? **Medical care, 40 (5): 387–94**

Schonberger, L., Bregman, D., Sullivan-Bolyai, J., et al. **(1979)** Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976--1977. **American journal of epidemiology, 110 (2): 105–23**

SciVerce **(2010) About Scopus [online]. Available from: http://www.info.sciverse.com/scopus/about/ [Accessed 5 August 2011]**

Sharma, M., Ortendahl, J., Ham, E. Van Der, et al. **(2012)** Cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in Thailand**.** BJOG: An International Journal of Obstetrics and Gynaecology**. 119 (2) pp. 166–176**

Shiell, A., Jorm, L.R., Carruthers, R., et al. **(1998)** Cost-effectiveness of measles outbreak intervention strategies**. Australian & New Zealand Journal of Public Health, 22 (1): 126–132**

Shim, E., Brown, S.T., DePasse, J., et al. **(2016)** Cost Effectiveness of Influenza Vaccine for U.S. Children: Live Attenuated and Inactivated Influenza Vaccine**.** American Journal of Preventive Medicine**. 51 (3) pp. 309–317**

Siddiqui, M. and Edmunds, W. **(2008)** Cost-effectiveness of antiviral stockpiling and near-patient testing for potential influenza pandemic. **Emerging infectious diseases, 14 (2): 267–74**

Silfverdal, S.A., Berg, S., Hemlin, C., et al. **(2009)** The cost-burden of paediatric pneumococcal disease in Sweden and the potential cost-effectiveness of prevention using 7-valent pneumococcal vaccine**. Vaccine, 27 (10): 1601–1608**

SINAIS/SINAVE/DGE/SALUD **(2011) Panorama Epidemiologico de la Pandemia de Influenza A(H1N1) -2009 en Mexico**

Skowronski, D.M., Janjua, N.Z., De Serres, G., et al. **(2011)** Effectiveness of AS03 adjuvanted pandemic H1N1 vaccine: case-control evaluation based on sentinel surveillance system in Canada, autumn 2009**. BMJ, 342 (feb03 1): c7297–c7297**

Stevenson, M., Beard, S., Finn, A., et al. **(2002)** Estimating the potential health gain and cost consequences of introducing a pre-school DTPa pertussis booster into the UK

child vaccination schedule**. Vaccine, 20 (13–14): 1778–1786**

Suarez, E., Smith, J.S., Bosch, F.X., et al. **(2008)** Cost-effectiveness of vaccination against cervical cancer: A multi-regional analysis assessing the impact of vaccine characteristics and alternative vaccination scenarios**. Vaccine, 26: F29–F45**

Tediosi, F., Maire, N., Penny, M., et al. **(2009)** Simulation of the cost-effectiveness of malaria vaccines**. Malaria Journal, 8**

Thiry, N., Beutels, P., Tancredi, F., et al. **(2004)** An economic evaluation of varicella vaccination in Italian adolescents**. Vaccine, (of Publication: 09 Sep 2004): 22 (27-28) (pp 3546-3562), 2004**

Thomson Reuters **(2002) Web of Knowledge Service for UK Education - Home Page [online] [online]. Available from: http://wok.mimas.ac.uk/ [Accessed 5 August 2011]**

Tibbits, M., Groendyke, C., Haran, M., et al. **(2014)** Automated Factor Slice Sampling. **J Comput Graph Stat, 23 (2): 543–563**

Tilson, L., Usher, C., Butler, K., et al. **(2008)** Economic evaluation of a universal childhood pneumococcal conjugate vaccination strategy in Ireland**. Value in Health, 11 (5): 898–903**

Tormans, G., van Doorslaer, E., van Damme, P., et al. **(1998)** Economic evaluation of pertussis prevention by whole-cell and acellular vaccine in Germany**. European Journal of Pediatrics, 157 (5): 395–401**

Trotter, C. and Edmunds, W. **(2006)** Reassessing the cost-effectiveness of meningococcal serogroup C conjugate (MCC) vaccines using a transmission dynamic model**. Medical Decision Making, 26 (1): 38–47**

El Universal Online **(2009a) México comprometió 2 mmdp para vacunas contra A (H1N1) [online]. Available from: http://www.eluniversal.com.mx/primera/33467.html [Accessed 5 June 2013]**

El Universal Online **(2009b) Mexico espera este mes vacunas contra AH1N1 (Octubre 2009) [online]. Available from: www.eluniversal.com.mx/notas/630685.html [Accessed 5 June 2013]**

El Universal Online **(2010) Era parar o un millón de muertos [online]. Available from: http://www.eluniversal.com.mx/primera/34816.html [Accessed 5 June 2013]**

Usher, C., Tilson, L., Olsen, J., et al. **(2008)** Cost-effectiveness of human papillomavirus vaccine in reducing the risk of cervical cancer in Ireland due to HPV

types 16 and 18 using a transmission dynamic model**. Vaccine, 26 (44): 5654–5661**

Valenciano, M., Kissling, E., Cohen, J.-M., et al. **(2011)** Estimates of pandemic influenza vaccine effectiveness in Europe, 2009-2010: results of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case-control study. **Simonsen, L. (ed.). PLoS medicine, 8 (1): e1000388**

Valenzuela, M.T., Jacobs, R.J., Arteaga, O., et al. **(2005)** Cost-effectiveness of universal childhood hepatitis A vaccination in Chile**. Vaccine, 23 (32): 4110–4119**

Vanagas, G., Padaiga, Z., Kurtinaitis, J., et al. **(2010)** Cost-effectiveness of 12- and 15-year-old girls' human papillomavirus 16/18 population-based vaccination programmes in Lithuania**. Scandinavian Journal of Public Health, 38 (6): 639–647**

Vanni, T., Karnon, J., White, R., et al. **(2011)** Calibrating Models in Economic Evaluation. A Seven-Step Approach**. PharmacoEconomics, 29 (1): 51–62**

Vanni, T., Mendes Luz, P., Foss, A., et al. **(2012)** Economic modelling assessment of the HPV quadrivalent vaccine in Brazil: A dynamic individual-based approach**.** Vaccine**. 30 (32) pp. 4866–4871**

Vespa, G., Constenla, D.O., Pepe, C., et al. **(2009)** Estimating the cost-effectiveness of pneumococcal conjugate vaccination in Brazil**. Revista Panamericana De Salud Publica-Pan American Journal of Public Health, 26 (6): 518–528**

Vynnycky, E. and White, R. **(2010) Infectious Disease Modelling. Oxford University Press**

De Wals, P., Coudeville, L., Trottier, P., et al. **(2007)** Vaccinating adolescents against meningococcal disease in Canada: A cost-effectiveness analysis**. Vaccine, 25 (29): 5433–5440**

De Wals, P., Deceuninck, G., Toth, E., et al. **(2012)** Risk of Guillain-Barré syndrome following H1N1 influenza vaccination in Quebec. **JAMA : the journal of the American Medical Association, 308 (2): 175–81**

Walwyn, L., Janusz, C.B., Clark, A.D., et al. **(2015)** Cost-effectiveness of HPV vaccination in Belize. **Vaccine, 33 Suppl 1 (S1): A174-81**

Welte, R., Dobbelsteen, G.V.D., Bos, J.M., et al. **(2004)** Economic evaluation of meningococcal serogroup C conjugate vaccination programmes in The Netherlands and its impact on decision-making**. Vaccine, 23 (4): 470–479**

WHO **(2009) World Health Organization Factsheet No. 211. (Influenza Seasonal) [online]. Available from: http://www.who.int/mediacentre/factsheets/fs211/en/**

[Accessed 30 November 2010]

WHO **(2010a) CHOosing Interventions that are Cost Effective (WHO-CHOICE) [online]. Available from: http://www.who.int/choice/costs/CER_levels/en/index.html [Accessed 6 June 2013]**

WHO **(2010b) Global Alert and Response (GAR). What is phase 6 [online]. Available from: http://www.who.int/csr/disease/swineflu/frequently_asked_questions/levels_pandemic_alert/en/ [Accessed 5 June 2013]**

WHO **(2010c) WHO Guidelines for Pharmacological Management of Pandemic Influenza A (H1N1) 2009 and other Influenza Viruses (part I and II)**

WHO **(2011) Global Alert and Response (GAR) [online]. Available from: http://www.who.int/csr/disease/swineflu/phase/en/ [Accessed 5 June 2013]**

Whyte, S., Walsh, C. and Chilcott, J. **(2011)** Bayesian calibration of a natural history model with application to a population model for colorectal cancer. **Medical decision making : an international journal of the Society for Medical Decision Making, 31 (4): 625–41**

Williams, J., DJ, N., GF, M., et al. **(1996a)** The transmission dynamics of hepatitis B in the UK: a mathematical model for evaluating costs and effectiveness of immunization programmes. **Epidemiology and infection, 116 (1): 71–89**

Williams, J., Nokes, D.J. and Anderson, R.M. **(1996b)** Targeted hepatitis B vaccination - A cost effective immunisation strategy for the UK? **Journal of Epidemiology and Community Health, 50 (6): 667–673**

Winters, J., Brown, D., Hazard, E., et al. **(2011)** Cost-minimization analysis of the direct costs of TPE and IVIg in the treatment of Guillain-Barré syndrome. **BMC health services research, 11 (1): 101**

Wutzler, P., Neiss, A., Banz, K., et al. **(2002)** Can varicella be eliminated by vaccination? Potential clinical and economic effects of universal childhood varicella immunisation in Germany**. Medical Microbiology & Immunology, 191 (2): 89–96**

Yin, J., Chow, M., Khandaker, G., et al. **(2012)** Impacts on influenza A(H1N1)pdm09 infection from cross-protection of seasonal trivalent influenza vaccines and A(H1N1)pdm09 vaccines: systematic review and meta-analyses. Vaccine**. 30 (21) pp. 3209–3222**

Zhuang, G.H., Pan, X.J. and Wang, X.L. **(2008)** A cost-effectiveness analysis of universal childhood hepatitis A vaccination in China**. Vaccine, 26 (35): 4608–4616**

Zimmer, S., Crevar, C., Carter, D., et al. **(2010)** Seroprevalence Following the Second Wave of Pandemic 2009 H1N1 Influenza in Pittsburgh, PA, USA **Kelly, K.A. (ed.). PLoS ONE, 5 (7): e11601**