

AN INTERNATIONAL STUDY OF THE USE OF PANDEMIC
VACCINES DURING THE 2009-10 INFLUENZA A(H1N1)
PANDEMIC: A QUALITATIVE METHODOLOGICAL APPROACH

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Abstract

Background: The 2009-10 influenza A(H1N1) pandemic was the first pandemic influenza of the twenty-first century and presented the first major opportunity for the use of influenza vaccines en-masse during a pandemic scenario. National anticipatory policies of pandemic influenza vaccine preparedness were implemented, and vaccine guarantee agreements were activated. Large quantities of vaccines were purchased and made available to identified citizens over the course of the pandemic. The use of pandemic influenza vaccines has been examined in this research.

Methods: A comparative health policy approach in five study countries (Sweden, New Zealand, Japan, Singapore, and Canada) was conducted. Qualitative interviews (n= 36) were undertaken in each country with key pandemic influenza response personnel (n = 39). Participants included public health officials, policy makers and clinicians engaged at national country response level. Interviews facilitated discussions surrounding the 2009-10 influenza A(H1N1) pandemic response and use of vaccines. Documentary examination of available records supplemented the analysis of the interview data.

Results: Several interview themes were identified following data analysis of the use of pandemic vaccines in the study countries. Themes of the vaccine use included: single or multiple vaccine supplier routes; hemisphere variation; historical pandemic legacy; targeted populations; setting vaccination priorities; side effect concerns; perceived effectiveness of vaccines during the pandemic influenza response. The themes which were most prominent comprised the sourcing and distribution of the vaccines during the response and the associated communication challenges. The necessary prioritisation of vaccines caused extensive discussions and uneasiness by the pandemic influenza response personnel as the initial vaccines arrived in small quantities and required allocation, especially in circumstances where country's intended for all/most citizens to eventually

have access to the vaccine. The variation in timing of the vaccination campaigns and disease activity would suggest that subsequent influenza wave morbidities and mortalities could have been reduced if vaccines had been available more promptly. The southern hemisphere country, New Zealand, exemplified the circumvention of vaccine safety concerns through the use of a trivalent vaccine inclusive of H1N1.

Conclusions: Pandemic vaccines were the cornerstone of two countries responses and were associated with high uptake rates. Vaccine discussions, such as prioritisation and essential workers estimates, can be established during interpandemic phases by pandemic influenza response personnel. The use of annual seasonal influenza vaccines that are inclusive of the novel pandemic influenza strain should play a greater role in future pandemic influenzas, should the vaccination campaign timing be appropriate, as this may reduce public anxiety concerning the perceived safety of novel vaccines. The use of the 2009-10 influenza A(H1N1) pandemic vaccines had varied in success and the lessons learnt from this event have important implications for future policy. Pandemic influenza response personnel are recommended to prepare as fully as possible during this interpandemic period.

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1. Introduction

This opening chapter begins with an introduction to the emerging infectious disease threats of the last decade and the associated international pandemic influenza preparations. The discussion moves on to provide a brief overview to the 2009-10 influenza A(H1N1) pandemic and common public health measure responses. The research interests are then explained in the project rationale, aims, and objectives. The evolution of the research project is conveyed through a discussion on the Ph.D. proposal which originally included four core policy areas. In the later stages, the thesis has concentrated on the use of pandemic vaccines, and this is reflected in the project write-up. The last part of this chapter breaks down the thesis chapter structure and provides a summary of the introduction.

1.1 Twenty-first century emerging infectious disease threats and global preparations

In 2005, the World Health Organization (WHO) recommended that all countries should prepare or strengthen their preparedness activities in the event of pandemic influenza, in order to limit the health and social effects should a pandemic occur (World Health Organization, 2005a). This report by WHO was published following outbreaks of A/H5N1 avian influenza in 2003, where 400 cases were reported, and a 60% case-fatality rate was experienced (Sellwood, 2010). There was not only the concern that avian influenza or another sub-type

could manifest into pandemic influenza at any time, but also, the concern that many countries did not have plans in place and, therefore, pandemic preparedness activities were considered essential. Many countries responded to the WHO call and, to a varying extent, developed pandemic influenza plans.

Some countries stockpiled antivirals with various treatment policies in place, which included the protection of healthcare workers, treating cases of influenza-like-illness (ILI), prophylactic use, etc. Some countries signed guarantee agreements with manufacturing pharmaceutical companies to ensure access to the developed pandemic influenza vaccine for at-risk groups, healthcare workers or the entire country population. In addition, other plans were made such as social distancing, communication strategies and surveillance strengthening.

1.2 The arrival of 2009-10 influenza A(H1N1) pandemic

On 18th March 2009, surveillance within Mexico observed outbreaks of ILI in certain parts of the country (World Health Organization, 2009a). 1,324 suspected influenza cases with severe pneumonia, and 84 deaths were reported between 17th and 27th April (Pan American Health Organization, 2009). On the 18th April, the United States reported two children in California with laboratory-confirmed A(H1N1) influenza (Pan American Health Organization, 2009). Over the course of the following weeks, the WHO communicated to the rest of the world the Swine influenza A(H1N1) laboratory confirmed cases

and deaths in other countries. The WHO declared that the A(H1N1) virus had reached Phase 6 pandemic status on the 11th June 2009 (World Health Organization, 2009b), which made it the first influenza pandemic of the 21st century. This was based on the evidence of a novel influenza strain of nearly 30,000 confirmed cases in 74 countries which were sustained by human-to-human and country to country transmission (World Health Organization, 2009b).

The WHO reported 18,449 deaths in 214 countries by 1st August 2010 (World Health Organization, 2010a). On the 10th August 2010, the WHO released a press report stating that the world had now entered a post-pandemic phase due to changes in the levels and patterns of A(H1N1) transmission (World Health Organization, 2010b).

1.3 Public health responses to the 2009-10 influenza A(H1N1) pandemic

During the 2009-10 influenza A(H1N1) pandemic, many nations attempted to mitigate the effects of the pandemic by various public health measures such as antivirals for case treatment and prophylactic use, administration of the pandemic vaccine, social distancing measures (quarantine, avoidance of mass gatherings, public transport suspension, international border closures, flight restrictions), and public health communications. Countries which opted to use the pandemic influenza vaccine experienced a delay due to the need for the developed vaccine to be based on the circulating virus. Therefore, when the first vaccination campaigns

commenced in September 2009, previous alternative public health measures may have been utilised after the first case reports in April 2009.

1.4 Project rationale and objectives

Now in the post-pandemic phase, many countries have conducted or are currently processing, national and regional evaluations of their response to the 2009-10 influenza A(H1N1) pandemic. However, fewer evaluations were carried out at international level, and those that took place predominately focused on the coordination and operational responses and discussed areas of difficulty in the response, such as appropriate communications to the public. It was felt that there was a gap in the evaluations, and there was a need to attempt to analyse the public health policy responses made within individual countries, e.g. decisions taken to use or not to use vaccines.

The intention of this thesis was to make specific international comparisons between health policies, in order to possibly improve future pandemic preparedness and highlight difficulties and problems that arose in pandemic influenza response. Such generated information would then feed into the 'risk behaviours' of governments as they balance preparedness for pandemic risk against alternative resource allocations.

This research project (also referred to as the thesis) was created in order for an international study to be conducted, to make comparisons and contrasts of countries experiences of

the 2009-10 influenza A(H1N1) pandemic. It was considered important to create a project which would not produce a quantitative international epidemiological analysis but rather examine the policy and implemented public health measures during a time of threat, uncertainty and pressure, and attempt to connect this information to the published epidemiological data. The purpose of this enquiry was that the questioning would delve beneath patterns identified in the epidemiological data. Due to these factors, the project became multi-disciplinary and incorporated the research fields of health policy, sociology, epidemiology and public health.

The studentship was an externally funded piece of research: GlaxoSmithKline (GSK) have provided the expenses covering the studentship at the University of Nottingham and fieldwork abroad in the five study countries. The research proposal was developed after the 2009-10 influenza A(H1N1) pandemic and the parameters reflected core policy areas of pandemic influenza response. GSK is a UK-created global pharmaceutical company that played a major role during the 2009-10 influenza A(H1N1) pandemic through the supply of millions of doses of A(H1N1) vaccine Pandemrix®.

Due to GSK's provision of healthcare products during the pandemic influenza, they have subsequently funded research in the post-pandemic period, one of which is this studentship. GSK's role in this research has been to provide the financial means to conduct the research, but essentially they have been silent partners. GSK has not played a role in directing this research since the project proposal.

The project proposal outlined above and in the GSK research proposal was broad in content (see Appendix A). As this project progressed and after the interviews had been conducted, it proved too vast to include all four of the original proposal public health measures (antivirals, vaccines, non-pharmaceutical measures, wider societal issues) in the thesis, and subsequently, vaccines became the focus of this thesis. Nevertheless, the interview data collected included discussions on all of the proposal public health measures. By capturing this data in the interview, it will be possible to analyse the antiviral, non-pharmaceutical and wider societal aspects of response at a later date and outside of this thesis. With the narrowed focus in mind, the aims and objectives of the Ph.D. are listed below.

1.5 **Aim of Thesis**

To explore countries use of pandemic vaccines during the 2009-10 influenza A(H1N1) pandemic: using qualitative interviews with key pandemic influenza response personnel in several study countries.

1.6 **Objectives of Thesis**

1. To review pandemic influenza policies and their implementation in selected countries (reference the core policy areas and timing (in relation to disease occurrence)).

2. To explore countries implemented vaccine measures using qualitative interviews with key pandemic responders.
3. To determine any apparent relationship between the vaccine policy implementation in countries and the pandemic influenza disease activity (in relation to the timing of response measures and disease activity; the extent and variation of vaccine policies in countries).
4. To review the implications for public policy in relation to pandemic preparedness and the response to future pandemics of potentially greater severity.

The objectives have taken a chronological order in this research project. Naturally, it was crucial to perform a literature review of the previous influenza pandemics, public health measures and pandemic influenza preparedness policies before undertaking interviews in the study countries.

The researcher's ambition for this research project was to undertake a systematic investigation of the 2009-10 influenza A(H1N1) pandemic in several countries. Indeed, the research conducted has resulted in the identification of transnational themes through the identification of similarities and differences by country comparison.

An important feature of this international study is the timing: it is well recognised that evaluations contributing to the field of pandemic influenza are significant at the start of an interpandemic phase. It is essential to capture this information post-response in order for it not to be forgotten. Before

undertaking this research project, the researcher wished for the study to add to the body of research in the field of pandemic influenza and unique findings will be presented in this thesis. This study has in instances provided information to clarify some unanswered questions about pandemic influenza vaccine response, and at other times, it has further contributed to areas of existing debate and further issues for consideration. It is possible that this research will support ongoing practice and will contribute to increasing the confidence of responders in their decisions during a future challenging emergency event of pandemic influenza.

1.7 **Thesis structure**

The structure of this thesis starts with a background of pandemic influenza, the thesis methodology, pandemic preparedness policies and vaccine findings, discussions and conclusions. Chapter 2 outlines a historical overview of pandemic influenza events of the twentieth century and public health management measures, specifically the development of influenza vaccines. The last section of chapter 2 outlines a study country timeline of the 2009-10 influenza A(H1N1) pandemic disease patterns and response measures. Chapter 3 discusses the methodological approach of this research and the research methods used. Chapter 4 outlines pandemic influenza preparedness, the policies of the study countries and vaccine deployment in 2009-10. Chapter 5 presents the findings pertaining to pandemic vaccines from the interview data. Chapter 6 arranges the vaccine findings in a wider

discussion of published literature. Lastly, chapter 7 draws conclusions on the pandemic influenza research project.

1.8 **Introduction summary**

This introduction chapter has presented the focus of this research, provided an overview of 2009-10 influenza A(H1N1) pandemic, and the common public health response measures utilised. A project rationale with the research aims and objectives has been discussed and lastly, a thesis structure has been included.

2 Pandemic Influenza and Public Health Management Measures

A brief history of influenza pandemics is introduced in the first part of this chapter, commencing with a very brief background of the influenza virus and the definitions of pandemic influenza. The focus of the history of influenza pandemics is on pandemics of the twentieth century, and specific reference is made to the experiences of the countries of study within this thesis; Japan, Singapore, New Zealand, Sweden and Canada.

The second part of this chapter will report on the development of public health measures that have been utilised to manage pandemic influenza historically.

The third part of this chapter will describe the characteristics of the epidemiology of the 2009-10 influenza A(H1N1) pandemic, with special reference to the study countries individual epidemiological patterns and national responses.

2.1 Influenza background

Influenza is a global infectious disease and a common acute respiratory illness that presents rapidly in humans. Besides from the respiratory symptoms such as cough, sore throat and hoarseness, influenza symptoms are wide ranging and can include fever, fatigue, headache, vomiting, diarrhoea as well as more serious secondary complications affecting a wide range of organs, such as acute bronchitis, pneumonia,

myocarditis, etc. At the other end of the scale, influenza can also be an asymptomatic infection. There are three types of virus serotypes A, B and C: C is one of the 300 viruses that causes the common cold, A and B are responsible for seasonal influenza, and pandemic influenza is only caused by A. In temperate regions of the world, influenza epidemics typically occur during the winter months leading to the term 'seasonal influenza' (also referred to as interpandemic influenza). In the tropics, the seasons are less well defined and influenza is less consistent (Nicholson, 1998; Van-Tam and Sellwood, 2013).

There are two epidemiological types of influenza: pandemic and interpandemic. Interpandemic influenza arises from the continuous circulation of familial influenza viruses that cause localised epidemics. Pandemic influenza refers to the rare instances where a novel influenza A virus emerges and causes high attack rates due to very low or no immunity in humans (Nicholson, 1998; Van-Tam and Sellwood, 2013). Although this research project is based on pandemic influenza, it is important to understand how interpandemic and pandemic influenza exist together as one disease. Familiarity with interpandemic influenza during an influenza pandemic, on the one hand, provides experience in public health responses, such as annual vaccination programmes, but on the other hand, it creates confusion due to the different epidemiological features of each influenza type.

2.2 Definitions of pandemic influenza

Annual (seasonal/interpandemic) influenza epidemics are the result of antigenic drift, whereas pandemic influenza is when the virus undergoes genetic reassortment (antigenic shift), and the consequence of this reassortment is the emergence of a new type A influenza virus (Potter 2001; Monto and Sellwood 2013). When this new influenza virus arises most, if not all, of the global population has little or no immunity and the influenza virus has the capacity to spread in major waves over several months. In order to discuss pandemic influenza further, the definition of pandemic influenza shall first be considered. Below are two pandemic influenza definitions presented in the literature to contemplate:

Definition 1

Monto and Sellwood (2013: p.40) set out the four criteria for pandemic influenza classification:

1. *"A new influenza A virus substantially different (antigenically) from the circulating pre-pandemic strains must emerge or evolve and circulate in humans.*
2. *There must be little or no pre-existing immunity to the new subtype in major segments of the global population.*
3. *The new virus must cause significant clinical illness.*
4. *The virus must be able to spread efficiently from person to person and as a results spread globally."*

Definition 2

"Two conditions must be satisfied for an outbreak of influenza to be classed as a pandemic. Firstly, the outbreak of infection, arising in a specific geographical area, spreads throughout the world; a high percentage of individuals are infected resulting in increased mortality rates. Secondly, a pandemic is caused by a new influenza A virus subtype, the haemagglutinin (HA) of which is not related to that of influenza viruses circulating immediately before the outbreak, and could not have arisen from those viruses by mutation (Webster & Laver 1975). Each influenza A virus subtype possesses one of 15 distinct HAs designated H1, H2, H3, and so on, which do not cross-react in serological tests: immunity to influenza is principally related to antibody to the HA, and the appearance of a new virus subtype with a different HA means that immunity acquired from past influenza infection confers no protection against the new virus subtype, and the spread of infection by the latter is unchecked." (Potter, 1998: p.3).

The two definitions offer an excellent starting point for examining pandemic influenza. Although the definitions are different, they are equally correct. For instance, when Potter wrote in 1998 of the 15 Haemagglutinin (H) subtypes of influenza A viruses, this was what was known at the time. However, since 1998, we now have 17 H-subtypes, and this highlights the continuously evolving knowledge and nature of pandemics. With the pandemic influenza definitions in mind, the historical occurrences of pandemics shall be explored in the following segment.

2.3 Pandemic influenza history

In order to understand pandemics and to prepare for a future pandemic influenza with effective public health measures, it is essential to conduct a detailed historical analysis of past epidemiological patterns of pandemics. Some questions remain regarding aspects of past pandemics, and this has public health implications for future pandemic responses (Taubenberger and Morens, 2006; Nishiura and Chowell, 2007).

2.3.1 Chronology of influenza pandemics

Reviewers of pandemic influenza have attempted to identify early pandemics from historical documents. It is difficult to ascertain, due to the poor recording of information, but it is possible that the first two influenza pandemics were in 1510 and 1557. However, 1580 is the time of the first documented pandemic influenza in which the spread of disease over time and geography are known (Potter 2001). Figure 1 shows a timeline of the emergence of pandemic influenza events.

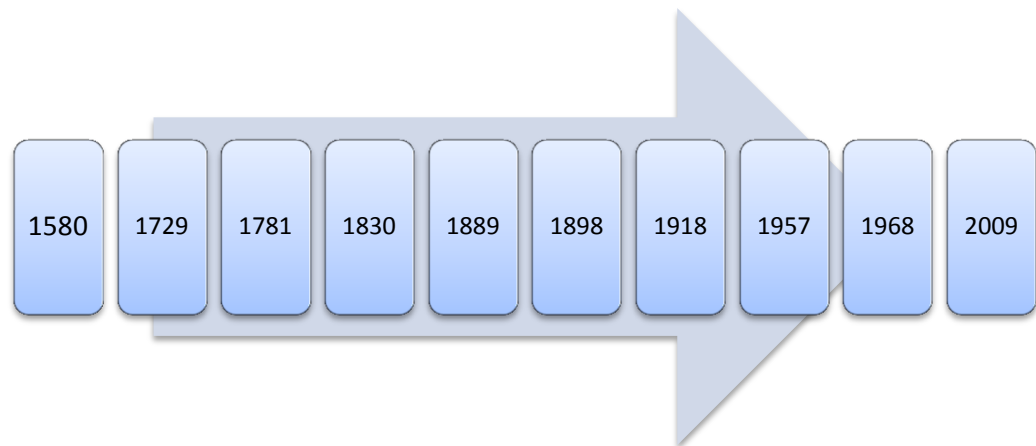


Figure 1: Year of influenza pandemics.

For this history section on influenza pandemics, only pandemic events from the last ~300 years will be discussed, providing only a general summary, as it is not possible to provide an exhaustive description. Pandemics before the 18th century will not be covered because there is insufficient global certainty prior to this date.

In the following section, Influenza pandemics between 1701 and 1900 are described briefly, before the influenza pandemics of the twentieth century are looked at individually and in more detail. This presentation of the history of twentieth-century influenza pandemics will have specific reference to the individual study countries included in the data collection of this thesis.

Figure 2 depicts influenza mortality in each influenza pandemic reported from 1701. As observed in Figure 2, the Spanish Influenza of 1918-1919 recorded the worst mortality outcome in comparison to all the influenza pandemics experienced in history. Table 1 provides an overview of

influenza pandemics from the eighteenth century, including the areas affected, origins, influenza virus types (if known) and epidemiological features.

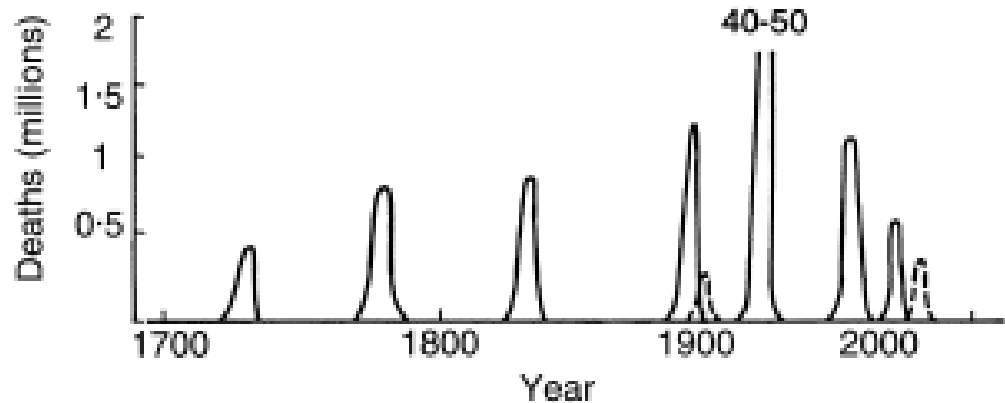


Figure 2: Illustration of timing of influenza peaks since 1700, illustrating relative mortality impact (Reproduced with permission from Potter, 2001).

Table 1: Influenza pandemics from the 18th-century summary (table assembled using information sourced from Monto and Sellwood, 2013; Potter, 1998; Potter, 2001).

Year	Areas reported affected	Origin	Subtype	Epidemiological features
1729-1733	Europe, Americas, Russia	Russia	Unknown	Two distinct waves; second wave more severe
1781-1782	Europe, China, India, N.America, Russia	Russia/China	Unknown	Reported high attack rate, notably in young adult population
1830-1833	Europe, China, India, N.America, Russia	China	Unknown	High attack rates of 20-25% of the population reported, but mortality rates low in comparison
1889-1892	Global	Russia	A(H2)?	First global influenza pandemic. Majority of mortality in later

				pandemic waves and in the elderly population. Global mortality rate estimated at 300,000 and attack rate estimates ranged between 25% and 50% of the population.
1898-1900	Europe, Americas, Australia	Unknown	A(H3)?	Mainly mild outbreaks
1918-1920	Global	United States/ China	A(H1N1)	Coincided with end of World War 1, pandemic responsible for more deaths than the war. Second wave much more severe than the first, with the third wave of moderate severity. Estimated to have infected 50% of world's population, with 40-50 million deaths. Particularly affected the young, working age population.
1957-1958	Global	China	A(H2N2)	Mortality rates high but low attack rate in the elderly population. Some countries reported similar severity in both waves of infection, whilst other countries reported a more severe second wave.
1968-1969	Global	China	A(H3N3)	North America reported majority of deaths during the first wave, whereas Europe and Asia reported greater deaths during the second wave. Symptoms described as mild, and elderly population had some protection from the influenza. Estimation of 1 to 3 million global deaths, meaning CFR of <0.5%.

Pandemics from 1701 - 1800

Two influenza pandemics occurred during the 18th century. In 1729, an outbreak originating from Russia spread to Europe

and became widespread within three years. High mortality rates were recorded, with the latter waves more severe than the earlier (Monto and Sellwood, 2013; Potter 2001).

In 1781-1782, a pandemic influenza, believed to have originated from China spread westwards to Russia and then Europe, as well as reaching North America and India. This pandemic influenza spread quickly across continents, and the attack rate was reported as high in the young adult population (Monto and Sellwood, 2013; Potter 2001).

Pandemics from 1801 - 1900

The 19th century witnessed the emergence of three influenza pandemics. In 1830, a pandemic influenza with high attack rate but low mortality rate emerged in China, spread southerly to Asia, then to Russia, Europe and North America over the course of about three years (Potter 2001).

In 1889 a pandemic influenza (possibly of A(H2) subtype) originated from Russia with a population attack rate reportedly between 25% and 50%, causing high mortality in older persons. The 1898 pandemic influenza (possibly of A(H3) subtype) saw outbreaks in Australasia, Europe, East Asia and the Americas, and documents indicate that these were mild (Monto and Sellwood, 2013).

Pandemics from 1901 - 2000

The twentieth century experienced another three influenza pandemics:

1. 1918-1920 Spanish Influenza A(H1N1)
2. 1957-1958 Asian Influenza A(H2N2)
3. 1968-1969 Hong Kong A(H3N3)

The following section will explore the three events of pandemic influenza during the twentieth century and make reference to the five study countries experiences.

2.3.2 Twentieth-century influenza pandemics

A review of the literature of twentieth-century influenza pandemics was conducted via a PubMed search last dated 20/02/2015. The keyword terms were "pandemic influenza" OR "influenza" and individual pandemics were specified ("1918" AND/OR "Spanish"; "1957" AND/OR "Asian"; "1968" AND/OR "Hong Kong") and study countries ("Sweden"; "New Zealand"; "Japan"; "Singapore"; "Canada"). For example: (pandemic influenza OR influenza) + (1918 AND/OR Spanish) + (Sweden). Specific focuses of the reviews covered epidemiology (arrival, waves, mortality, age-specific patterns, and impact) and public health measures. Only English language texts were examined. Reference lists were scrutinised to identify original authors, and a grey literature search was also conducted.

2.3.2.1 1918 Pandemic Influenza

It is argued that the 1918 pandemic influenza emerged either from the United States or from China before spreading to the United States (Hsieh et al., 2006). The United States first noted outbreaks in several locations including army camps in March 1918 (Detroit, South Carolina and San Quentin Prison), before appearances of the influenza were made in France and other parts of Europe, including areas associated with United States troop boat landings in World War One during 1918 (Oxford, 2000; Hsieh et al., 2006). Outbreaks continued to occur during the course of the northern hemisphere summer of 1918 (see Figure 3). However, the virus became more severe and widespread by autumn of 1918 (Oxford, 2000). Over the following two years to 1920, A(H1N1) Spanish influenza spread globally in an eastwards direction at first, and along shipping trade routes (Potter, 2001).



Figure 3: The 1918-20 influenza pandemic depicting first waves and second wave direction of infection spread and months timeline (Reproduced with permission from Potter, 2001, with study countries labelled).

Taubenberger and Morens (2006: p.16) report three global general waves of influenza activity over the course of a 12 month period for the northern hemisphere region: "*The first pandemic influenza wave appeared in the spring of 1918, followed in rapid succession by much more fatal second and third waves in the fall and winter of 1918–1919, respectively*". The Spanish influenza is believed to have infected 50% of the global population, of which half developed major clinical infections (Hsieh et al., 2006).

Given the rate of infection, a major lesson learnt from the 1918-19 A(H1N1) Spanish influenza pandemic was that it could cause severe illness and deaths in otherwise healthy persons, which lead to this pandemic ranking as one of the worst epidemics in human history comparable with historical events such as the Black Death (Potter, 2001). Although shipping routes provided a rapid mean of spreading, countries such as Australia managed to delay the arrival of infection for several months through implementing quarantine measures. The influenza characteristics evolved during the course of the pandemic meaning that the second and third waves of infection were more severe than first. Hospitals, morgues and the workforce, in general, were overwhelmed, and war strategies were hampered by the spread of infection and resulting deaths. The 1918–20 A(H1N1) Spanish influenza outbreak demonstrated that an influenza pandemic can pose as much risk, threat and uncertainty within the global population to rival war, natural disasters and other diseases.

In the 1918-19 A(H1N1) Spanish influenza pandemic, Japan was the first of the countries studied in this thesis to have a mild first wave of influenza in April-May in 1918. This was followed by a severe second wave in August-October 1918 and the third wave in January-March 1919. The death rate from the influenza pandemic was 4.5 per 1,000 persons across the three waves (Rice and Palmer, 1993). The Ministry of Home Affairs within the Government of Japan requested that prefecture governors regularly report influenza cases (Yoshikura, 2014).

Singapore and New Zealand shared some similarities during the 1918-19 A(H1N1) Spanish influenza pandemic: both countries reported their first cases in June 1918 (Lee, et al., 2007; Potter, 2001) and neither reported the third wave. Singapore's first wave was mild and occurred in June-July 1918 with a peak in early July (Lee, et al., 2007), whereas New Zealand's first wave was later in August-September 1918 and was also recorded as mild (Pool, 1973). The second waves were severe and experienced at similar times; Singapore experienced the second wave in October-November 1918, where cases peaked at the end of October (Lee, et al., 2007) and the second wave in New Zealand occurred in October-December 1918 (Pool, 1973), peaked in the North Island in mid-November, then later in the South Island (Wilson and Baker 2008).

The Spanish influenza event has been recorded in New Zealand's history as 'Black November' (Rice, 2005). It was noted that New Zealand's neighbour Australia kept influenza out in 1918 through operating marina quarantine measures. However, Sydney eventually followed a similar pattern to New

Zealand's experience of a mild first wave in January-April 1919 and a severe second wave in May-August 1919 with no apparent third wave. Subsequently, this pattern was replicated in time across the other Australian States. Australia reported a death rate far lower than New Zealand at 2.3 per 1,000 persons compared to 7.4 per 1,000 (Rice, 2005). Interestingly, New Zealand experienced a severe second wave of influenza outside of their annual influenza season; by comparison, Australia's severe second wave coincided with their winter seasonal influenza months.

Sweden, similarly to Singapore and New Zealand, reported the A(H1N1) Spanish influenza pandemic in June 1918 with reports that the virus arrived in the southern region of the country from Norway and Germany (Holtenius and Gillman, 2014). However, Sweden experienced a different timing of waves compared to Singapore and New Zealand. The first wave was spread out between July 1918 and February 1919. Initially, it was slow and mild but later became severe, peaking between October-November 1918. Two further mild waves were experienced in March-June 1919 and January-May 1920 (Karlsson, Milsson and Pichler, 2014). It has been calculated that an estimated 20-60% of the population in Sweden became infected with pandemic influenza (Holtenius and Gillman, 2014).

Canada's experience of 1918-19 A(H1N1) Spanish influenza pandemic was different to the other study countries. Canada first reported cases in July 1918 in the Quebec province, with outbreaks first appearing at ports, before outbreaks appeared across Canada with remote areas not initially infected (McGinnis, 1977). Influenza was spread across Canada by

soldiers who had returned from World War 1 duties abroad and spread along railway transportation routes westwards towards Vancouver between 1918 and 1919 (Public Health Agency of Canada, 2006). Specific pandemic influenza disease activity waves were not found in the literature search for Canada, as local and regional waves of influenza activity were recorded rather than at the national level, primarily due to the vastness of the country. Indeed, twenty-first-century Canadian pandemic influenza planning and the response is conducted at provincial and territorial level with an overarching coordinating national organisation; influenza activity is reported regionally and locally, and then incorporated into the national surveillance system FluWatch (Public Health Agency of Canada, 2006).

A comparison of the timing of the waves and severity of the 1918-19 A(H1N1) Spanish influenza pandemic for the study countries are pictorially emphasised in Figure 4 below. In the figure the star indicates the first case recorded in the literature. The coloured lines indicate the waves with red for first, blue for second and green for third waves. Where the lines are thick this refers to literature that mentioned a severe wave and a thin line signifies a mild wave. Where a line fades, such as in the example of Canada, this indicates that the start of a wave was recorded and cases were reported in the literature but no wave end was found in the literature.

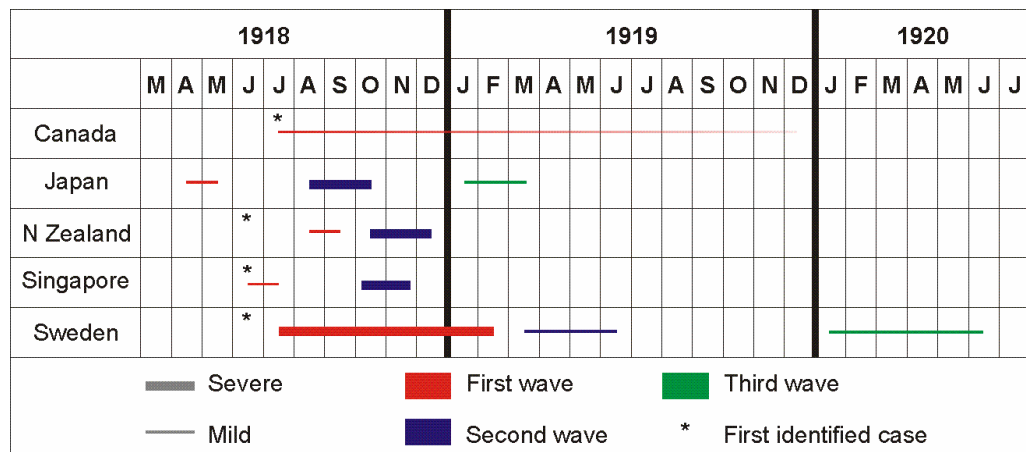


Figure 4: Study countries disease activity during 1918-19 pandemic influenza.

The 1918 pandemic influenza mortality rates plotted against age (Figure 5) give a W-shaped curve, meaning that mortality was raised in infants, the elderly and young adults. In typical interpandemic periods, the curve is U-shaped with fatalities in persons who are at opposite ends of the age spectrum: very young children and the elderly (Figure 5). Figure 5 shows the U-shaped curve of influenza disease activity in the interpandemic period of 1911-1917 in comparison to the W-shaped curve during 1918 pandemic. The high mortality in young adults aged 20-40 years during the 1918 pandemic influenza was unusual (Luk et al., 2001). Over the course of months, the influenza virus became more virulent and resulted in a rapid death rate increase, making it accountable for more deaths than the war. Global mortality reporting is estimated to be more than 40 million deaths, but this calculation is debated (Hsieh et al., 2006; Monto and Sellwood, 2013; Potter 2001).

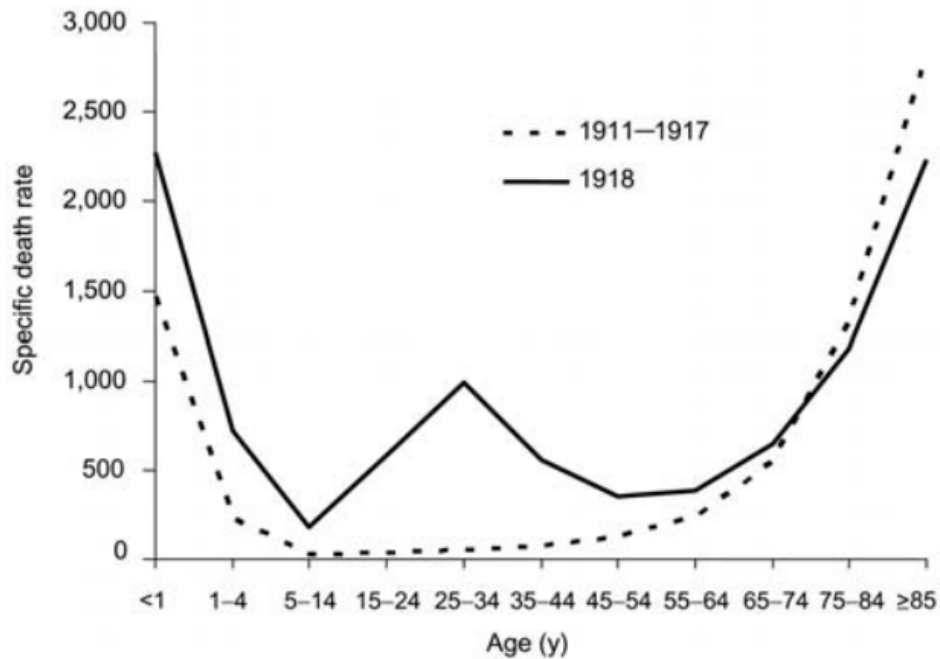


Figure 5: Influenza and pneumonia mortality per 100,000 by age groups in the United States between 1911 and 1918 demonstrating the contrasting U and W-shaped curves (Reproduced with permission from Taubenberger and Morens, 2006).

In Sweden, there were 34,374 (5.9 per 1,000 persons) pandemic influenza deaths in the 12 months from July 1918, with a 35% increase in acute pneumonia deaths. This gave 7.1 per 1,000 persons to be the mortality rate for pandemic influenza and acute pneumonia between July 1918 and June 1919 (Holtenius and Gillman, 2014). Karlsson et al. (2014) reported that there were nearly 38,000 deaths due to pandemic influenza overall, which at the time signified approximately 1% of the Swedish population. In Sweden, younger persons experienced higher infection rates and working-aged persons had the highest mortality rate. The 20-40-year-old age group experienced a mortality rate rise of

nearly 200%, and the Swedish life expectancy decreased to 50 years old in 1918 from 59 years in the previous year 1917 (Holtenius and Gillman, 2014). Figure 6 shows the record of influenza deaths in Sweden during Spanish influenza. *“With respect to the number of deaths caused, the Spanish flu is one of the most severe calamities ever to affect Sweden.”* (Karlsson et al. 2014: p.5).

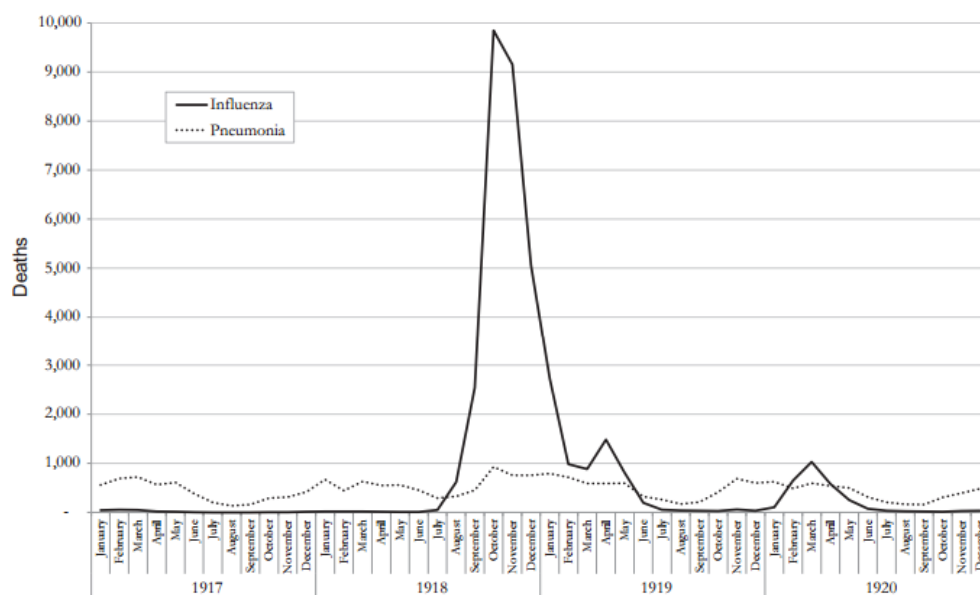


Figure 6: Influenza and pneumonia deaths in Sweden between 1917 and 1920 (Reproduced with permission from Karlsson et al. 2014).

New Zealand experienced higher mortality rates from pandemic influenza in the urban areas of the country (cities and towns) than compared to rural counties. This historical analysis contributed to *“the limited evidence that remoteness provided some protection in past influenza pandemics”* (McSweeney et al. 2007: p. 46). Wilson and Baker described

the impact and how the "1918 influenza pandemic remains the worst single human health disaster in recorded New Zealand history." (2008: p.136). The grey literature search found a report from Christchurch City Library (2015) where it was explained that New Zealand had succumbed to widespread infection by November 1918, and there was uncertainty regarding which ship had brought the influenza virus to the country. Mortality rates were reported as high as 80% in some of the town's populations and in other regions the rates were low.

Pool (1973) reported that the Maori population had a higher incidence of pandemic influenza infection, which was more likely to result in death than the non-Maori population in New Zealand. The crude mortality rate for the Maori population was calculated as 22.6 per 1,000 persons in comparison to 4.5 per 1,000 non-Maori population; with males (27.7 per 1,000 persons) more seriously affected than females (16.3 per 1,000 persons). These numbers are represented in Figure 7. Pool postulated medical availability, pre-existing immunity to influenza and living conditions as factors leading to this difference between the two groups. Other research presents that the Maori population was worse affected, with a mortality rate of approximately seven times that of the non-Maori/European population of New Zealand (Wilson and Baker, 2008). However at the time military personnel based overseas were not included in these rates so this may have skewed the results.

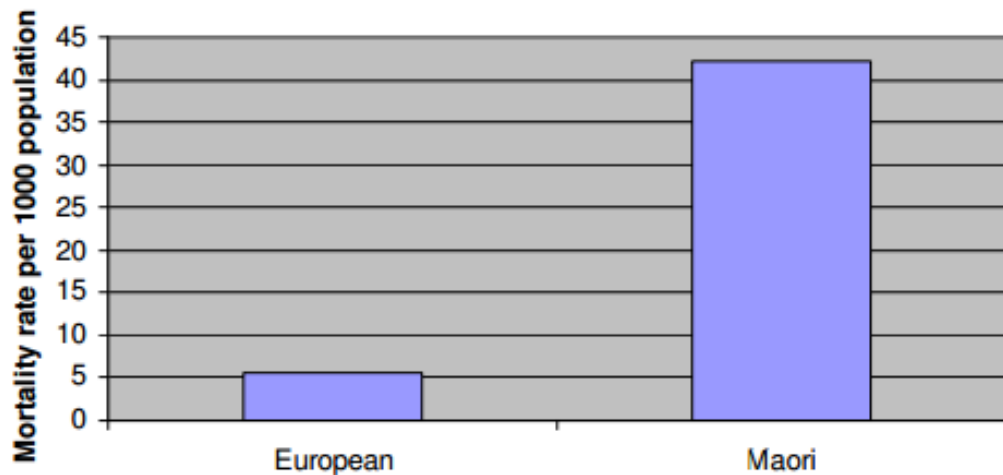


Figure 7: Mortality from pandemic influenza in 1918 in New Zealand (Reproduced with permission from Wilson and Baker, 2008).

The records showed that Japan had three waves according to Yoshikura (2014). The first wave covered August 1918 to July 1919 with 21,168,398 cases and 257,363 deaths reported; the second wave covered October 1919 to July 1920 with 2,412,097 cases and 127,666 deaths; the third wave covered August 1920 to July 1921 with 224,178 cases and 3,698 deaths. The case-fatality rates were determined as 1.22%, 5.29% and 1.65% respectively (Yoshikura, 2014). Conversely, the number of deaths reported elsewhere in the literature differ from Yoshikura (2014), with a lower report of 350,000 deaths by Patterson and Pyle (1991) and higher report of 481,000 deaths by Richard et al. (2009). Johnson and Mueller, and Palmer and Rice, cited 388,000 deaths (Chandra, 2013) which would correspond to Yoshikura's (2014) figure for when the three waves death figures are combined. As explained by Chandra (2013), all these various estimates tend to be lower than other country's reports, and Chandra argues that the

dependence on official health statistics has led to repetitive published underestimations. Through utilising census data, Chandra (2013) puts forward a 4% loss of population (approximately 2 million persons) from the 1918-19 pandemic influenza in Japan, making it more on par with other densely populated countries. Furthermore, Chandra argues that this larger estimate presented shows that *"Japan is not an exception to be studied for possible solutions or measures that might ameliorate the effects of such an epidemic in the future. Rather, its experience is typical of that of other Asian countries for which we have more reliable estimates."* (Chandra, 2013: p.621).

Even in 1918, Singapore was considered a global trading hub and documented two waves of pandemic influenza occurring in June to July and October to November resulting in more than 2,870 deaths (Lee et al., 2007). However, Lee et al., (2007) calculated the excess mortality rate during the pandemic influenza in Singapore to be 7.76 per 1,000 persons, but this was raised to 18 per 1,000 (6,656 deaths) when using Murray et al.'s formula (Lee et al., 2007). Figure 8 shows Lee et al.'s, (2007) calculation of excess deaths in the 1918-19 pandemic influenza in Singapore.

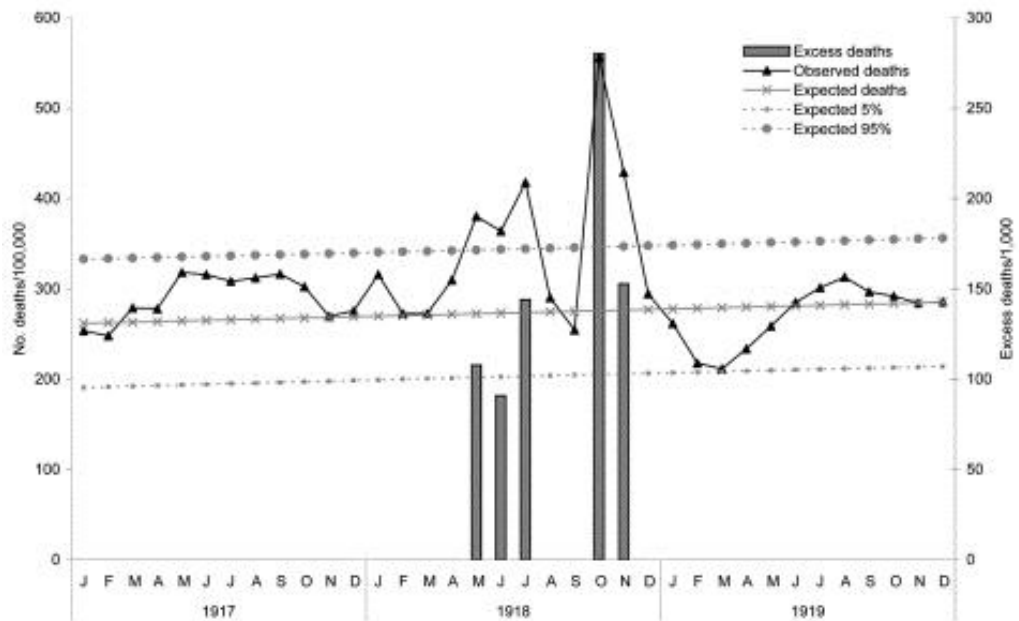


Figure 8: Excess mortality rate in Singapore during 1918-19 pandemic influenza (Reproduced with permission from Lee et al. 2007).

Singapore’s second wave peaked at the end of October with 97.6 per 1,000,000 deaths reported (Lee et al., 2007; Lee et al. 2008). Singapore experienced a mortality rate comparable or higher than temperate countries but lower than neighbouring countries in Asia, as shown in Figure 8 (Lee et al., 2007).

2.3.2.2 1957 Pandemic Influenza ‘Asian Flu’

The second pandemic influenza of the 20th century occurred in 1957, most likely originating from China, and was of the A(H2N2) influenza subtype, termed ‘Asian Flu’. In February 1957, it originated from the province of Yunan in China, spread across China during March, to Hong Kong by April, and

onwards to Taiwan, Singapore and Japan (Potter, 2001; Payne 1958).

By May, infection was reported in Indonesia, India and Australia, and by June, Europe, North America, Pakistan and the Middle East were infected. In July infection reports came from South Africa, South America, New Zealand and the Pacific Islands, and in August large regions of Africa, Eastern Europe and the Caribbean had the novel influenza (Potter, 2001; Payne 1958).

Two transmission routes were identified as across land from Russia to Europe, and from a large international gathering in Iowa, United States. As well as these two events, infection was spread along sea routes. The influenza was considered to have spread throughout the globe in six months from onset, as seen in Figure 9 (Potter, 2001).



Figure 9: Spread of 1957-58 pandemic influenza (Reproduced with permission from Potter, 2001, with study countries labelled).

The information available on the disease pattern within Singapore was limited due to influenza not being of notifiable disease status, and because sections of the population did not engage in Western type medical care (Lim et al., 1957). Payne (1958) noted that Singapore was the first country to notify the World Health Organisation in May of experiencing "*an extensive outbreak of influenza*" and it was believed to have been imported into the country from Hong Kong (Payne 1958: p.29).

Asian pandemic influenza first appeared in Japan on the 10 May 1957 (Sonoguchi et al., 1986). Fukumi (1959a) noted the virus was imported into Japan but from an unknown country, that the first case was recorded in a school in Tokyo and that the epidemic established in large cities first and then spread out across Japan to smaller urban and rural areas.

Singapore reported the first wave of influenza activity lasting the month of May 1957, with a peak in mid-May (Kanagaratnam, 1957), with Japan's timing reported as slightly later in June to July 1957 (Sonoguchi et al., 1986). Sweden reported cases between July 1957 and January 1958 with a peak in November (Skog et al., 2014). Unfortunately, journal article searches focusing on New Zealand only revealed that the epidemic reached New Zealand by July 1957 (Payne, 1958; Oxford, 2000). Influenza H2N2 peaked in October and November 1957 (PHAC, 2010).

Japan reported a second wave between October and December 1957 (Sonoguchi et al., 1986). Canada reported a much delayed second wave during the winter of 1959 (PHAC, 2010). A second wave was not found in the literature search for Sweden, Singapore and New Zealand.

A comparison of the timing of the first cases and waves of the 1957/58 Asian influenza pandemic for the study countries are illustrated in Figure 10. In the figure the star indicates the first case recorded in the literature. The coloured lines indicate the waves with red for first and blue for second waves. Where question marks have been placed on a country line, such as in the example of New Zealand, this indicates that no waves were explicitly found in the literature. This is not to say that no waves were experienced, and in some countries there were reported elevated rates of illness that were not initially linked to pandemic influenza.

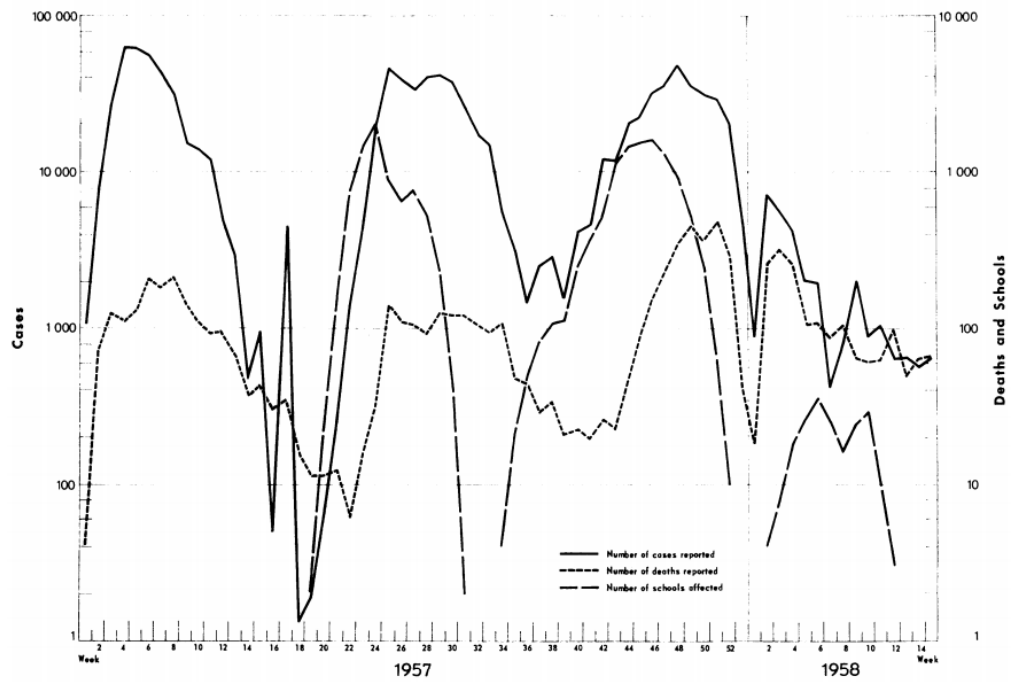


Figure 11: Number of 1957 Asian influenza cases, deaths and schools affected in Japan (Reproduced with permission from Fukumi, 1959a).

Globally, the younger population experienced high attack rates, but the majority of deaths were in the very young and old. It is proposed that the lower attack rate observed in older persons may be due to this group's earlier exposure to the influenza virus (of possible A(H2) subtype) which appeared during the nineteenth century (Monto and Sellwood, 2013; Potter 2001).

Payne (1958) observed that age distribution of Asian flu cases in most countries affected young persons. It was noted that in Bombay, India, 85% of cases were present in people up to the age of 40 years old, and the United States had most cases falling within the five to 19 years age range. Bombay, United

States, Chile and the Philippines all reported very few cases affecting older persons (Payne, 1958).

However, despite the attack rate age distribution, the mortality was most experienced in younger and older persons. It was reported that 38% of deaths in Leningrad were for children aged ≤ 2 years old, 53% of deaths in Manila were < 4 years old, 22% of deaths in Santiago were < 12 months old, 10% of deaths in the Netherlands were < 4 years old, 20% of deaths in Tokyo were < 10 years old (Payne, 1958). It was reported that 22% of deaths in Leningrad were in adults > 45 years old, 11% of deaths in Manila were > 50 years old, 55% in Santiago were aged > 55 years old, 40% of deaths in the Netherlands were in persons aged > 60 years old, $> 50\%$ of deaths in Tokyo were aged > 50 years old (Payne, 1958).

2.3.2.3 1968-1969 Hong Kong Pandemic Influenza

Only a decade later, the third pandemic influenza, A(H3N2) originated from China in 1968. Quickly, Hong Kong reported 500,000 cases in two weeks, and from this, it gained the term 'Hong Kong Flu'. The morbidity rate was likened to the previous 1957 pandemic, but the mortality was found to be lower. Again, as experienced during the previous pandemic influenza, older persons seemed to have some protection from their exposure to earlier similar influenzas, and this theory is supported by the serological link to the 1898 pandemic influenza (believed to be an (H3) subtype) (Monto and Sellwood, 2013; Potter 2001).

The 1968 A(H3N2) Hong Kong influenza pandemic first cases occurred in Asia in July 1968 and arrived in Singapore by August (Potter, 1998). Japan also reported imported cases in August (Fukumi, 1969).

Cases did not take hold in Japan until October 1968, with a wave peaking in January to February 1969 (Fukumi, 1969). Cases peaked in Singapore in mid to late August 1968 (Lee et al. 2008). Canada's first wave occurred in the winter of 1968 and peaked in January 1969 (PHAC, 2010).

Canada's second wave was milder and occurred in the winter of 1970 (PHAC, 2010). European countries typically reported mild first waves and severe second waves, but Canada experienced the opposite pattern (PHAC, 2010). Singapore reported excess mortality between May and June 1970, which Lee et al. (2007) hypothesise may have been due to the second pandemic influenza wave.

No literature on the 1968 A(H3N2) Hong Kong influenza pandemic was found for the Sweden, which may be reflective of the search only including English language sources. However, no literature was found for New Zealand either. The lack of literature for Sweden and New Zealand in regards to the 1968 pandemic influenza may instead be a reflection of the lower severity of disease compared to the previous two pandemics. It is speculated whether or not it was perceived as a 'non-event' in these countries.

A comparison of the timing of the first cases and waves of the 1968 A(H3N2) Hong Kong influenza pandemic for the study countries are illustrated in Figure 12. In the figure the star

In comparison to the previous two pandemics of 1918 and 1957, the 1968 pandemic in Singapore was the least severe. The epidemic lasted just a few weeks; it began at the beginning of August, and the excess mortality rate was calculated as 0.27 per 1,000 persons (Lee et al., 2007). The 1968 Hong Kong influenza in Singapore caused widespread sickness and work absenteeism, but was reviewed as mild and short lasting, and as such no significant public health measures were implemented (Lee et al., 2007, Lee et al., 2008).

2.3.3 Future pandemic influenza predictions

Pandemic influenza predictions prior to 2009 were found in the literature search. For instance, Wilson et al. (2005:P.93) stated: *"Even so, a future influenza pandemic virus strain may be far more virulent and infectious than those of the past, and it would arrive into a society with much higher levels and speeds of intra-country transport."* In addition: *"with the increase in travel and trade, a future pandemic may reach a globally connected city before preparedness plans can be fully activated."* (Lee et al. 2007: p.1056). This demonstrated a commonly held concern about the global interconnectedness of modern day living and the uncertainty surrounding pandemics.

Other literature explained the potential speed of infection transmission of future pandemics. It was found that the pandemics of the twentieth century had completed widespread transmission within 4 to 6 weeks within Singapore. It was

advised that *"future plans must be able to weather this full impact over a short period of time."* (Lee et al., 2008: p.475).

2.4 Pandemic influenza public health management measures

The public health responses to pandemic influenza have been dependent on the discovery of measures at that point in time, as well as factors such as the affordability of measures by nations and how quickly a country is affected by a novel influenza. Historically, early measures included social distancing, border closures and quarantine enforcements. This section shall include country-specific literature referring to instances of public health measure responses to previous pandemics.

2.4.1 Travel restrictions

It has been described by Rice (2005) that the 1918 pandemic influenza rapidly spread along the transport routes of the coasts and rail services and Wilson et al. (2005) put this forward as a failure in New Zealand at controlling the pandemic influenza with public health measures.

Kanagaratnam (1957) reported that during the Asian 1957 pandemic influenza in Singapore, no quarantine measures were taken involving restricting the international movement of ships and aircraft because the disease did not warrant these actions.

Travel restrictions have remained a topic of discussion in pandemic influenza management. Mateus et al. (2014) examined the effectiveness of travel restrictions in delaying influenza spread and found that travel and country border restrictions may delay influenza spread by one week and up to two months. Effectiveness was diminished if measures were not promptly implemented in the early weeks of pandemic influenza. The researchers concluded that these measures were ineffective without the implementation of other public health measures. Restriction may delay, but ultimately not prevent the spread of disease.

2.4.2 Personal protective measures

Nishiura and Chowell (2008) reported that the Kanagawa prefecture in Japan educated the general public about the hazards and transmission of influenza through leaflets and posters during the 1918-19 pandemic influenza. Also, face mask use was recommended to medical staff and the general public. Although Nishiura and Chowell did not go on to mention the effectiveness of these measures, the authors indicated that social distancing of individuals in rural areas of Kanagawa may have been important for minimising the risk of death from infection.

In Singapore during the 1918-19 pandemic influenza, the government and physicians recommended the public to self-isolate themselves in the instance of influenza-like-illness, seek early medical attention, maintain high cleanliness of

public floors and to avoid high people traffic areas (Lee et al., 2007; Lee et al. 2008).

2.4.3 Social distancing measures

In Singapore, it was put forward that visitors to hospitalised patients should be restricted or banned, and during the Spanish Influenza second wave, schools were closed for one week. Early treatment measures typically focused on treating patients' symptoms. For example, during the 1918 pandemic influenza in Singapore, physicians worked in treating patients fatigue and increasing ventilation (Lee et al., 2007). Lee et al. noted that at the time of Spanish Influenza these measures were enacted without evidence of the effectiveness of the procedures, and in the twenty-first century the effectiveness of measures such as school closures remains disputed.

The Coromandel County of New Zealand reported a successful local public health containment measure in 1918. The small isolated town of Coromandel isolated ferry visitors on a nearby island for 24 hours and following a medical examination these visitors were allowed into the town. Travellers by road were stopped by barricades and required a medical certificate to visit the town. At the time, the medical officer reported no cases in the town of 1000 occupants and endorsed strict home isolation of houses in the nearby Maori community with reported cases (Wilson et al, 2005). Wilson et al.'s (2005) analysis found that the European mortality rate was statistically significantly lower in Coromandel County in comparison to the wider area. However, the reduced Maori

mortality rate was not statistically significantly lower in Coromandel County (Wilson et al, 2005).

The social distancing measures of public health officials, not simply the rurality of the Coromandel County, appeared to be the factor responsible for no cases in this example from New Zealand. In contrast, Nishiura and Chowell (2008) found that rurality without social distancing measures was not a protective factor in the Kanagawa prefecture in Japan in the 1918-19 pandemic influenza. The village location had higher incidence compared to cities and towns which Nishiura and Chowell hypothesised this may have been due to the interconnectedness of village communities. The authors noted that rural areas had larger mean household size compared to large towns and cities. Towns and cities were advantageous compared to rural areas in that officials in the Kanagawa prefecture closed factories during outbreaks and imposed individual movement restrictions. Nishiura and Chowell (2008) expected that future pandemic influenza infection risk could be reduced through social distancing protective measures. Whilst villages had the highest morbidity levels, towns and cities had the highest case fatality rate which Nishiura and Chowell (2008) postulated could be due to different demographics e.g. young adults in urban areas, the worse health of persons in urban environments and poverty.

During the 1918-1919 pandemic, influenza was not a notifiable disease in Sweden and as such individuals with influenza-like-symptoms (ILI) were not treated in epidemic specific hospitals outside of cities but rather local hospitals. Without notifiable classification and low mortality rates early on, the health authorities and Swedish Medical Board

reportedly did not implement any strategies to contain the pandemic influenza spread which led to criticism by the Swedish Medical Society (Holtenius and Gillman, 2014).

Canada isolated patients with ILI during the 1918 influenza pandemic, however *"the medical officer of health for the province of Alberta concluded that forced home isolation of patients, posting signs on houses, and "quarantine" (details unspecified) captured only ≈60% of patients in the community because of diagnostic difficulties involving mild cases and failure to notify cases to authorities."* (World Health Organization Writing Group, 2006: p.86). Successful small-scale isolation measures in remote communities have also been reported in Canada by using 1918-19 influenza historical data. However, Sattenspiel and Herring (2003) found that very low mobility rates are required for success.

In the United States, during the 1918-19 influenza pandemic, a number of social distancing measures were attempted. Bootsma and Ferguson (2007) found that a variety of measures were implemented in some United States cities but at different times. Measures included school closures, mask wearing, isolation of the infected and hygiene measures. It was found that the early timing of such measures slowed the localised epidemic and resulted in a notable reduction in mortality rates. However, other United States commenters have expressed how public health measures of this nature in practice proved difficult to implement; primarily as city dwellers did not stay at home. School and work attendance continued, and food shopping and recreational pursuit activities remained. *"In the years immediately following the pandemic, commentators would continue to reflect on the*

difficulty of controlling the urban 'masses' during a public health emergency.” (Tomes, 2010: p.59).

During the Asian 1957 pandemic influenza, “A WHO consultation in 1959 concluded that the 1957 influenza pandemic tended to appear first in army units, schools, and other groups where contact was close. Also noting the reduced incidence in rural areas, the consultation suggested that avoiding crowding could reduce the peak incidence of an epidemic and spread it over many, rather than a few, weeks” (World Health Organization Writing Group, 2006: p.86).

Singapore closed schools between 8th May and 20th May 1957 during the Asian pandemic influenza (Kanagaratnam, 1957). The general public was encouraged to avoid crowded areas through the media and medical centres, and it was observed that cinema attendances dropped at the peak of the epidemic. However, not all persons with ILI symptoms stayed in their homes (Kanagaratnam, 1957).

Interestingly, the WHO consultation in 1959 also discussed the role of schools during the 1957 Asian pandemic influenza and *“concluded, “In the Northern hemisphere at least, the opening of schools after the summer holidays seems to have played an important role in initiating the main epidemic phase” (World Health Organisation, 1959). Despite the propensity of influenza epidemics to be amplified in primary schools (Neuzil et al., 2002), data on the effectiveness of school closures are limited. Apparently no data or analyses exist for recommending illness thresholds or rates of change that should lead to considering closing or reopening schools.” (World Health Organization Writing Group, 2006: p.86).*

2.4.4 Healthcare structure

The United States, as in other countries, put on emergency hospital facilities during the 1918-19 Spanish influenza to provide treatment centres for the sick (Monto and Sellwood, 2013).

Singapore implemented changes in their healthcare structure during the Asian 1957 pandemic influenza. Singapore cut back on elective surgery to free up medical staff to treat influenza patients. The maternal and child health centres and school health centres located across Singapore opened their doors to people presenting with ILI in order to relieve pressure from health services (Kanagaratnam, 1957).

2.4.5 Antivirals

The '*1st Conference on Antiviral Substances*' was held in the 1960s. In 1967, Kates and McAuslan published on the first viral enzyme, the first systematic basis for selective antiviral drugs. In 1969, the '*2nd Conference on Antiviral Substances*' was held which heard that "*amantadine had been shown not only to inhibit influenza virus, but also to cause resistance development (Oxford et al., 1970), later proposed to be a hallmark of selective antiviral effect (Hermann & Hermann 1977).*" (Littler and Oberg, 2006: p.155).

Developments in the area of antivirals launched from infections of herpes (1970s) and HIV (1980s). Over the course

of decades, there has been ongoing research to develop drugs against influenza. The 1960s saw the discovery of amantadine against influenza, particularly in prophylactic use (Dawkins et al 1968). Amantadine was not used extensively, primarily due to the presence of a strong vaccine lobby against chemotherapy, and also, that Amantadine was only effective against some type A influenza viruses (Littler and Oberg, 2006).

The influenza-specific antivirals, Amantadine and the later produced Rimantadine, work against influenza through exploiting the M2 ion channel blockers (Littler and Oberg, 2006). In 1999, the drugs zanamivir and oseltamivir were released which are active against both A and B influenza (Littler and Oberg, 2006; Nguyen-Van-Tam et al., 2014).

Even with the apparent usefulness of these antivirals, wide scale use was not reported at the start of the twenty-first century. *"...sales of oseltamivir in 2002 were only approximately £200 million (which in itself was a 184% increase from the previous year) and factors such as increased vaccination do not explain this poor use of what are good drugs. These sales figures were obtained during an interpandemic period – one may only speculate what the sales could be during a pandemic. However, unless a pandemic could be anticipated or planned for (by stockpiling drugs) it is unlikely that compound supply could keep pace with patient demand."* (Littler and Oberg, 2006: p.159)

More recent research, post the 2009-10 pandemic, has indicated that the use of oseltamivir and zanamivir were effective in prophylaxis treatment (Okoli et al., 2014) and

significantly reduced mortality in hospitalised adult patients (Nguyen-Van-Tam et al., 2014).

2.4.6 Influenza vaccines

Early attempts at injecting an influenza virus into human subjects were first conducted in the United States during the 1930s. The work tested to see if the humans injected with an influenza virus would go on to produce an antibody response. *"This pioneering work was done with A/PR/8/34 (H1N1) and it was observed that neutralizing antibodies developed in serum, peaked after 2 weeks and persisted for up to 6 months."* (Wood and Williams, 1998: p.317). Work in the 1930s in the United States and the UK followed with inactivated influenza virus, however, the results were unconvincing and possibly due to low dosage or inappropriate use of vaccine strains (Wood and Williams, 1998). In the early 1940s, works by Burnett, and Hirst and Hirst et al. sparked exploration into *"...large-scale growth of virus in hens' eggs, purification of virus by adsorption to red blood cells and assessment of vaccine potency by haemagglutination. These techniques were used consistently during the next decade in the quest to demonstrate that vaccines were effective."* (Wood and Williams, 1998: p.317).

In the early 1940s, the United States Army conducted a number of clinical studies using a large number of individuals whereby inactivated influenza A and B was injected, and a comparison control group was monitored. An influenza A epidemic occurred that winter and it was observed that the

control group had ILI 3.5 to 6 times more frequently than the vaccinated group, as well as a greater incidence of hospitalised cases. This was the start of the evidence supporting the effectiveness of influenza vaccination. By 1945, licences for United States companies to produce civilian vaccines were issued. Influenza vaccines were quickly utilised worldwide but the vaccination efforts during the winter of 1947 provided little protection because although there was a great response to the vaccine strain, there was a lack of antibody response to the epidemic strain circulating. This experience led to the incorporation of the previous year strain in the following vaccines, and this practice has continued on in the production of modern influenza vaccines (Wood and Williams, 1998).

During the 1957 Asian pandemic influenza, Fukumi (1959a) reported that several manufacturers in Japan worked towards producing a vaccine after isolating the new influenza virus in May 1957. The new vaccine was ready for the vaccination campaign from November 1957 in a limited amount and this timing corresponded to the second wave peak in Japan. It was reported that most vaccinations were conducted in the months of November and December (Fukumi, 1959a). However, due to the limited early availability of the vaccine, its usefulness during the pandemic was constrained "*as a large proportion of the vaccine was furnished for public use a little too late, it was very difficult to evaluate its protective efficiency or to make a plan for mass vaccination.*" (Fukumi, 1959b: p.355).

Over the years, influenza vaccines enquiry worked towards producing a more concentrated virus and solving the problem of reactogenicity in young children. Over the course of

development, it was discovered that split vaccines produced significantly less febrile reactions. Split vaccines licences were first introduced in 1968 in the United States, and later clinical trials showed that second doses of a vaccine were required for adequate immunogenic response in unprimed individuals; influenza split vaccines have continued to be used (Wood and Williams, 1998). Later scientific developments from split vaccines involved "*the purification of haemagglutinin (HA) and neuraminidase (NA) surface antigens*" (Wood and Williams, 1998: p. 319) resulting in surface antigen vaccines licenced in the UK by 1980. Later vaccine work focused on increasing the virus yield to produce adequate quantity of vaccine (Wood and Williams, 1998).

The history of influenza vaccines demonstrates how influenza vaccines were not a possibility during the 1918-19 Spanish influenza, but has had a minor role to play in just a few communities within a limited number of countries during the 1957 Asian pandemic influenza and the 1968 Hong Kong pandemic influenza. The challenges were to produce enough quantity of new influenza vaccines during these latter pandemics and before nations are heavily infected with the novel virus.

Vaccination timing during pandemic influenza is challenging as it takes six to eight months before the new vaccine is available in large quantities (Leese and Tamblyn, 1998). As such, solutions to this issue have been sought. Pre-pandemic influenza vaccines have been explored in more recent years. From 2007, some countries stockpiled pre-pandemic vaccines of A(H5N1) as an insurance and preparation measure in response to the threat of avian influenza at that time.

A(H5N1) was a novel virus and had a high mortality rate in those infected, and therefore, there was a great concern for the consequences if it managed to develop into a pandemic (Carrasco and Leroux-Roels, 2013).

Until now, this chapter that introduced the concepts of interpandemic and pandemic influenza, discussed the pandemic events up until the twentieth century and provided an overview of past public health management measures. The following section is concerned with the timeline of events of the 2009-10 influenza A(H1N1) pandemic in the five study countries.

2.5 Pandemic Influenza A(H1N1)pdm09

This section will describe the time, place and person characteristics of the epidemiology of pandemic influenza A(H1N1)pdm09 (also referred to as A(H1N1) and the 2009-10 influenza A(H1N1) pandemic), with special reference to the study countries individual epidemiological patterns and national responses. This section is structured in chronological order and spans from March 2009 until August 2010. It chronicles the first cases of (H1N1) influenza, WHO pandemic phases, response measures adopted, epidemiological data and the study country vaccination programmes.

2.5.1 Novel influenza virus emerges

On 18th March 2009, surveillance within Mexico observed outbreaks of ILI in parts of the country (World Health

Organization, 2009a). The area of Veracruz experienced an outbreak and, in accordance with the International Health Regulations, the then Mexican General Directorate of Epidemiology reported the occurrence of respiratory illness to the Pan American Health Organization on 12th April 2009. On 17th April, Mexico enhanced surveillance across the country in response to the increased cases and hospitals were requested to report and sample patients presenting with respiratory illness symptoms (Centers for Disease Control and Prevention, 2009a). Meanwhile in the United States in southern California, two unrelated children presented with respiratory illness and the CDC testing found that the infections were caused by influenza A(H1N1) of swine origin on 17th April. It was reported that this *"new strain of swine influenza A (H1N1) is substantially different from human influenza A (H1N1) viruses, that a large proportion of the population might be susceptible to infection, and that the seasonal influenza vaccine H1N1 strain might not provide protection"* (Centers for Disease Control and Prevention, 2009b: p.1). Laboratory confirmation of several cases in Mexico on April 23rd also detected influenza A(H1N1) virus of swine origin and a case definition was created detailing suspected, probable and confirmed case criteria (Centers for Disease Control and Prevention, 2009a). The Canadian National Microbiology Laboratory identified the new influenza A(H1N1) virus in the samples provided from Mexico and these were found to be identical to the California samples. On the 25th April, the WHO Director-General Dr. Margaret Chan announced an international public health emergency (World Health Organization 2009d).

Retrospective data analysis in Mexico covering 1st March to 30th April found 1,918 suspected, and 97 confirmed cases and 84 deaths (Centers for Disease Control and Prevention, 2009a). The majority of these cases were from Mexican hospital reports therefore underestimating can be assumed. At the end of April, all Mexico City schools were closed, airport advice was provided to travellers about ILI symptoms, and encouragement was given regarding seeking fast medical attention, mass media circulated personal hygiene messages, masks and alcohol sanitizers were distributed, and social distancing measures encouraged (Centers for Disease Control and Prevention, 2009a).

The Mexico and United States developments fulfilled the initial WHO criteria for an influenza pandemic in April 2009. By 29th April, the WHO Director General released a statement declaring that the influenza pandemic alert had escalated to a Phase 5. At this time, it was recommended that country pandemic influenza preparedness plans were brought into action and national surveillance systems monitored for ILI outbreaks. This Phase 5 announcement not only initiated international and national pandemic response activities, but it also signalled a time of action to pharmaceutical companies regarding antivirals and vaccines, and charitable organizations tasked with providing resources to developing countries (World Health Organization, 2009a).

2.5.2 The arrival of first cases and initial responses in study countries (and the UK)

The first H1N1 case announced in Canada occurred on the 23rd April 2009, shortly after the first case was reported in Mexico (Brien et al., 2012). New Zealand reported the first southern hemisphere case of pandemic A(H1N1) virus on the 25th April 2009. It was imported by, and detected in, a group of high school students returning from Mexico. These identified cases triggered the New Zealand Influenza Pandemic Plan (NZIPP) into activation (Jennings, 2013).

On the 27th April 2009, the United Kingdom reported the first European cases in two people returning to Scotland from Mexico, and the WHO announced Pandemic Phase 4. The Foreign and Commonwealth Office advised for only essential travel to Mexico on the 27th April 2009; this advice ceased on 15th May 2009 (Hine, 2010). By 28th April, Canada had reported six cases (Centres for Disease Control and Prevention, 2009c). The UK implemented their first school closure on the 29th April 2009. Soon after, the UK reported their first confirmed cases of human-to-human transmission on 1st May 2009 (Hine, 2010).

The first two confirmed cases occurred in Sweden in early May 2009 (World Health Organization 2009d), and a 'search-and-contain' strategy was adopted (Örtqvist et al. 2011). At a similar time, Japan reported their first laboratory confirmed cases of pandemic A(H1N1) virus at Narita International Airport through the quarantine screening programme in people returning from Canada on the 9th of May 2009. These passengers were isolated in hospital for seven days as per the

Japanese Governments plan (Shimada et al. 2009). The first non-travel related laboratory-confirmed cases were identified on 16th May in high school students (one case in Osaka prefecture, four in Hyogo prefecture). Further outbreaks were reported in neighbouring regions, and this resulted in over 4,200 school closures (accounting for approximately 650,000 students) in these areas for one to two weeks, which is reported to have decreased the number of new laboratory-confirmed cases (Shimada et al. 2009). The first A(H1N1) case in Singapore was identified on 26th May 2009 in a Singaporean female student aged 22 years old who had travelled from New York City (Cutter et al. 2010). This first detected case occurred one month following the announcement of the first cases of novel A(H1N1) influenza in California (Cutter et al. 2010).

Singapore adopted a containment strategy on 27th April 2009 which involved active screening of travellers from affected countries with respiratory symptoms, and all confirmed cases were admitted to the Communicable Disease Centre. Liang et al. (2009) reported the first ten imported cases clinical characteristics which were identified between 26th May and 3rd June 2009. It was discovered that nine cases had travelled into Singapore from the United States, six were found to have travelled specifically from New York, and the one other case had travelled from the Philippines. Patients reported the onset of symptoms a mean of 1.4 days after arrival in Singapore and received emergency department treatment at a mean of 2.7 days. Symptoms included fever (90%), cough (70%), coryza (40%), sore throat and myalgia/arthralgia (30%). All received antiviral treatment of oseltamivir had uncomplicated courses

of influenza, and clinical features appeared mild for influenza A(H1N1) (Liang et al. 2009).

Over the course of the following weeks, the WHO communicated to the rest of the world the Swine influenza A(H1N1) laboratory confirmed cases and deaths in other countries. The UK implemented a policy of containment between May and June 2009 to try to slow the spread of the virus and to gather more information (severity, transmissibility, risk groups). This included measures such as swab testing of individuals with suspected A(H1N1), antiviral treatment of individuals meeting case definition without laboratory confirmation, contact tracing and close contact antiviral prophylaxis, school closures, self-isolation of community cases, etc. (Hine, 2010). By 12th May, there were 330 confirmed cases to the WHO in Canada, seven cases in New Zealand, four cases in Japan and two cases in Sweden (World Health Organization, 2009d) in the countries of interest to this research project. By 20th May 2009, these confirmed cases increased to 496 (one death) in Canada, nine in New Zealand, 210 in Japan and three in Sweden (World Health Organization, 2009e). All Canadian provinces and territories had reported cases of A(H1N1) by the 11th June 2009 (Brien et al., 2012).

2.5.3 Pandemic influenza declared

The WHO declared that the A(H1N1) virus had reached Phase 6 pandemic status on the 11th June 2009 (World Health Organization, 2009b), which made it the first influenza

pandemic of the 21st century. This was based on the evidence of a novel influenza strain of nearly 30,000 confirmed cases in 74 countries which were sustained by human-to-human and country-to-country transmission (World Health Organization, 2009b). By 11th June 2009, there had been 144 deaths, four of which were in Canada and the majority were in Mexico. The average age of a Canadian case was 17 years old, and 90% of the confirmed infections in Canada had no recent travel history (World Health Organization, 2009f) indicating extensive community transmission.

2.5.4 Surveillance and response measures

New Zealand made A(H1N1) influenza a notifiable and quarantinable disease on 30th April 2009 (Jennings, 2013). In comparison, the Swedish Communicable Disease Act made influenza A(H1N1) virus a notifiable disease on the 15th May 2009 (Örtqvist et al. 2011). In both incidences, these countries made the disease notifiable within just a few days of it being discovered within their nations. Perhaps in future, this notifiable disease listing could be implemented before the first national cases emerge, based on intelligence gathered and shared from other countries. This would require mandatory reporting in line with WHO phase announcements.

New Zealand had prepared six phases of strategy response in the NZIPAP and, once activated, containment measures were implemented in the early weeks. This involved border management (the 'Keep It Out' campaign) and cluster control (the 'Stamp It Out' campaign) strategies between 25th April

and 22nd June. At the end of June 2009, New Zealand switched strategy to the 'Manage It' phase of the response. The extensive containment measures are believed to have delayed community transmission of A(H1N1) by six weeks (Jennings, 2013).

Auckland International Airport conducted a screening programme for influenza A(H1N1) in airline passengers between 27th April and 22nd June 2009 at the direction of New Zealand's Ministry of Health. Air passengers travelling from influenza A(H1N1)pdm09 infected countries where community transmission had occurred were screened, and a screening procedure was followed. Screening was increased to all passengers from any country as of 29th April 2009. If the cabin crew became aware of unwell travellers during a flight, a notification prior to landing was made so that public health officials could meet the aircraft and triage the travellers. A scripted health message was read by cabin crew to air passengers requesting that if they had symptoms to notify staff. All disembarked passengers left through a public health checkpoint where ill travellers were recommended to take up screening. Public health officials also observed passengers and targeted those with overt symptoms. Some thermal screening was utilised but not for every passenger. Unwell individuals were screened by nurses and medical officers to see if their illness met the definition of a suspected case. Where case definition was met, nasopharyngeal swabs were taken, oseltamivir offered and isolation instructed. Reverse transcription PCR was conducted in order to confirm infection (Hale et al. 2012).

The quiet lead-in period to June 2009 enabled the New Zealand Emergency Management Steering Group (EM-SG) to review surveillance, front-line capacity, diagnostic services and primary and secondary health care, whilst following the global situation. Importantly, this time enabled key public health messages to be released regarding hygiene and social distancing (for example, staying home when unwell) and when to seek medical advice. These public health messages were delivered by radio, television, regular press releases, posters and websites. In addition, 'Healthline', a free telephone service triaged patients and provided health information (Jennings, 2013).

New Zealand enhanced influenza surveillance from April, and this measure was in accordance with the NZIPAP plan. There were two existing sentinel general practitioner systems which reported epidemiological and virological data for disease burden calculations, identifying circulating virus strains and real time A(H1N1) pandemic information. The EM-SG used the MoH newly developed HealthStat system which reported ILI data electronically each week from >100 general practices. As influenza A(H1N1) was a notifiable disease, EpiSurv recorded all laboratory confirmed cases and cases from primary and secondary care. With the introduction of the 'Manage It' phase in June, changes to virological testing occurred, as testing was only conducted on severe cases, so an underestimation is probable (Jennings, 2013).

The Ministry of Health in Singapore created an A(H1N1) Taskforce to provide public health control measures and supervise the nation's medical services during the 2009-10 influenza A(H1N1) pandemic. The Taskforce included experts

in policy, clinicians, infectious disease specialists and other experts (Tay et al. 2010). Alterations were made to the Infectious Diseases Act to make it compulsory for all confirmed 2009-10 influenza A(H1N1) pandemic virus cases to be reported to the Ministry of Health within 24 hours of diagnosis on 27th April 2009 (Tay et al. 2010, Cutter et al. 2010). The timing of this alteration corresponded to the WHO Phase 5 announcement.

In 2008, Singapore had nearly 10 million tourist arrivals which were approximately double the size of the Singaporean population (Department of Statistics Singapore, 2008). This demonstrates Singapore's global connections through tourism, business and education, and reflects the Ministry of Health's expectation during pandemic influenza planning that a novel influenza virus would enter the country by travel very soon after being discovered in another country.

Singapore had three phases for the management of pandemic influenza (Hospital Influenza Workgroup Singapore, 2009):

1. Preparedness phase – no A(H1N1) cases identified in Singapore
2. Containment phase – imported cases or small clusters
3. Mitigation phase – sustained community transmission

When the World Health Organization pandemic alert level was Phase 3, the Singaporean DORSCON (Disease Outbreak Response) was Green Alert Level 1, when WHO was increased to Phase 4 the Singaporean DORSCON was raised to Yellow Alert Level, and then when WHO announced Phase 5, the Singaporean DORSCON became Orange Alert Level. However,

when the virus was believed to be less severe than first thought, Singapore reduced the DORSCON to Yellow Alert Level on 7th May 2009 but continued enhanced influenza surveillance, border control, and ensured that laboratory, infection control measures and clinical management protocols remained in place and were reviewed (Tambyah and Lye, 2009).

Case-fatality ratio (CFR) is used in calculating the pandemic severity index (PSI), and the PSI is a pre-pandemic planning tool that has a scale 1 to 5. Singapore also uses the FluAid modelling software from the United States CDC, which uses CFR to calculate the hospitalisations, outpatient visits and deaths from pandemic influenza in order to estimate the potential impact to health services. This FluAid software was used by the Ministry of Health in Singapore during pandemic preparations. It was calculated using data from the 1968 pandemic and 25% attack rate in the population of 4.2 million, which projected that there would be 1,900 deaths and 11,200 hospitalisations. Transmissibility could be reduced if public health interventions such as quarantine, isolation, social distancing and treatment were used (Hospital Influenza Workgroup Singapore, 2009).

The Singaporean Ministry of Health adopted a national containment strategy between 25th April and 18th June 2009 which was a period when imported cases were identified in individuals that had previous overseas travel history (Ang et al., 2010). Travellers who had arrived from infected countries and who were identified by thermal screening at border entry, in addition to individuals displaying acute respiratory illness symptoms, (Chan et al., 2010) were referred to Tan Tock

Seng Hospital (TTSH) Communicable Disease Centre, the designated screening centre for A(H1N1) (Leo et al. 2010). The suspected and confirmed cases were isolated to individual rooms and infection control procedures were followed (Ang et al., 2010). National mass media broadcasted that any persons who were at risk of 2009-10 influenza A(H1N1) pandemic infection due to travel history, fever, and respiratory systems, should attend TTSH for screening. Testing included collecting combined nasal and throat swab specimens (Leo et al. 2010).

Before the first positive case of 2009-10 influenza A(H1N1) pandemic was identified in Singapore, 300 individuals underwent screening for influenza infection between 27th April and 24th May 2009. 244 reported returning from an affected country with respiratory illness, and 56 had symptomatic contacts. H3N2 subtype influenza was found in 24%, seasonal subtype A(H1N1) was found in 1.6%, influenza B was found in 2.7%. Common symptoms included fever (92.9%), cough (82.4%), sore throat (57.6%) and rhinorrhoea (62.4%). The median age was 36 years, and some had co-morbidities (14.7%) (Leo et al. 2010).

Community contact tracing was undertaken with A(H1N1) infected patient's contacts of 24 hours before symptom onset to isolation, with contacts offered chemoprophylaxis and quarantine measures to avoid local transmission. Healthcare workers in Accident and Emergency wards and the isolation facility had N95 respirators, eye protection, gloves and gowns. When community transmission was identified, all healthcare workers working in clinical areas wore surgical masks from 19th June 2009 (Ang et al., 2010).

Tan Tock Seng Hospital continued the enhanced surveillance through the emergency department, and it was not until the week beginning 14th June 2009 that A(H1N1) influenza was detected in the community, after which the incidence rate rapidly increased until 25th July 2009 week. By 25th July 2009 the A(H1N1) influenza cases had suppressed the seasonal circulating influenza viruses, and Tan Tock Seng Hospital emergency department had seen 838 individuals with confirmed A(H1N1) influenza. The patients had a median age of 22 years, and common symptoms of fever (85.3%), cough (87.2%) and sore throat (55.4%) (Leo et al. 2010).

The Hospital Influenza Workgroup Singapore (2009) recommended the following management strategies against 2009-10 influenza A(H1N1) pandemic in hospitals:

- Basic infection control measures (hand hygiene, cough etiquette, personal protective equipment (PPE), airborne and contact precautions for staff)
- Masks (surgical, high filtration, powered air purifying respirator (PAPR) (specific situations)
- Gown and gloves
- Eye protection (specific situations)
- Environment infection control (disinfecting contaminated surfaces)

The study by Chen et al. (2010) found that healthcare workers at the Tan Tock Seng Hospital who treated confirmed A(H1N1) pandemic influenza cases, were at no greater risk of contracting A(H1N1) than individuals in the community. The authors indicate the high level of pandemic preparedness and infection control measures as likely factors which minimised

the incidence rate and indicated that they were effective. However, whilst healthcare workers, in general, were not at greater risk, the authors found that nurses were disproportionately affected which indicated that specific occupations had increased risk, and future pandemic preparedness should account for this (Chen et al., 2010).

Sweden had various surveillance and reporting systems in use during the influenza pandemic. SMI reported the systems and methods used to gather surveillance information concerning the pandemic influenza, which covered (Swedish Institute for Communicable Disease Control, 2011):

- Population-based surveillance (Sjukrapport)
- Web search
- Telephone advice line
- Sentinel surveillance
- Sentinel laboratory testing
- Mandatory Laboratory Reporting of Influenza A(H1N1)
- Aggregated Voluntary Laboratory Reporting of Denominator Data
- Mandatory Clinical Reporting – All Cases of Influenza A(H1N1) (13May09 to 15Jul09)
- Mandatory Reporting of Hospital Admissions (16Jul09 to present)
- Intensive Care Data (Partly retrospective reporting, 14Dec09 to 30Apr10)
- Mandatory Reporting of Deaths and Official Death Registry
- Sero-epidemiology
- Virus Characterisation
- Vaccine Coverage

Following early illness characterisation from Mexico and United States, authorities and experts in Sweden predicted that 25% of the country's population could contract the novel swine influenza. The NBHW evaluated that there was considerable risk that A(H1N1) influenza would spread to Sweden, and, therefore, A(H1N1) influenza became a notifiable disease under the Swedish Communicable Disease Act on 15th May 2009 (Swedish Civil Contingencies Agency & Socialstyrelsen, 2011).

When it was announced that a new influenza A(H1N1) virus had emerged and the WHO had made announcements, the Ministry of Health, Labour and Welfare of the Japanese Government began surveillance for cases of this new infection. This accompanied the existing system which monitored seasonal influenza strains. People who travelled from the affected countries (Mexico, United States and Canada), went through entry screening from 28th April 2009 (Shimada et al. 2009). Those displaying ILI had a rapid diagnostic test for influenza performed by a quarantine officer, and positive results for influenza A required a polymerase chain reaction (PCR) test for the 2009-10 influenza A(H1N1) pandemic virus. The Quarantine Law and PIPAP recommended that confirmed cases and close contacts of confirmed cases were isolated either in hospital or at home for approximately seven days (Shimada et al. 2009). Suspected and confirmed case definitions were developed for the monitoring of the epidemiological disease patterns.

On 29th April 2009 the Japanese National Institute of Infectious Diseases released the developed "*primers for conventional and real-time RT-PCR for the detection of*

A(H1N1)v virus”, and by 4th May all 75 prefectural and municipal public health institutes and quarantine stations became ready to perform conventional and real-time PT-PCR testing (Shimada et al. 2009: p.1).

A review of Canada’s surveillance system during the influenza pandemic reported that Canada had one of the world’s leading surveillance systems for monitoring patient pathways covering hospitalisations, ICU admissions and mortalities for health analysis. However, there were limitations to the system during the influenza pandemic because the data was not generated in real time (Eggleton, 2010). During a public health emergency, such as an influenza pandemic, public health professionals require real-time data to make informed decisions for an effective response.

The independent provincial and territorial areas of Canada have led to variations in surveillance across Canada. For instance, in terms of monitoring vaccination rates Quebec province collects this information, whereas the province of British Columbia does not (Eggleton, 2010). This disparity of information collection across Canada respects the independent decision making in provinces and territories. However, this approach would be a challenge for public health professionals responding to an emergency, and could place limitations on the effectiveness of response in some areas.

New Zealand identified community transmission of A(H1N1)pdm09 in the week of 16th June 2009 within three main population areas, and it became no longer possible to contain all the clusters. Public health services and virus diagnostic services were reportedly stretched to full capacity.

The national response was moved into management phase on 22nd June. At this time, the disease was mainly in the large population areas and had not reached some small population centres in the country (Jennings, 2013).

In the management phase, those cases with moderate to severe disease were the priority. Antivirals were used for cases, particularly for individuals at risk of severe outcomes, and antiviral prophylaxis treatment was no longer continued. Cluster control community measures were no longer implemented and 'Flu Centres' were opened to manage ILI patients in some District Health Boards (there are 21 DHBs in New Zealand). In some instances, pharmacists could prescribe oseltamivir through remote telephone triaging (Jennings, 2013).

Community mitigation measures covered complete or partial school closures (<20 schools or childcare centres formally closed, others were closed due to high absenteeism levels) and education to individuals about transmission reduction. The school holidays in New Zealand occurred between 4th and 19th July 2009 which could have played a part in transmission reduction as it occurred at the peak of disease reports (Jennings, 2013). School closure due to influenza goes back many years in Japan. In 1958, Japan enacted a law (School Health Law) which enables school authorities to close schools when infectious diseases are experienced, which includes ILI disease. For example, a class may be closed if 5 to 10 absentees are reported, and a school may be closed if 2-3 classes are closed (Shimada et al. 2009).

Canada has two antiviral stockpiles, one owned, funded and held by the federal government for use in an influenza pandemic and the other provided by provinces and territories. The national supply came into use "*during the H1N1 pandemic and that its use increased significantly between the first and second waves resulting in a reduction in complications, hospitalizations and death.*" (Eggleton, 2010: p.35). Roche Canada, the Tamiflu antiviral supplier, noted that half a million doses were prescribed over the eight months of May and December 2009 in Canada. When the influenza pandemic emerged, it was initially professed that "*antivirals would only be effective if administered within 48 hours of the onset of symptoms. However, it was later determined that they should be administered even after that time period, despite perhaps having a diminished effectiveness.*" (Eggleton, 2010: p.35).

In 2007, the UK's Department of Health and the Cabinet Office published '*Pandemic Flu: A national framework for responding to a pandemic*' and prepared an antiviral stockpile with the capacity of treating half the UK's population. However, when the 2009-10 influenza A(H1N1) pandemic emerged, the Prime Minister Gordon Brown announced on 29th April 2009 that the antiviral stockpile would be increased to cover 80% of the UK's population. This raised the 33.5 million dose stockpile to 50 million doses (Hine, 2010). The UK had approximately two months of containment policy period between May and June 2009 where antiviral treatment was prescribed based on case definition, not laboratory confirmation.

In Singapore, all influenza patients belonging to high-risk groups were recommended for antiviral treatment, as well as patients without associated risk factors that were hospitalised

with ILI. Treatment was recommended within the first 48 hours of symptom onset time window. Antiviral treatment recommendations covered both containment and mitigation phases of a pandemic according to the pandemic severity index rating (Hospital Influenza Workgroup Singapore, 2009).

Lee et al. (2010) evaluated the effectiveness of public health measures in three groups (normal, essential, healthcare) of military personnel in Singapore. The authors found that enhanced surveillance, isolation involving home leave and small group segregation measures were effective in limiting influenza transmission in closed environments.

Singapore ran a campaign to educate the public about 2009-10 influenza A(H1N1) pandemic. The campaign included "*the importance of personal hygiene and social responsibility*" e.g. temperature control (Lee and Pang, 2013: p.218). Front-line healthcare workers in Singapore were given personal protective equipment, visitor numbers were regulated and temperature screening used, all of these measures may have reduced healthcare workers risk of infection (Lee and Pang, 2013).

Singapore wanted the response to be in proportion to the pandemic severity, so the Asian Youth Games 2009 took place in Singapore as planned, which ran alongside mitigation strategies, contingency planning and communication (Lee and Pang, 2013).

The Singaporean Ministry of Health altered the containment strategy to that of mitigation on 25th June 2009 due to evidence of community transmission. Individuals with chronic

medical conditions and those at high risk of complications were the only screened people for A(H1N1) and antiviral treatment reserved for these individuals. Not all A(H1N1) confirmed cases were admitted to hospital, only those who required care (Ang et al., 2010). During the mitigation phase, the response policy emphasis was that of outpatient care (Chan et al., 2010). Contact tracing was stopped when this phase was introduced. Between 19th June and 21st July 2009, Tan Tock Seng Hospital treated 689 confirmed A(H1N1) patients (Ang et al., 2010).

2.5.5 2009-10 influenza A(H1N1) pandemic disease activity

The epidemiological knowledge is limited by national surveillance practices and the proportion of cases of A(H1N1) that presented to health services. The typical structure of patient presentation to health services is well demonstrated in the influenza experience of disease population pyramid by Watson and Pebody (2013). Figure 13 is an adaption of the pyramid explained by Watson and Pebody.

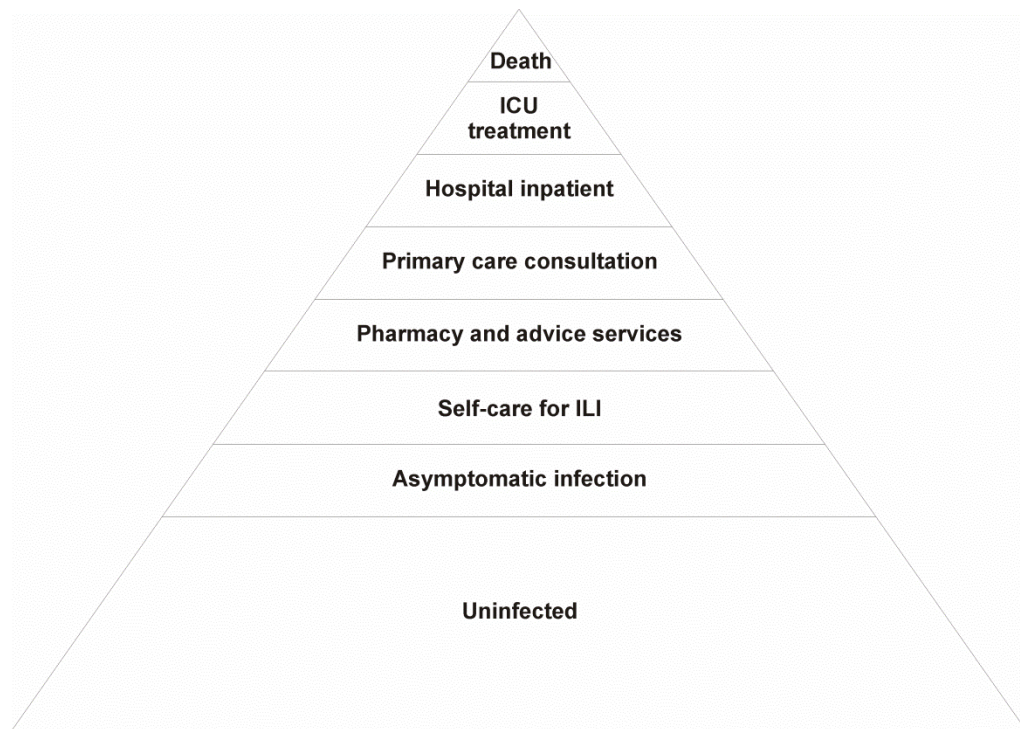


Figure 13: Influenza experience of disease population pyramid.

The pyramid shows an example of one million persons during a pandemic influenza wave; 80% do not contract influenza infection, 10% have asymptomatic infection, 8% treat influenza themselves, and the remaining top part of the pyramid represent the 2% of the population that engage with health services with varying healthcare needs. Much of the information in this section corresponds to the top of the pyramid: mortality; intensive care unit patients; hospital admissions. A broad timeline approach has been taken from May 2009 to August 2010.

By 20th May 2009, Canada had reported their first fatality due to A(H1N1) influenza (World Health Organization, 2009e).

On the 4th June 2009, Japan had reported 401 laboratory confirmed cases in 16 of the 47 prefectures, of which 357 cases were in the two prefectures of Osaka and Hyogo. Many cases date of onset occurred between 14 and 20 May. Shimada et al. (2009) reported that none of the cases by 4 June 2009 had reports of pneumonia/respiratory failure, and no ventilator support was reported. Only three of the cases required hospitalisation for medical reasons (due to these cases having underlying medical condition), however, 135 cases were hospitalised for isolation as part of the Quarantine Law and the Pandemic Influenza Preparedness Action Plan of the Japanese Government. By the 4th June 2009, it was considered that the severity of disease was similar to that of seasonal influenza. However, it was expected that the winter season would bring more severe cases (Shimada et al. 2009).

The UK reported 1,000 influenza cases on the 13th of June 2009, shortly after the WHO Pandemic Phase 6 announcement and soon after reported their first A(H1N1) fatality on 15th June 2009 (Hine, 2010). By the 17th June 2009, the number of global cases reported neared 35,000 across 74 countries and included 163 fatalities. Whilst in the UK, the number of cases reported had doubled since the previous week to 1,582 in two geographic regions (Hine, 2010).

Singapore's first locally infected case of 2009-10 influenza A(H1N1) pandemic virus was reported on 18th June 2009 indicating community transmission, with 80% of local cases reporting between 27th May and 9th July 2009 experienced by 10-29-year-olds (Cutter et al. 2010). On 18th July 2009 a 49-year-old man with co-morbidities was the first 2009-10 influenza A(H1N1) pandemic virus death case in Singapore.

There were no reported deaths in pregnant women during the pandemic (Cutter et al. 2010).

In Singapore's first 50 adult confirmed cases of 2009-10 influenza A(H1N1) pandemic virus, 44% of people were aged between 20 and 29 years old, and the cases had a median time of 3 days from symptoms onset to hospital admission. Of these first 50 cases, 50% were female, all had travelled into Singapore, and 62% were Singaporean residents. Symptoms reported by patients included fever (90%), respiratory symptoms (92%), gastrointestinal symptoms (4%), temperatures $\geq 37.8^{\circ}\text{C}$ (56%). Only 46% of patients met the influenza-like-illness case definition provided by the United States CDC, so the use of active screening and testing of travellers resulted in more confirmed case. All were admitted to the Tan Tock Seng Hospital (Singapore's Communicable Disease Centre) between 26th May and 18th June 2009 and received antiviral treatment involving oral oseltamivir 75mg twice daily. Patients required two negative consecutive combined nasal and throat swabs >6hours apart before hospital release. All patients recovered, and the mild symptoms were compared to other common influenzas (Chan et al., 2010).

In Singapore, the first locally infected case of pandemic A(H1N1) virus was reported on 18th June 2009 indicating community transmission, with 80% of local cases between 27th May and 9th July 2009 experienced by 10-29-year-olds (Cutter et al. 2010). In the first few weeks in Japan, 74% of confirmed cases were in people aged between 10 and 19 years old making the median age 16 years old. Nearly all cases had clinical symptoms of fever, and most had cough, however,

only clinical symptom information was available for 217 of the confirmed cases. Of these 217 cases, 90% received antiviral prescriptions of either oseltamivir or zanamivir (Shimada et al. 2009).

A government review of Canada's response to the pandemic reported that Canada had two waves; the first wave during spring with a peak at the beginning of June 2009 and the second wave during autumn with a peak at the beginning of November 2009. Overall, Canada had 40,185 laboratory confirmed cases, of which 8,678 were hospitalised, of whom 1,473 cases were admitted to ICU and 60% needed ventilation. 428 people died, creating a mortality rate of 1.3 per 100,000 population (Eggleton, 2010).

The Singaporean Ministry of Health required hospitals to provide daily admission information on severe cases of A(H1N1) which resulted in Intensive Care Unit (ICU) treatment from the 4th July 2009, reporting epidemiological, demographical, symptoms and hospital management of patients in reports. Chien et al. (2010) reviewed all confirmed A(H1N1) ICU cases between 4th July and 30th August 2009 admitted to Singapore General Hospital. In total, 15 patients were cared for in SGH ICU with a range ICU length of hospital stay of between two and 50 days, aged between 34 and 76, admitting diagnosis were pneumonia (n=7), heart disease (n=5), sepsis (n=1), bronchitis (n=1), upper respiratory tract infection (n=1), males (n=9)/females (n=6); all received oseltamivir antivirals with one having oseltamivir and then amantadine. In total, two patients died (Chien et al., 2010).

In Sweden, the first wave peaked in epidemiological week 29 with 179 laboratory confirmed cases mostly (80%) from overseas travel. The second wave peaked in week 36 with 197 laboratory confirmed cases found and the timing occurred at the end of August, which is when a new school year commenced, and many adults returned to work following summer vacation (Figure 14) (Swedish Institute for Communicable Disease Control, 2011).

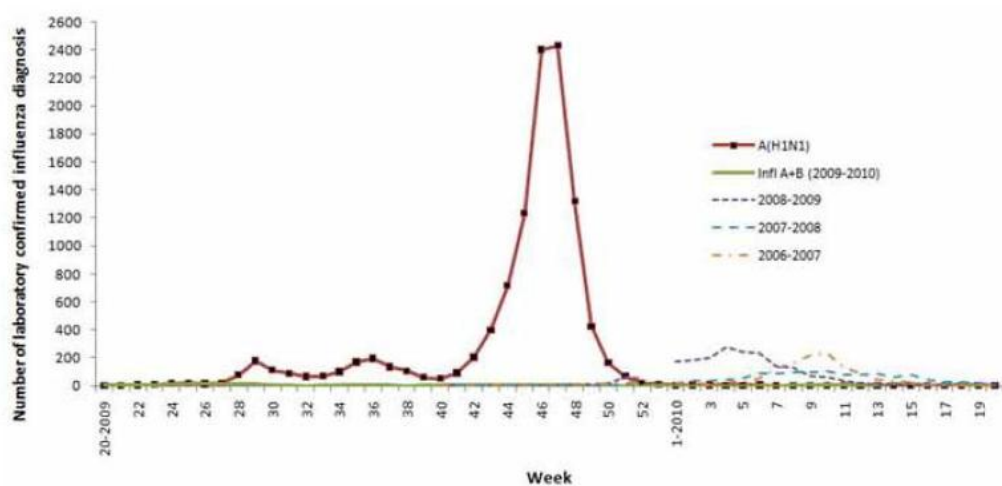


Figure 14: Weekly influenza reporting between 2006 and 2010 (Reproduced with permission from Swedish Institute for Communicable Disease Control, 2011).

In New Zealand, there had been 3,179 notifications (74.5 per 100,000 population) of A(H1N1) influenza, with 98% of these as laboratory-confirmed cases by late August 2009. 972 of these cases were hospitalised and 114 admitted to ICU. In total, 16 died of pandemic influenza as the primary cause. During this time, there was significant geographical variation of hospitalisation cases with 0.0 per 100,000 in the Wairarapa

district compared to 52.9 per 100,000 in the capital city Wellington (Baker et al. 2009).

New Zealand's first wave of 2009-10 influenza A(H1N1) pandemic occurred between April and December 2009. Influenza activity rapidly increased during June 2009, peaked in July and then fell back by August 2009, spanning an eight week period (Jennings, 2013). In this time, 3,211 laboratory confirmed cases were reported, with 1,122 hospitalisations and 48 deaths (Bandaranayake et al. 2011). A seroprevalence survey estimates that 18.3% of the national population were infected in the first wave, including infection of one-third of children (Bandaranayake et al. 2010).

Sweden abandoned the search-and-contain strategy which had been in place to delay the spread of influenza in the country on the 15th July 2009 and adopted a mitigation strategy instead, aiming to protect the most vulnerable population groups, as the disease could not be stopped from spreading (Swedish Civil Contingencies Agency & Socialstyrelsen, 2011). Children and teenagers returned to school in August, and this was associated with a small increase in reported cases. However it was not until October that the pandemic cases rapidly increased (Figure 15) (Örtqvist et al. 2011).

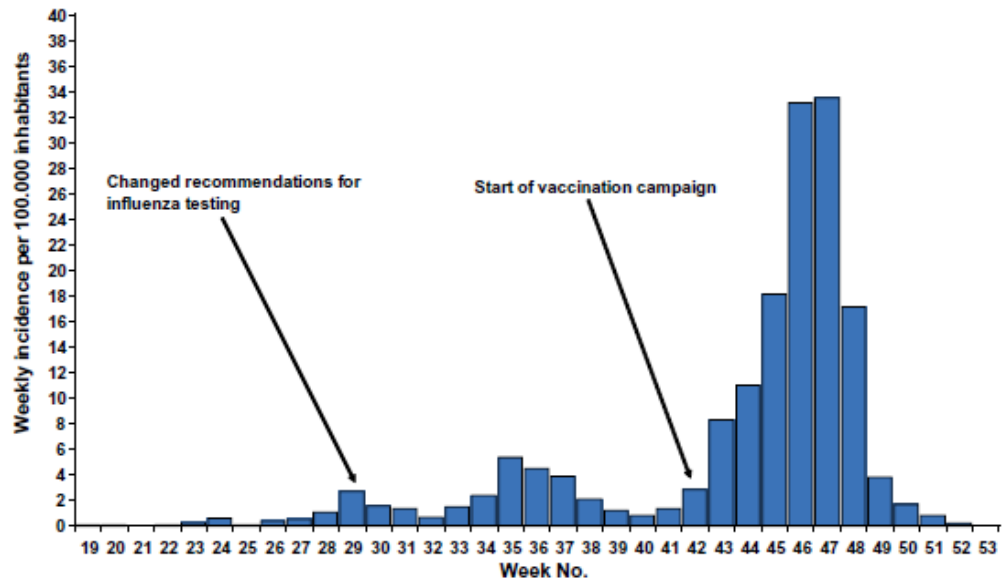


Figure 15: Weekly incidence of A(H1N1) in Stockholm county, Sweden (Reproduced with permission from Örtqvist et al. 2011).

From the 5th October, the number of cases reported rapidly increased. Cases firstly affected school children, then infants and young adults, then middle-aged people, and later older people. Overall, the 2009-10 influenza A(H1N1) pandemic predominately affected children and young adults in Sweden. During 2009, Sweden had 11,000 laboratory confirmed cases, with nine cases reported in Spring 2010 and this was five to ten times higher than seasonal influenza. Of the 11,000 people, 1,600 required hospitalisation and 135 required ICU treatment. In total, 31 deaths were reported, of which 23 deaths were people from risk groups and two fatalities were children. Sweden reported lower pandemic fatalities compared to other countries; the October 2009 vaccination program is argued to have contributed to this outcome. 60% of the national population were vaccinated against A(H1N1)

influenza. The virus in Sweden reportedly spread from north to south, and by the time the disease reached southern Sweden a larger proportion had been vaccinated (Swedish Civil Contingencies Agency & Socialstyrelsen, 2011).

The Swedish Association of Local Authorities and Regions (SKL) and the National Board of Health and Welfare funded the Swedish Association of Anaesthesia and Intensive Care to electronically collect a national register of people with laboratory-confirmed influenza A(H1N1) that required ICU treatment during the pandemic. These parties also identified further cases from reviewing information held with the Swedish Institute for Communicable Disease Control. Only adult cases were included in the study (Brink et al. 2012). Between August 2009 and February 2010, 136 influenza A(H1N1) cases required ICU treatment in Sweden, which was an incidence of 1.5 per 100,000 inhabitants. For the Brink et al. study (2012), 126 (95% of ICU influenza A) cases were used. It was identified that ICU admission had an uneven geographical spread, with a higher incidence in the northern region (3.3 per 100,000 inhabitants in the four most northern healthcare regions) compared to central and southern regions of Sweden (1.2 per 100,000) (Brink et al. 2012).

The characteristics of the 126 ICU patients in Sweden included a median age of 44 years with just 7% of patients over 65 years old, 56% were male, co-morbidities were identified in 41% of cases, and obesity in 39% which is double that of the national Swedish adult population (Brink et al. 2012). The Brink et al. (2009) study found similar patient characteristics for age and risk factors (cardiorespiratory diseases, diabetes mellitus, haematological malignancies, obesity, pregnancy)

that had been published in other studies. Also, they reported that the 11% mortality risk within 28 days was comparative to other countries similar to Sweden.

The Brink et al. (2012) study found that ICU patients were treated with non-invasive ventilation (NIV) (59%), with two-thirds of NIV receiving patients having to be converted to invasive ventilation. Interestingly, they also reported that 56% of admitted patients had firstly presented to a health-care centre with flu symptoms and that antibiotic prescriptions (54%) were far more often prescribed than antiviral oseltamivir prescriptions (5%). The authors were unable to determine whether this was a drug prescription reluctance on behalf of the outpatient services or if the oseltamivir treatment were typically highly successful in preventing critical illness and thus did not lead to these cases presenting to ICU.

Brink et al. (2012) reported that 1.5 per 100,000 Swedish residents required ICU treatment during August 2009 and February 2010 which was comparable to Denmark but different to ICU reports by Australia and New Zealand of over double this incidence. Brink et al. (2012) refer to Sweden's timing, availability and high uptake of the pandemic vaccine as a possible explanation for a reduced need for ICU treatment.

Towards the end of 2009 in Japan, 85 confirmed deaths were reported by the 1st December 2009, with 27% of these in the 0-14-year-old categories (Kamigaki and Oshitani, 2009).

New Zealand's second wave in 2010 coincided with the country's usual influenza season, with cases peaking in August

(Figure 16). Between January and middle of October 2010, there were 1,768 laboratory confirmed cases, with 732 hospitalisations and 15 confirmed deaths (Figure 17) (Bandaranayake et al. 2011).

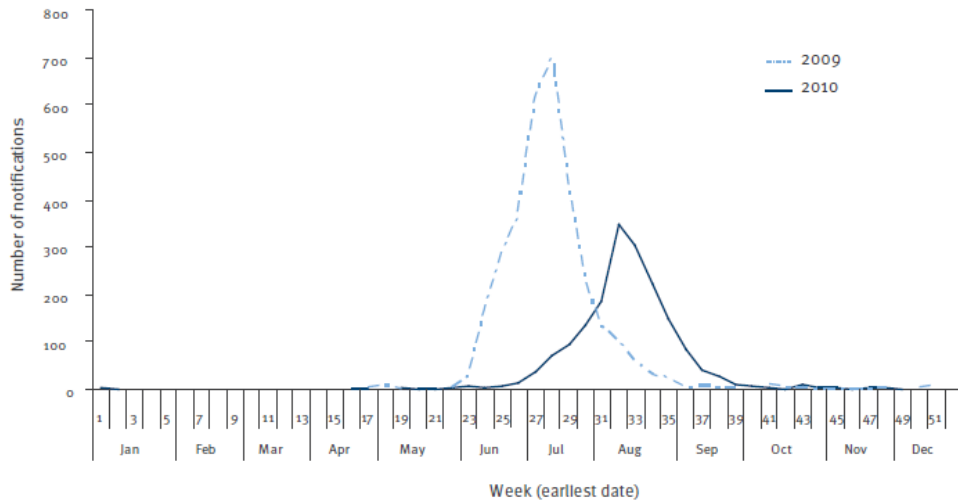


Figure 16: Influenza A(H1N1) 2009 pandemic notifications in 2009 and 2010 in New Zealand (Reproduced with permission from Bandaranayake et al. 2011).

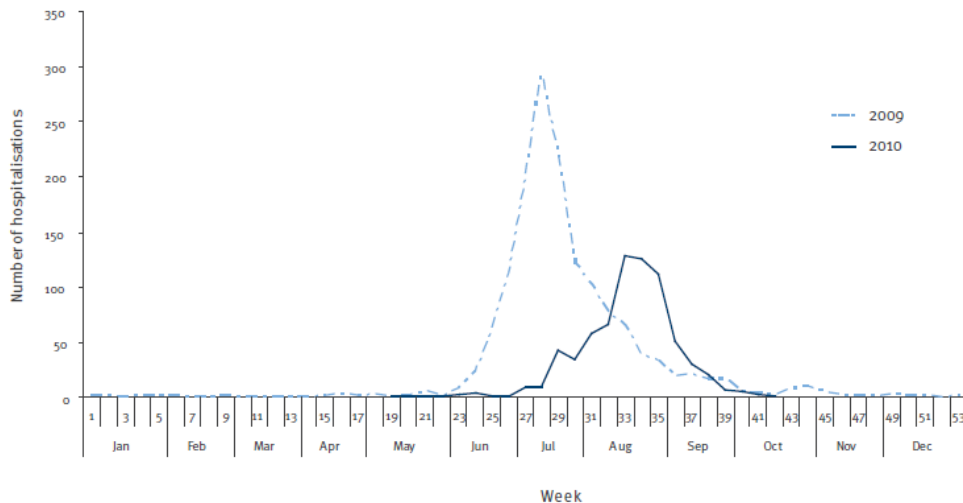


Figure 17: Influenza A(H1N1) 2009/10 pandemic hospitalisations in 2009 and 2010 in New Zealand

(Reproduced with permission from Bandaranayake et al. 2011).

There have been reports that remote and isolated communities in Canada experienced higher incidence and more severe disease outcomes than urban populations. Hospitalisation rates during the first wave varied, with reports from Nunavut of 2.44 per 1,000 in comparison to 0.033 per 1,000 population in Ontario. Similarly, Nunavut had ICU admission rates of 0.20 per 1,000 whereas Ontario had 0.0056 per 1,000. These populations have a differential prevalence of health conditions, including diabetes, pregnancy, and morbid obesity, which previous research has focused on for providing an explanation of differing severity of the 2009-10 influenza A(H1N1) pandemic. The northern territories have predominately aboriginal populations compared to the provinces. Research by Mostaço-Guidolin et al. (2012) suggests that there was differential transmissibility of infection, with the remote and isolated communities in the territories experiencing more affected individuals and faster spread. The authors postulate that this may be due to environmental and demographic factors. For instance, Nunavut has a low average age of 23 years old with only 2.7% of the population being >65 years old and a high average number of people per household. This low average age may have meant that these communities lacked the buffering effect of pre-existing immunity, as well as crowded living conditions which may have provided the opportunity for the spread of infection (Mostaço-Guidolin et al. 2012).

By the 18th March 2010, 457 UK deaths had been reported (342 in England, 69 in Scotland, 28 in Wales, 18 in Northern

Ireland) (Hine, 2010). The WHO reported 18,449 deaths in 214 countries by 1st August 2010 (World Health Organization, 2010a).

When the WHO announced on the 10th August 2010 that the world was now in the post-pandemic period, the WHO referenced that some countries, such as New Zealand, would still be dealing with A(H1N1) transmission. In August 2010, New Zealand reported that there was a lot of regional variation and at that time cases were localised in the centre of the North Island. By August 2010, there had been 332 hospitalisations for laboratory confirmed A(H1N1), 46 ICU admissions and 10 fatalities in 2010 (Hunt, 2010).

By using publically data available on the FluNet website, the five study countries have been included in the graph in Figure 18. The graph reflects the 2009-10 influenza A(H1N1) pandemic cases reported in the study countries. Whilst Canada and Sweden reported the highest rates of cases per 100,000 persons in the Autumn of 2009; this may, in fact, indicate a surveillance and notification bias. This highlights the difficulty of data reporting during pandemic influenza and the challenges posed to international organisations reporting on the global epidemiological situation, as well trying to make comparisons between nations. Some countries may have scaled back their reporting before the WHO announced that the pandemic influenza was technically over, and this may be reflective of their national disease activity or resources.

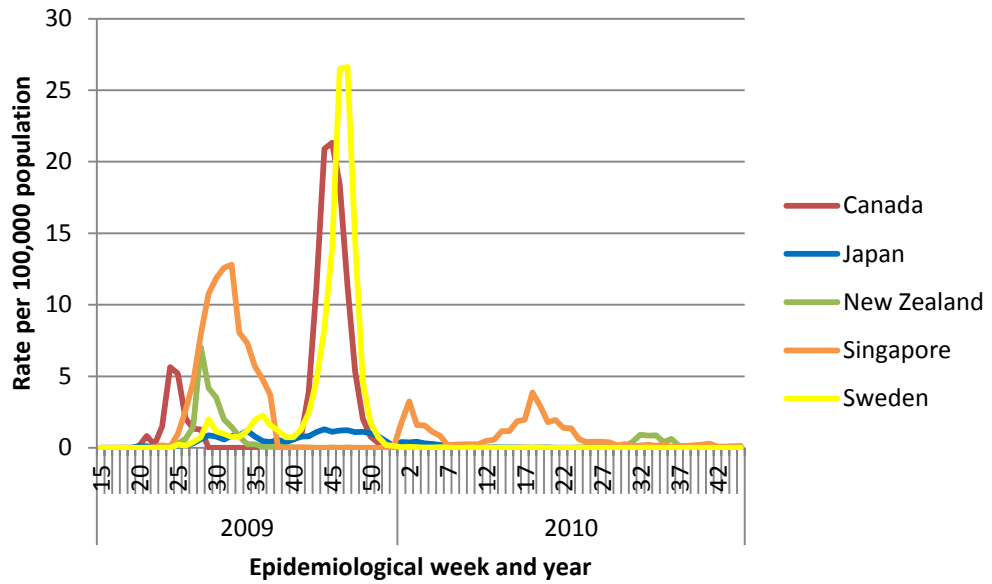


Figure 18: 2009-10 influenza A(H1N1) pandemic cases detected in study countries (data sourced from FluNet World Health Organization, 2013)

2.5.6 2009-10 influenza A(H1N1) pandemic vaccination

During early May 2009, Ministers in the UK decided ahead of the WHO Phase 6 announcement that the UK would secure A(H1N1) vaccines to cover 45% of the population. The advance-purchase agreements for vaccines were triggered when the WHO raised the pandemic Phase to 6 on 11th June 2009 (Hine, 2010). Following the Phase 6 Pandemic Alert announcement the Ministers in the UK agreed to purchase enough A(H1N1) vaccines for 100% of the population. On 26th June 2009, 132 million doses of A(H1N1) vaccine was contracted with GlaxoSmithKline and Baxter Healthcare (Hine, 2010).

The UK began their vaccination programme in October 2009 and rolled it out in phases. Phase One began on 21st October

2009 and prioritised front line health care workers and at-risk patients. Phase Two commenced on 19th November 2009 for children aged between 6 months and 5 years old (Hine, 2010).

Canada secured a pandemic influenza domestic vaccination supply contract in 2001 to source enough coverage for the entire Canadian population in the event of a novel influenza. The order for the number of doses was made once the novel influenza had emerged. Canada requested 50.4 million doses, based on the need for two doses per person and an uptake of 75% of the population. However, as the same experience shared by other countries, it emerged over the course of the influenza pandemic that one dose would suffice to provide protection, so Canada reduced their initial order with this information (Eggleton, 2010). Therefore, Canada had enough vaccines for the entire population.

On the 16th of September 2009, Canada published their A(H1N1) vaccine priority (pregnant women, health care workers, persons based in remote community locations, persons aged <65 years old with chronic conditions, children aged between 6 months and 5 years old) in preparation for the launch of their vaccination campaign roll out. At the beginning of October, a media sensation regarding a First Nation reserve in northern Manitoba broke. A community health professional had ordered a supply of body bags which was perceived as preparation for 2009-10 influenza A(H1N1) pandemic outbreak, but it was emphasised by the Health Minister that this was not related to the pandemic management. At this time, a poll of Canadians reported that approximately 33% intended to have A(H1N1) vaccination,

which was a reduction from 45% a few weeks early (Canadian Pharmacists Journal (no author listed), 2009).

Canada distributed 2 million doses of A(H1N1) vaccines to the provinces and territories on the 19th October and on the 21st October the vaccine was approved by Health Canada for use. At this time, the largest disease activity was reportedly underway in the British Columbia (western region of Canada) and a localised second wave was present. New Brunswick (eastern region) was purportedly the first province of Canada to begin vaccinating people and initially priority access was provided to pregnant women and persons located on reserves (Canadian Pharmacists Journal (no author listed), 2009).

Sweden received the inactivated AS03-adjuvanted monovalent vaccine (Pandemrix®) against pandemic influenza from GlaxoSmithKline and in the middle of October 2009, the first doses were distributed for Sweden's mass vaccination campaign. The timing corresponded with the beginning of the major peak of pandemic influenza in the country. At the start of the campaign, it was recommended that everyone receive two doses of the vaccine: 0.5mL for persons 13 years and older; 0.25mL for children aged between 3 and 12 years. Children with chronic conditions aged between 6 months and 3 years old were offered the vaccine, but this was expanded to include all children this age four weeks into the campaign. **Error! Not a valid bookmark self-reference.** shows the age distribution of the delivered campaign in Stockholm County (Örtqvist et al. 2011). Inhabitants of Sweden were offered the vaccine for free or at low cost (Brink et al. 2012).

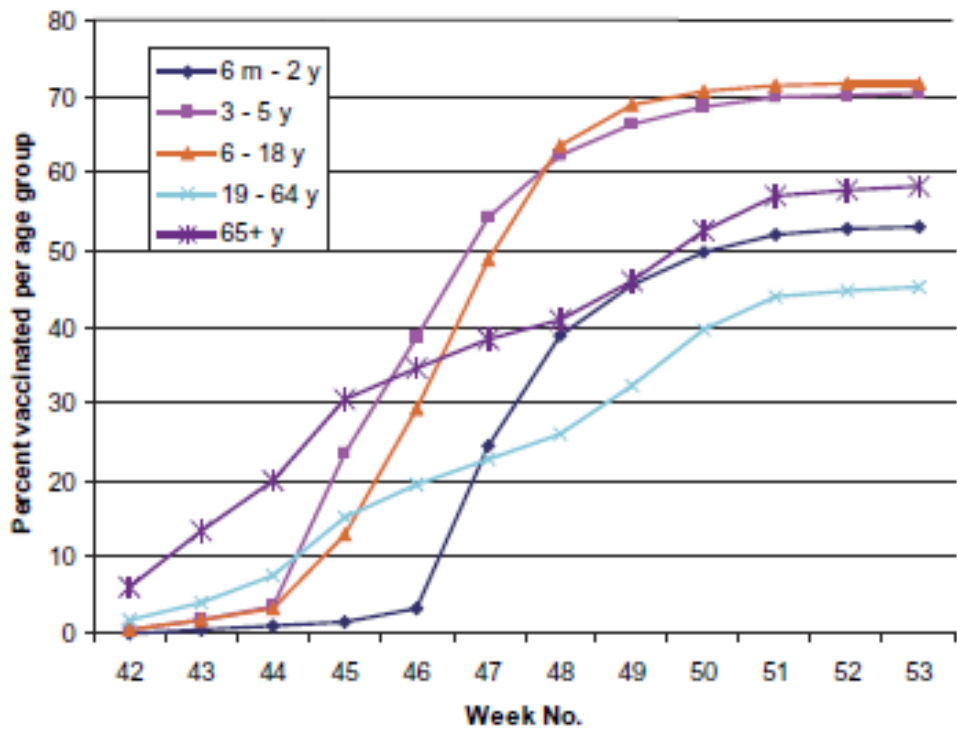


Figure 19: Cumulative percentage of Stockholm county population which received pandemic vaccine dose in 2009 by age groups (Reproduced with permission from Örtqvist et al. 2011).

The vaccination campaign uptake was reported in Stockholm County which accounts for 2 million inhabitants (approximately 22% of Sweden’s population). The majority of the uptake was in medical risk groups, especially in the first few weeks of the campaign; in pregnant women the take up was 80%, and was 100% in people with chronic diseases by week 50 (Figure 20). By the end of 2009, 52% of the Stockholm County population had received one dose or more of vaccine (Örtqvist et al. 2011).

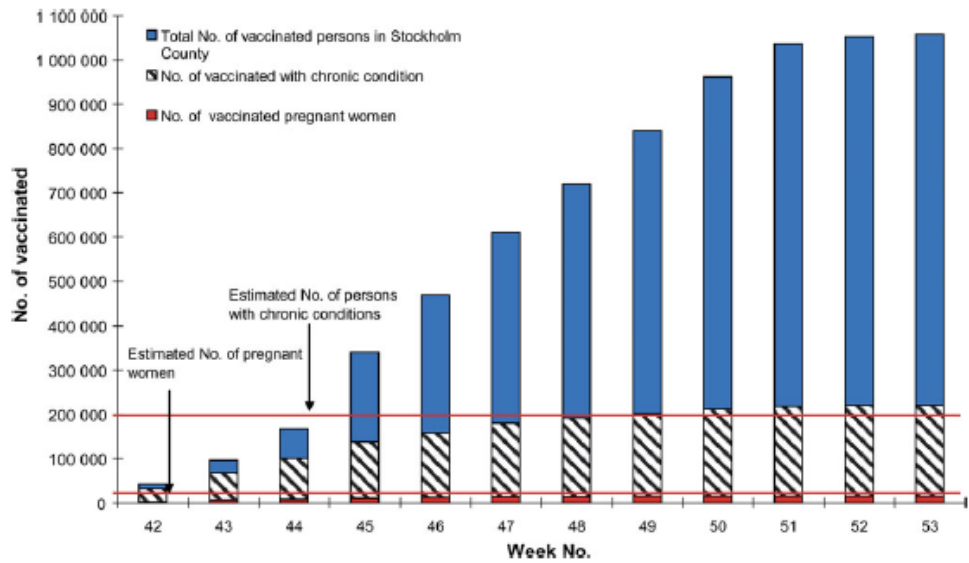


Figure 20: Cumulative number of people vaccinated from the start of the vaccination campaign until the end of 2009 by priority groups and total in Stockholm county (Reproduced with permission from Örtqvist et al. 2011).

During 2009, when 52% (n=1,051,316) of Stockholm County population received the vaccine, there were 2,594 diagnoses of influenza A(H1N1) in people aged over 6 months of age, of which 11% (n=285) were hospitalised, and 0.4% deaths (n=11). Of the 2594 diagnoses, 7% (n=188) were in people that had received the vaccination, of which a small group (n=25) required hospital care, however, none of these vaccine failure patients died (Örtqvist et al. 2011). Örtqvist et al. (2011) conclude that the monovalent AS03-adjuvanted influenza vaccine was highly effective, with 87%-95% effectiveness over the vaccine campaign weeks.

The Swedish Institute for Communicable Disease Control statistics indicated that approximately 50% of the national

population received a minimum of one dose of Pandemrix® vaccine by December 2009 (Figure 21), and this gradually rose to 60% by February 2010 (Brink et al. 2012; Socialstyrelsen, 2011).

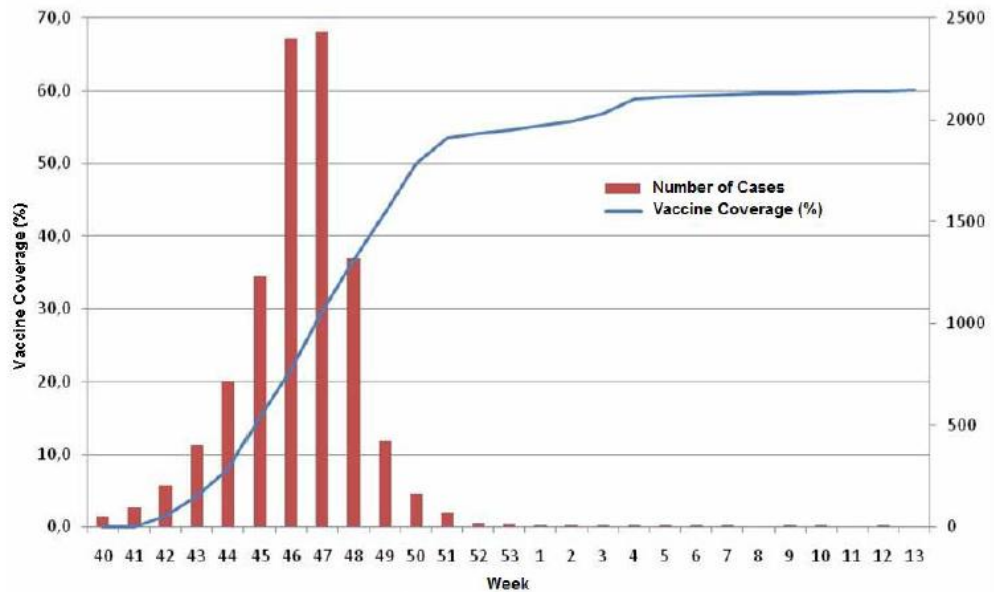


Figure 21: 2009-10 influenza A(H1N1) pandemic disease activity and vaccination coverage in Sweden (Reproduced with permission from Swedish Institute for Communicable Disease Control, 2011).

Singapore purchased the greatest number of pandemic monovalent vaccine doses per capita in South-east Asia at 25,560 per 100,000 (Gupta et al. 2012). In December 2009, it was reported in a media article that Singapore had purchased two vaccine products; 700,000 doses of Panvax® (with 300,000 extra doses expected to be delivered) and 300,000 doses of Pandemrix®. At this point in time, 405,000 doses had been used. The Singaporean Ministry of Health

recommended that pregnant women had the Panvax® dose for safety because it did not contain adjuvant (Vaughan, 2009).

Japan was not able to instruct mandatory pandemic influenza vaccination under the Japanese Vaccination Law, due to the novel influenza virus emerging and the time required to produce a sufficient number of vaccinations for the population. Therefore, vaccination was centred on emergency measures, not the Vaccination Law, and led by the national government with the support of prefectures, municipalities and medical institutions. Nationally there was a standard vaccination programme, but this could be amended according to individual prefectures situations. Four Japanese manufacturers produced the pandemic vaccines; one produced 10ml vials and the other three provided 1ml vials (Shobayashi, 2011).

The Japanese vaccination campaign commenced in November 2009. Japan had to prioritise the vaccines as in the early stages of development, supply was limited, but this increased over time. Vaccinations began with pregnant women, persons with chronic illnesses, children ≤ 5 years old and people aged $65 \geq$ years old. The A(H1N1) vaccine became widely available to all in January 2010 (Yi et al., 2011). However, a low uptake was reported nationally. 99.7 million doses were not used, and this accounted for 81.8% of the total influenza vaccines ordered (Wada and Smith, 2013).

New Zealand's vaccination campaign resulted in approximately 1.05 million people receiving the vaccination by the end of June 2010. This amounts to one-quarter of the country's population (The ANZIC Influenza Investigators, 2011).

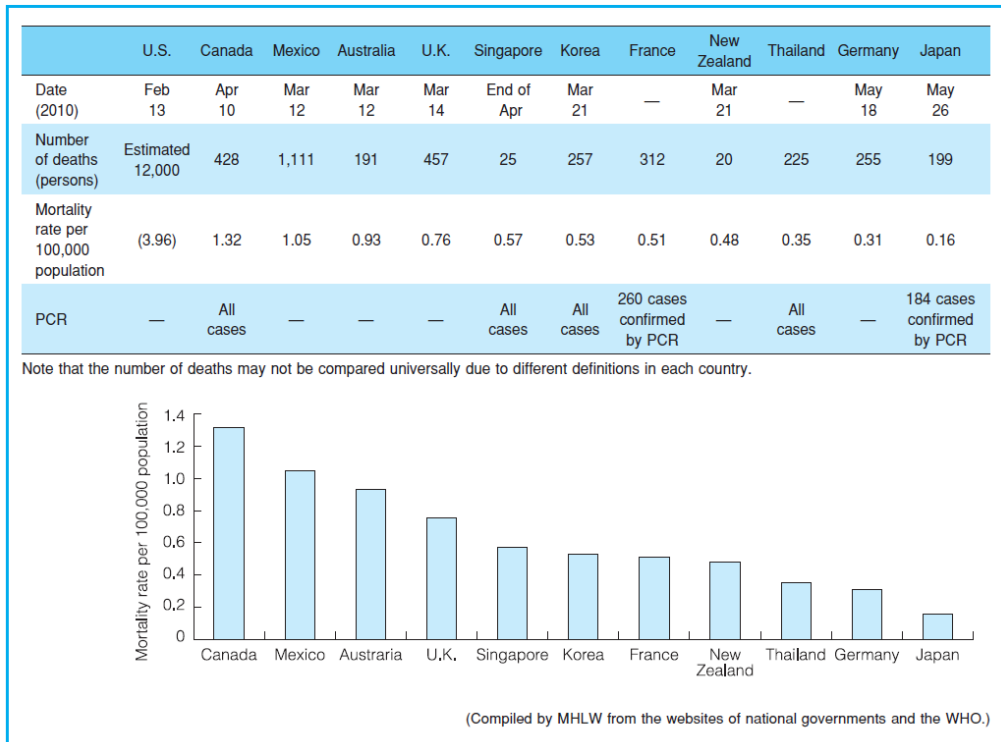


Figure 22: Japanese Ministry Health Law and Welfare source showing country comparisons of 2009-10 influenza A(H1N1) pandemic death rates from 2009 (Reproduced with permission from Shobayashi, 2011).

All study countries except Sweden are highlighted in this graph from Japan showing an international comparison of mortality rates from pandemic influenza A(H1N1) (Shobayashi, 2011).

2.5.7 Pandemic declared over

On the 10th August 2010, the WHO released a press report stating that the world had now entered a post-pandemic phase due to changes in the levels and patterns of A(H1N1) influenza transmission (World Health Organization, 2010b).

2.5.8 Chapter summary

This chapter introduced interpandemic and pandemic influenza, discussed the pandemic events up until the twentieth century and provided an overview of public health management measures. The main components of this chapter were the experiences of the five study countries of Sweden, New Zealand, Japan, Singapore and Canada and greater weight was given to the public health measure of vaccine use. The focus of the five study countries and vaccine use was explained in the previous introduction chapter.

This chapter also provided an overview of the 2009-10 influenza A(H1N1) pandemic in the five countries included in the research project. The WHO pandemic phases were provided in chronological order of events during 2009-10. Information about reports of cases, hospitalisations and fatalities have been provided as well as the various response measures attempted. Towards the end of the discussion, the chapter focused on the study countries vaccination programmes. The chapter was structured by country comparisons, although it was difficult to build a complete picture for comparison due to data record differences. For instance, countries stopped collecting 2009-10 influenza A(H1N1) pandemic data at different dates and the record keeping quality varied between countries.

This chapter has provided the necessary background to move the discussion on to the research methodology of this thesis.

3 Research Methodology

This chapter discusses the methodology and methods used in this project. The first section on methodology begins with the rationale for the thesis and the comparative nature of using the study countries to find similarities and differences in addition to cross-cutting themes. The appropriateness of selecting a qualitative enquiry is explained, as well as the administrative anthropology approach taken in this project. This first section finishes with a discussion on the quality of qualitative research.

The second part of the chapter discussion includes the study methods. It begins with the core policy areas focused upon in the interviews, and the sampling of the study countries is explained. The last part of the chapter explains the data collection and analysis undertaken.

3.1 Methodology

At the beginning of this thesis, when the research was at the proposal stage, it was intended that an international study would be conducted. Thus comparing and contrasting countries formed the foundation of the research approach. The intention behind this funded research was for several countries to be selected. After undertaking the country sampling approach (outlined towards the end of this chapter) and where access was successful, Sweden, New Zealand, Japan, Singapore and Canada were included. The research was

concerned with asking questions about four types of public health measures implemented in each country. These four measures included the extent of use of antiviral drugs, pandemic vaccines, non-pharmaceutical measures and wider societal issues during a pandemic influenza response. As explained in the introduction chapter, vaccine use formed the focus of this thesis at a later date, but the methods are reflective of including all four public health measures and indeed the data collection has included all. Therefore, with the desire to conduct research that was comparative in nature and asking questions about pandemic influenza response, it was found that the best way to do this was to use an approach using comparative health policy and qualitative interviews coupled with documentary analysis of available records.

3.1.1 Comparative element of the research

The comparative element of this research project is important and has been incorporated in the design, data collection, analysis, and discussion. Bryman (2004) discussed how comparative research design can be utilised in both quantitative and qualitative research and that this design frequently lends itself to cross-national research whereby explanations are sought through the examination of similarities and differences in various nations.

The use of qualitative methods offers a reflexive and in-depth understanding of the complexity of policy making. Where just one case is used in health policy analysis, there is the danger that the analysis will simply provide a descriptive account. The

comparison element provides further depth of explanations and generalisability to the dynamics of policymaking and provides an approach to structure qualitative analysis. This allows for the transferability of frameworks that are applicable to not one but a range of cases: *"...comparison therefore presupposes analytical frameworks that surpass the specific case so that the cases to be compared can be interrogated in relation to each other, allowing the search for both similar and different dynamics (Bradshaw and Wallace, 1991)."* [...] *"[T]he term comparative health policy traditionally refers to comparisons across countries, states or nations."* (Wrede, chapter within Bourgeault, Dingwall, and De Vries, 2013: p.89). Within each country, there are different contexts, but it is useful to identify cross-cutting 'transnational' themes.

The textbook by Blank and Burau (2014) regarding comparative health policy selected ten study countries for inclusion in their health policy analysis (which usefully included the countries of interest Sweden, New Zealand, Japan, and Singapore). Their selection of countries for comparison included countries that had three broad types of healthcare systems: National Health Services (e.g. UK, Sweden, New Zealand), social insurance (e.g. Japan), and private insurance (e.g. Singapore). Canada, the study country not included in Blank and Burau's (2014) comparison, has a healthcare system that is a form of socialised health insurance plans (Canadian Health Care, 2007). Both this thesis and that conducted by Blank and Burau (2014) have provided a comparative sample that covers a range of health systems, but all countries share Western-type medical systems and are

developed nations that have wealthy populations with associated expectations and demands.

Interestingly, Blank and Burau's (2014) in-depth analysis found that frequently used countries in comparative analysis include the UK, United States and Sweden, and is biased towards North American and European based literature. However, countries such as New Zealand are included less frequently, as well as Japan and Singapore, which provide important insights into health policy and demonstrate a gap in the literature. As Blank and Burau note, there is a wide range of health care system variation globally but the inclusion of countries from other categories (e.g. former communist-socialist and less economically developed countries) entails further complications at analysis level, thus the preference for only including similarly developed countries. Also, covering several countries will not provide a comprehensive analysis of each specific country's health policy; rather it will provide an overview of each country.

Additional comparative analysis studies in health research have included a study by Lee et al. (1998) regarding family planning policies and programmes in eight study countries. Lee et al.'s (1998) research is different to this project framework because they matched countries to form four pairs. The countries were matched based on political, social and geographical similarities. The Global Fund Tracking Study (Brugha et al. 2005) also involved a cross-country comparative analysis of four countries experiences of funding applications and implementation of health systems. Similarities and differences between the countries were reported, and overall generic lessons stated.

The comparative health policy approach was applicable to this piece of research due to the multiple study country structure. The sampling of study countries is explained in detail in section 3.2.2, the methods section, of this chapter. In line with previous comparative health studies, such as the Blank and Bura (2014) research, this project has analysed trends within and across countries.

3.1.2 The research inquiry paradigm

The research proposal outlined that an international study would be conducted that involved visiting several study countries to further understand the use of public health measures during the 2009-10 influenza A(H1N1) pandemic. As with any research, unpicking the research purpose led to further exploration surrounding: the methods that would be used; the methodology directing the choice and use of methods to fulfil the research intentions; the theoretical perspective underpinning the methodology; the epistemology rooted in the theoretical perspective. Each of these four elements is entwined into the other (Crotty, 1998). The epistemology of this research project will be considered in this section.

Epistemology is the theory of knowledge. It has a philosophical foundation that enables the researcher to delve into the types of knowledge, its possibilities, that they are appropriate and valid (Crotty, 1998). Before the epistemology embraced in this research is acknowledged, described and

justified, a range of possible epistemologies will first be outlined.

There are several epistemologies, of which objectivist, constructionism and subjectivism are frequently discussed. Objectivism is where knowledge is acquired through reason, through reality, where humans use their physical senses to give consideration of what it means to know. The research participants will objectify these understandings. For instance, a bird in the rainforest exists as a bird before it was seen, heard, touched by any humans, before any humans had knowledge of its existence. The discovery of the bird in the rainforest provides humans with the knowledge of the bird, but it's existence was there before the human knowledge. In undertaking a project, the research may reveal knowledge but the subject will have existed before, the researcher may discover the objective truth (Crotty, 1998).

On the other hand, constructionism differs to objectivism. Constructionism rejects the premise that objective truths are out there waiting to be revealed. Rather it is the interaction with realities that brings knowledge into existence and these meanings are not possible without a mind. Where objectivism discovers, constructionism constructs meaning. This is how meanings have changed over the course of history. Meaning in constructionism is created from the interaction between subjects and objects. Another epistemological positioning is subjectivism, where meaning is applied to the object by the subject (Crotty, 1998).

The epistemological perspective of this research has been constructionism: the 2009-10 influenza A(H1N1) pandemic

was an interaction of disease, human activity and public health measures. This interaction of objects and subjects has constructed meaning and it was the intention of this project to uncover, document and reflect upon these meanings to contribute to knowledge of pandemic influenza. The method of qualitative interviewing allowed for participants to explain their experiences and understanding of the 2009-10 influenza A(H1N1) pandemic and to offer reflections on their country's public health response measures.

3.1.3 Choosing the research methodology

The essence of research is *"about asking questions, exploring problems and reflecting on what emerges in order to make meaning from the data and tell the research story."* (Clough and Nutbrown, 2012: p.4). Research is concerned with 'finding out' (Goodwin and Goodwin, 1996) and as such the process of research is often investigative, exploratory and enquiring, with the purpose of understanding phenomena further, or even contributing to situational change (Clough and Nutbrown, 2012). It results in knowledge construction and an improved understanding of the study subject (Goodwin and Goodwin, 1996). Through the research process, an important aspect is that no harm is caused (see the latter part of this chapter regarding ethical considerations) and that an appropriate research methodology is applied. Therefore, the quantitative and qualitative possibilities were examined in reference to this research project.

It can be argued that research in public health, as Ziebland and Coulter (2013) reason in regards to healthcare, is a knowledge-based system. Ziebland and Coulter outline four distinct knowledge types: "*scientific knowledge about biological processes*"; "*epidemiological knowledge about patterns of disease and risk factors*"; "*clinical knowledge about how to treat medical problems*"; "*how people experience health, illness, treatment and the delivery of care*" (2013: p.1). The first three of these knowledge types, biological processes, epidemiology and clinical practice, typically utilise quantitative research strategies. The latter, health experiences, may more frequently be favoured by qualitative research methods.

The distinction between quantitative and qualitative research is that quantitative research uses measurement and quantification of data, whilst qualitative research is more concerned with words (Bryman, 2004). There is extensive work detailing the differences concerning research theory (e.g. deductive and inductive theory), epistemological considerations (positivism and interpretivism) and ontological considerations (objectivism and constructionism). However, space is only given in this section to explore the differences between research designs.

Features of quantitative research include measurement, causality, generalisation and replication (Bryman, 2004). Quantitative research methodologies in medicine often utilise randomised control trials. For instance, newly developed drugs by pharmaceutical companies will need to progress through various stages of randomised control trials (RCTs) before drugs are available for prescription to the general public. RCTs

are focused on testing for outcomes (e.g. does x vaccine provide protection against y disease in 500 people?), and the results can be statistically analysed (i.e. to determine the effectiveness of vaccine). RCTs are important in research and play a significant role such as in the development of drugs, however, there are limitations to the scope of RCTs. RCTs will not provide findings on experiences: for instance the experience of people undergoing trials and the reasons for participation. Also, RCTs also do not provide information about experiences in implemented public health measures, such as: why were antivirals used infrequently during pandemic influenza response in x study country?; why were vaccines used at x time during the response?; why was there a low uptake of vaccines?

Other forms of quantitative research methods include (but are not limited to) surveys, structured interviews, and questionnaires, which provide an opportunity to ascertain text regarding experiences in a rigidly structured format. Likewise, as explained previously regarding RCTs, these quantitative methods have strengths such as in generating large quantities of data and are less researcher-resource intense in the field, but will not provide detailed and rich information about experiences. In order to examine experiences, such as the social phenomenon of pandemic influenza response, a qualitative research method is more appropriate.

The features of qualitative research generally include meaning attributed to the environment (seeing through the eyes of those studied), detailed participant context, process importance, relaxed and flexible structures of data collection and concepts and theories emergent from data (Bryman,

2004). Types of qualitative research methods include ethnography and participant observation where a researcher immerses themselves in the environment of study for extended periods of time. Qualitative interviews refer to several types of interview method which are less controlled and formal than quantitative structured interviews. Focus groups are also a form of interview that engages with several participants to generate discussion on a particular research issue. Language focused research, such as conversation analysis and discourse analysis is concerned with determining linguistic structures and framework of concepts and events in the social world (Bryman, 2004).

Ethnography and participant observation were not possible in this research project because the 2009-10 influenza A(H1N1) pandemic was being studied after moving into the interpandemic period. The pandemic quickly emerged and lasted several months so it was unlikely that a researcher from outside of an organisation would gain access. Also, this project is concerned with several study countries and key response personnel which span more than one institution, therefore, the above approaches would have been impossible given the resources available. Language focused research would have been inappropriate due to the multiple study country approach, different mother tongue languages and the difference of meaning attributed to words and phrases between countries. The use of focus groups, for example, one focus group per study country, would have been logistically difficult as not all participants would be located in the same location or would be available at the same time. Also, by using focus groups, the student researcher would have less control

than interviews offer with regards to steering the conversation to focus on the work packages. It is also possible that one participant (e.g. most senior person) would have responded and perhaps simply restated organisational policies and rhetoric. If focus groups had been pursued, then it may have reduced the number of participants, for instance 'this person from the Ministry of Health can tell you all about x country's pandemic influenza response'.

Qualitative interviewing was by far the most appropriate research method because it allows for flexibility, probing, follow-up questions, interviewer-interviewee build-up of rapport and the opportunity of a greater breadth of coverage of the research topic.

3.1.4 Administrative anthropology

This research was concerned with making country comparisons of national pandemic influenza response during 2009-10. As explained in the earlier part of this chapter, it has used a comparative health policy framework as supported by similar previous health research in the outlined case studies. Asking questions about the public health measures used naturally led to the use of qualitative interview methods and this approach has been informed by the literature. In order to provide a complete picture of the core public health measures utilised (ultimately, the thesis has focused on the use of vaccines), it was necessary to support the qualitative interviews with documentary analysis. This led to the inclusion

of an administrative anthropology approach in the research project.

"That rather eclectic field which includes historical documentary analysis, structured interviews and observation of practice. We might call it "administrative anthropology."" (Korman and Glennerster 1990: p.6).

This study has utilised an administrative anthropology approach because it has examined documentary health policy in the form of pandemic influenza plans, conducted interviews with key pandemic influenza response personnel and reviewed published data on epidemiological trends and public health measures implemented in countries. It also explored respondents' perceptions of change during the pandemic process. Thematic analysis, the interviewing method, and triangulation of data will be explored in the second part of this chapter.

3.1.5 Quality in Qualitative Research

Thought has been given towards quality in this qualitative research; such as validity, reliability, generalisability, reflexivity and sensitivity to context.

In terms of validity, the researcher has strived to avoid an anecdotal approach in the analysis of the data by employing methods such as triangulation and the constant comparative element of the study countries (Silverman, 2005). It is recognised that triangulation alone cannot provide validity in qualitative research: triangulation does not simply operate to

provide a complete picture, but it can support findings (Murphy and Dingwall, 2001; Melia, 2013).

With regards to the external validity of findings from the five study countries in this project to the generalisation of other countries, it is accepted that transnational themes may or may not be applicable to other countries due to varying pandemic influenza responses, national context, and disease activity experiences. The sampling technique approach employed in this project, as discussed later on in this chapter, attempts to provide a diverse sample of countries to enable greater generalisability across other countries.

This research has avoided internal reliability issues due to the student researcher undertaking all data collection and analysis in person. With regards to reflexivity and sensitivity to context, it is recognised that the researcher's UK background presents limitations to conducting international research. In order to address this concern, the researcher studied each country prior to undertaking data collection in the field and had a key contact in each study country to discuss both pandemic influenza response and wider issues relating to cultural contexts (Potvin, Bisset and Walz, 2013; Bryman, 2004). For example, one contact explained business meeting etiquette that they had learnt from their experience of working in Japan for over ten years. The researcher believed that this additional knowledge enabled interviews to proceed smoothly and respectfully observe each contextual country setting.

3.2 **Methods**

3.2.1 Study Design

The thesis focused on policy, public health response and nationally available data concerning the 2009-10 influenza A(H1N1) pandemic from several countries, with the intention of an investigation that is of a comparative nature. Face-to-face qualitative interviews with key pandemic influenza response personnel in each country, with the assistance of an aide memoire, was the data collection method in this thesis. The data analysis strategy followed the analytic induction process, and the hypotheses were built from the data; no hypotheses were pre-conceived before data collection.

This research project used qualitative interviews to explore health decision-making and policy implementation in light of the 2009-10 influenza A(H1N1) pandemic disease activity in various countries.

3.2.1.1 Core policy areas studied

At the beginning of the research project, the intention was to study the four key areas listed below, and the interviews that followed reflected this. However, the results and discussion in this thesis have focused on pandemic influenza vaccines due to word count constraints. The data on antivirals, non-pharmaceutical measures and the broader societal aspects of the pandemic influenza response in 2009-10 have been

collected and provide an opportunity at a later date to include this information in journal papers.

A. Antiviral drugs

Examine, compare and contrast selected countries overall use or non-use of antiviral drugs (for post-exposure prophylaxis in households, aimed at the slowing of initial spread within countries and for the treatment of cases). This will include an examination of the potential impact of policy differences related to 'treat all' or 'treat high-risk only' policies.

B. Pandemic influenza vaccines

Based on selected countries, this will examine the use or non-use of monovalent pandemic influenza vaccines, including the timing of deployment and type (inactivated, live, adjuvanted, etc.), policy intention (pre-pandemic) versus policy implementation (and reasons for any discordance).

C. Non-pharmaceutical measures used during pandemic

Based on selected countries, this will examine public health (non-pharmaceutical) measures such as restrictions on mass gatherings, border closures/restrictions, suspension of urban mass transportation systems to the limited extent that these were practiced during the 2009-10 pandemic influenza.

D. Societal communication, coordination and roles for the pandemic response

An examination of broader societal aspects of the pandemic response in 2009-10. To include: the role of the media; the effectiveness of government health communications; the

impact of centralised vs. decentralised health communication; the role of HCPs in providing a pandemic response (use of existing health care provision vs. establishing special vaccination centres etc.).

3.2.1.2 Research Questions

How were antivirals used during the 2009-10 influenza A(H1N1) pandemic?

How and when were the pandemic influenza vaccines used in reaction to the 2009-10 influenza A(H1N1) pandemic?

What other public health measures were used during the 2009-10 influenza A(H1N1) pandemic?

What were the other societal aspects of the 2009-10 influenza A(H1N1) pandemic response?

3.2.1.3 In-depth Interviews

Wrede explains that "*policy researchers commonly use interviewing to explore policy processes and related action, and to systematize information about policy making and about the views of specific policy actors vis-à-vis the issues in question.*" (2013: p.98). Interviews of this nature are conducted with key informants (experts) and at a macro level, and this is the type of interview used in this research project. Wrede furthermore describes how the interview allows participants to speak on their area of expertise. For example,

in this research project, the in-depth interviews allowed participants to spend longer discussing their specific area (e.g. antivirals and social restrictions) and spend less time in the interview on topics which may not concern their work. Therefore, as later discussions will show concerning the interview aid memoire, the interviews were semi-structured but allowed for flexibility in response to the participants.

An important point raised by Wrede is the need to be familiar with the terminology used by experts in each study country. This issue can be addressed by the researcher through documentary research. "*Documentary research conducted prior to interviews serves as a method of identifying key 'vocabularies' and 'dialectal uses' of the shared policy terms.*" (Wrede p.99).

There are three broad types of interview that can be used in research and the structure chosen will impact on the generated data. In qualitative interviews, researchers typically use unstructured or semi-structured types of interviews. These involve the interviewer asking a few prepared factual questions at the start and then broad open ended questions with the use of prompts as and when required (Holloway and Galvin, 2017).

At the beginning of this research, it was apparent that the structured interview would be inappropriate to use. The structured interview utilises prepared questions that are asked in the same way and order, similar to a job interview experience or a verbal survey (Holloway and Galvin, 2017). The inflexibility of this structure and the quantitative type data

was contradictory to the aims of the qualitative research of this project.

In the planning phase, it was apparent that the interviews in this research were going to be either unstructured or semi-structured. However, determining the particular type required time to read further about qualitative research methods. Following this, it was felt that the breadth of the research topics to discuss during meetings and the singular country visits would require the use of a semi-structured interview type to ensure that the meetings covered the necessary content. Table 2 provides detail of the semi-structured interview content concerning vaccines and this was used by the researcher when questioning, prompting and probing in response to participants' accounts.

Table 2. Vaccine related content in semi-structured interviews.

Did [country name] use the monovalent pandemic influenza vaccine? How many vaccines were ordered? What were the major considerations and decisions which had to be made about pandemic vaccine? Can you tell me about the national vaccination strategy? Was prioritisation a feature? When did the vaccination campaign begin? How did this compare to the annual seasonal influenza vaccination campaign? Were the vaccine supplies appropriate? Tell me about the vaccine uptake. Was the vaccination timing ideal for Canada in respect to influenza activity at the time? Were there any particular difficulties or challenges that concerned the pandemic vaccine in [country name]? Some countries did not purchase the pandemic influenza vaccine, do you think that [country name] may ever do this? If we were to have pandemic influenza in the future that was of greater severity, do you think that the pandemic vaccination

approach taken by [country name] would be used again? What might be different?
Is there anything else of interest relating to the vaccines used during the 2009-10 influenza A(H1N1) pandemic that we have not covered today?

3.2.2 Sampling

The study countries and matched reserves were chosen after undertaking consultations and a literature review of pandemic preparedness plans and research articles. The selected countries required an element of differing public health policies in relation to the 2009-10 influenza A(H1N1) pandemic response. This was in addition to the need for sufficient epidemiological data in order for some description of disease activity and intensity at the national level.

3.2.2.1 Selection of study countries

The process of selecting study countries involved consultations with some leading influenza specialists who worked during the 2009-10 influenza A(H1N1) pandemic influenza. With an awareness of the thesis objectives, these experts made suggestions of countries to consider for study. The consultations were held with the supervisors, the WHO influenza working group, an influenza specialist at the United States Communicable Disease Centre (CDC) and the project funders GlaxoSmithKline.

In July 2012, members of the WHO influenza working group in Geneva were consulted, which resulted in many country

suggestions for a variety of reasons. The deputy director of the CDC influenza division made five country suggestions. All of these suggested countries had been mentioned by the WHO influenza group and Professor Van-Tam. No suggestions were made by the funders GlaxoSmithKline as they did not wish to influence the direction of study. With the list of suggestions made during the consultations as a starting point, these countries and some others not brought up in consultation were further researched, in order to create a list that best reflected the aims and objectives of the thesis. The suggestions were then placed into a Venn diagram to assess similarities and differences.

Japan, Argentina, and Chile were suggested by all parties which made these three priority countries to study. Singapore was suggested by three of the four contributors, thereby making it a strong suggestion. A total of fifteen countries were nominated by two of the four contributors. The remaining thirteen countries were only suggested by one of the four contributors. Countries which fell outside of the suggested list were not prioritised because the list had been developed after reviewing information and backgrounds about individual countries in line with the thesis' aims and objectives.

The final eight countries selected for study in the thesis were:

1. Chile
2. Argentina
3. Japan
4. Singapore

5. Canada
6. New Zealand
7. Sweden
8. Turkey

Following the review process, it was believed that these eight countries would provide excellent material to compare and contrast in the thesis according to the work packages. The countries have strong epidemiological data concerning the 2009-10 influenza A(H1N1) pandemic which formed an essential component of the thesis. The country choice included both high and low use of pandemic influenza vaccines and antivirals. Some of the countries implemented strong social distancing measures and invested in strong societal health communications whereas other countries encountered unexpected problems and public resistance to public health measures. Risk perceptions from island nations in comparison to those landlocked with open border crossings could also have formed an interesting component of the research. The list included a selection of northern and southern hemisphere countries, and some of the countries had global events scheduled during the pandemic which would have allowed risk perception during mass gatherings to be explored. The selected countries offered a mix of those immediately affected by confirmed cases following the WHO announcement compared to countries which did not report confirmed cases until weeks later. The selection also offered an assortment between the burden of confirmed cases and deaths per countries.

3.2.2.2 Reserve study countries

Reserve countries were prepared in the event that any of the chosen countries could not participate. The reserve countries were matched to the selected countries on the basis of sharing similar criteria during the 2009-10 influenza A(H1N1) pandemic. The following criteria were considered important in the assessment of identifying the reserve countries:

- Good epidemiological data collected during the pandemic
- Likeness of experience of confirmed cases and deaths per 100,000 in country
- Similar use of antivirals and/or pandemic vaccine
- Similar non-pharmaceutical measures taken
- Located in the same geographical region as the refusal country
- Same geographical characteristics as selected country

Where possible, reserves were selected from the consultation pool. The selected countries matched to reserve countries were:

1. Chile – Brazil
2. Argentina – Brazil

3. Japan – Taiwan
4. Singapore – Thailand
5. Canada – United States
6. New Zealand – Australia
7. Sweden – Finland
8. Turkey – Ukraine

After pursuing study countries to include in the project, Japan, Singapore, Canada, New Zealand and Sweden were secured. When Chile and Argentina refused, Brazil was approached, but no significant developments followed. Other than New Zealand, no other study country was from the southern hemisphere which was regrettable, and there was concern that imbalance would form in the reporting of the results. There was initial interest from Turkey, but no interviews could be secured later on in communication. After speaking to the thesis funders and supervisors, several months after the fifth country visit, it was agreed that sufficient data had been gathered from five study countries and that no further study countries would be pursued.

3.2.2.3 Purposive and snowball sampling

Gatekeepers were encountered in gaining access to potential participants in the sampling process. Overt participant access was sought.

The research utilised purposive sampling by the identification of key individuals who were involved in a national response to the 2009-10 influenza A(H1N1) pandemic. The key individuals were able to give an overview of their country's national response. These participants were asked if, in their opinion, the researcher should speak with any other individuals who had important roles in their national pandemic influenza response. Therefore, the study was primarily a purposive sample, but the snowballing technique was also used in the country during the fieldwork phase.

Sadler et al. (2010) explain that snowball sampling is an effective strategy in instances of trying to recruit hard to reach groups. The researchers describe the usefulness of adapting the snowball sampling technique in health. Purposive sampling with the snowballing technique was considered the most effective method to use in this study due to the limits associated with one person only being able to visit a country for a short amount of time. Multiple interviews were scheduled before embarking on a country visit, to ensure productivity, as no budget was available for return country visits.

An excel document (Table 3) was compiled regarding mapping the project scene for participants:

Table 3: Identifying potential interview participants

Name	Role	What we might learn

3.2.2.4 Key actors involved in national response to pandemic influenza

The 2005 WHO checklist for influenza pandemic preparedness planning discusses the need to consult with the following representatives (directly extracted from World Health Organization, 2005b, p.12) in the development of countries national and regional plans:

- *national and regional public health authorities including: preventive, curative and diagnostic services; the national drug regulatory authority; the national influenza centre(s); and representatives of physicians' associations (e.g. general practitioners and respiratory disease specialists), nurses and pharmacists;*
- *recognized national virologists and epidemiologists, and representatives of scientific and academic institutions;*
- *veterinary authorities and experts in animal influenza viruses;*
- *representatives of public or private organizations that monitor health indicators, use of health-care facilities and pharmaceuticals;*

- *representatives of pharmaceutical manufacturers or distributors;*
- *representatives of social service administrations;*
- *representatives of military or other government emergency response organizations or teams;*
- *representatives of nongovernmental and voluntary organizations, such as the national Red Cross or Red Crescent Society;*
- *representatives of telecommunications, and media relations experts.”*

The key stakeholders to speak with were identified after reading the WHO guidelines (2005b, 2005c) and study countries national pandemic influenza preparedness plans. Interviews were held with individuals who were involved in the national response to the 2009-10 influenza A(H1N1) pandemic and had a health decision-maker role. The sample reflected members of multi-agency, national pandemic influenza preparedness, and response committees.

To identify potential key participants, the following three approaches were taken to develop the sampling strategy:

1. Exploration of the literature to identify key stakeholders at national level.
 - a. WHO reports (e.g. 2005 checklist, 2009) and guidelines

- b. National pandemic plans, guidelines and appendices (environmental scan)
 - c. Journal publications
2. Consultation with pandemic influenza specialists
3. Review of other similar work conducted in this field.

The key individuals' roles included:

- Public health official
- National medical officer
- Policy maker
- Epidemiologist
- Virologist
- Public health researcher - Influenza academic

The organisation names varied by country, but included derivatives of:

- Ministry of Health
- National public health authority
- Emergency service
- National Influenza Centre
- University

Contacts were sought and approached by way of an introductory letter (see Appendix D). Where possible, this was assisted by the project supervisors. The WHO offered assistance, in areas where the project supervisors did not have contacts, to help connect with key individuals in countries.

3.2.2.5 Sample size and saturation

The concept of data saturation is used in qualitative research to denote that new data from more participants will result in no further findings (Glaser and Strauss, 1967). This concept of saturation in relation to the sample was considered following each country visit and after five study countries formed the research sample.

The literature regarding saturation in qualitative interviews offers varying opinions about what is an adequate sample size and factors that determine sample size. Charmaz (2006) argues that the study aims will be reflected in the design and thus sample size. Morse (2000: p.3) presents several factors to consider for sample size: *"the quality of data, the scope of the study, the nature of the topic, the amount of useful information obtained from each participant, the number of interviews per participant, the use of shadowed data, and the qualitative method and study design used."*

Interviews were with key pandemic response personnel and included clinicians, government officials, medical officers, surveillance, agency staff, policy makers, etc. Before embarking on study country visits, it was intended that 6-8

interviews per study country would be secured with the intention of gaining an understanding of similarities and differences in pandemic response. This was based on the assumption that every participant would provide useful information.

Mason (2010) investigated sample size in published thesis studies using qualitative interviews. Mason reported 429 grounded theory studies, of which 174 were used after exclusion criteria were applied. The number of interviews ranged between 4 and 87, and a mean of 32 interviews conducted. This thesis research project generated 36 interviews, which is slightly above the average given by Mason.

The assessment of reaching data saturation was reviewed after the interviews were conducted and analysed. Although no return country visits were budgeted in this research, the possibility of conducting telephone interviews with new participants from the existing study countries was raised in the event that the sample size was inadequate and saturation was not obtained. Fortunately, the robust sampling methods deployed ahead of the country visits meant that no additional data collection was required per study country and the saturation was reviewed after country visits.

3.2.3 Research and Ethics Committee approval

As the thesis involved conducting research with human participants in various countries outside the UK the ethical guidance produced by the British Sociological Association and

the International Sociological Association was considered. A University of Nottingham research governance officer was consulted, and the thesis proposal was submitted for ethical approval through the University of Nottingham School of Sociology and Social Policy.

The ethical issues that this thesis needed to consider in the research design, conduct, and analysis were (Bonita et al. 2006):

- Informed consent
- Confidentiality
- Respect for human rights
- Scientific integrity

3.2.3.1 British Sociological Association guidance

The 'Statement of ethical practice for the British Sociological Association' (2002) provides guidance and raises a number of ethical issues which potentially could involve sociological research practice. After consideration of this guidance, it was found that the following ethical points required addressing for this research project:

Professional Integrity of sociological inquiry

The need to report the research findings accurately and truthfully were recognised. In addition, the need to adhere to

national laws and regulations e.g. Data Protection Acts, Human Rights Act was also understood. The relevant national laws and regulations were explored for each study country prior to country visits.

Consideration was given to the safety issues concerning the research data collection in relation to travelling alone, and a person based at the University of Nottingham was designated to be the main contact whilst research was being undertaken in other countries.

Relations with and Responsibilities towards Research Participants

It was recognised the rights of individuals participating in the study and that these rights came before the goals of the research project. The research did not harm the physical, social or psychological well-being of those participating.

The research required undertaking the process of gathering informed consent from all individuals partaking in interviews. This involved providing participants with enough information about the study, the researchers working on it, the financiers, the justification for the project and how the findings will be disseminated and used. Informed consent covers participation refusal rights, anonymity, and confidentiality, rejection rights of tape recorders, copyright or data protection laws, copyright clearances for audio recordings, clarification of interview transcript access and adjustments, and publication consultation. Where access to a research setting involved

negotiation with a gatekeeper, informed consent was also required from individual participants.

Covert research

No covert research or methods were used in the study.

Anonymity, privacy, and confidentiality

Research participants had the right to anonymity and privacy in the study, and any personal information was kept confidential. Generated data were stored securely. The reputation of the sociology discipline needs to be maintained for future researchers.

Relations with & Responsibilities towards Sponsors and/or Funders

The studentship was funded by GlaxoSmithKline. GlaxoSmithKline had a distanced role in the research project so that the research could progress without their involvement.

Clarifying obligations, roles, and rights

A written contract was signed by three parties - the student, the supervisor, and the funders, which outlined obligations of the research project by each party. Raw data from this thesis

was not shared with the funders due to confidentiality reasons.

Pre-empting outcomes and negotiations about research

GlaxoSmithKline incorporated research direction flexibility into the proposal, and the research was not restricted by GlaxoSmithKline in terms of publications of any research results.

Obligations to sponsors and/or funders during the research process

Any major changes to the original proposal were notified to GlaxoSmithKline after discussions with the project supervisors.

3.2.3.2 International Sociological Association (ISA)

The ISA has a code of ethics (2001) for research members to follow. After reading the code of ethics, no additional items or conflicting comments to the information provided in the more detailed guidance produced by the British Sociological Association were found.

3.2.3.3 School of Sociology and Social Policy Ethics Committee

This thesis shared joint registration with the School of Medicine and the School of Sociology and Social Policy. An application for ethical approval from the School of Sociology and Social Policy Ethics Committee was submitted, and the project gained ethical approval prior to country visits (see Appendix C).

3.2.4 Data Collection: In-depth interviews

After a period of liaising with potential participants, meetings were organised and interviews were conducted during country visits. The interviews were completed by Spring 2014.

3.2.4.1 Interview aid memoire

An interview aid memoire was prepared before each country visit to help guide the interviews and to ensure that the interviewer covered the work packages. The aid memoire covered each subject area with prompts of questions or topics to help the interviewer. Aid memoires are similar to interview guides which help to supply the interviewer with prompts of what is to be covered during the interview (Bryman, 2004). Appendix E provides further information about the aid memoire used.

The interviewer used the national overview section at the start of each interview to act 'introductory questions'. During the

course of the interview, the interviewer asked 'follow-up questions' and 'probing questions.' 'Structuring questions' (e.g. I am now going to move on to antiviral drugs) were useful for focusing the following conversation to the topic at hand and 'interpreting questions' were useful for clarifying meaning. Also 'silence' was important at times to allow interviewees space to continue with their response. These six of the nine types of qualitative interview questions outlined by Kvale (1996) were most frequently used in this research.

3.2.4.2 Pilot interviews

Two pilot interviews were undertaken in England prior to the overseas data collection phase. These pilot interviews were valuable as they provided the opportunity to use the aid memoire with the English equivalent key pandemic influenza response personnel. Piloting served different purposes (Silverman, 2010), including the development of interview technique and trialling of the question types and structure (e.g. which questions required clarification). It also provided an indication of which lines of questioning generated more or fewer data than others. These interviews were coded and transcribed, which helped with the aid memoire review phase.

3.2.4.3 Fieldwork timetable

The audio recordings of the interviews from one country visit were transcribed before undertaking the following country

visit. The timetable of the data collection stage is shown in Table 4.

Table 4: Fieldwork timetable

	2013							2014											
	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	
Pilots	*																		
Sweden				*															
New Zealand					*														
Japan						*													
Singapore								*											
Canada									*										
Turkey											?	?	?	?	?	?	?	?	?
Brazil											?	?	?	?	?	?	?	?	?

3.2.4.4 Interview venues

Interviews were conducted in participants' work locations, either in personal offices or meeting rooms.

3.2.4.5 Confidentiality and data security

Data was stored in compliance with the University Of Nottingham regulations, and research participants remained anonymous.

3.2.4.6 Transcribing the interview data

All the interviews were audio recorded, with the consent of the participants, to enable the transcription of the interview content. The process of reproducing the spoken words into typed text was conducted entirely by the researcher upon return to the UK using the aid of a foot operated stop-start pedal and the Express Scribe software that offers audio speed modifications. These two tools were helpful in improving the speed of transcription and helped to determine speech in instances where interviewees spoke quickly, quietly or mumbled. As Silverman notes, "*transcribing takes a great deal of your time*" (2010: p.200), but it was very important part of the process of beginning to analyse the data in this research project.

Verbatim transcripts were created from the audio recordings. The transcripts mainly comprised of the text of the participants spoken word, but it also contained responses ("yeah", "mmm", "eerrr"), vocalisations such as laughter (recorded as [laughter]), interruptions [phone call], recollections of what someone else had said (text was put in quotes and italics), repetition ("no, no, no, no"), muffled or mumbled speech [inaudible timestamp], reference to published material in interview (e.g. "You see here, 400,000 doses were purchased" [participant points at page in book whilst answering question]). No details that could not be conveyed from the audio recordings were recorded, such as visual data (facial expressions, gestures, body language). Also, the researcher did not attempt to interpret how things were said (e.g. speech speed, tone, emphasis) because this could be a source of inaccuracy such as when participants

conversed in English but this was not their first language (Halcomb and Davidson 2006; Bailey 2008).

One interview diverged from the typical interviews conducted in this research project: in Japan, an interview was accompanied by a translator. During the interview, the interviewer asked a question in English, the translator repeated the question in Japanese, the participant spoke in Japanese and the translator reproduced each sentence into English until the participant had finished their response. The interviewer paused to listen and often reframed the answer or asked a follow up response to clarify that they had understood the participant and that the translation was conveyed as the participant had intended - this again followed the interviewer-translator-participant-translator pattern. The English translated content of the audio recording was transcribed by the researcher.

3.2.5 Qualitative Data Analysis

3.2.5.1 Analytic induction

The principles of inductive methodology were used to generate theory from the conducted research, although the strategy used is based in the analytic induction process. In analytic induction, a hypothesis is built from the collected data and is not pre-conceived. Figure 23 shows a flow chart of analytic induction as a process in research data collection and analysis.

Lindesmith goes on to explain the theory of addiction to opiates, to answer the central theoretical problem of why similar circumstances result in some people becoming addicts whilst others do not.

Lindesmith (1968) discusses the analytic induction method as an evolving process, in which a theory is constructed, and evidence goes on to force change in theoretical structure. He argues that by observing the negative instances, the researcher should arrive closer to theory. Lindesmith (1968) explains analytic induction through an excerpt from Znaniecki (1934) about the method. Znaniecki explains that botanists and zoologists describe and categorise species, but that further discoveries may contradict their generalisations. New findings would lead to new research that may confirm their theory or invalidate their generalisation requiring them to develop a new, more appropriate theory.

Lindesmith's (1968) work shows a practical example of analytic induction (Shaw, 2000) that is useful for the data collection and analysis phase of this research project. Analytic induction was useful in this research project because each country became a case. An example of a worked hypothesis used for the specific public health measure of vaccines is presented in Table 5.

Table 5: Worked example of analytic induction used in this research project.

Hypothesis: early vaccination increased uptake rates and low mortality rates were reported		
Case	Does the hypothesis fit?	Comments
Sweden	Yes	Early vaccination campaign compared to other countries, high uptake rates and low national mortality
New Zealand	Yes	Late vaccination campaign, low uptake rates, some mortality
Japan	No	Late vaccination, low uptake rates but low national mortality
Revisit phenomena		
Revision: early disease activity and other public health measures affected vaccination uptake rates and mortality rates		
Case	Does the hypothesis fit?	Comments
Japan	Yes	High use of antivirals early on, late vaccination deployment, low uptake rates, low mortality
Singapore	Yes	Vaccines arrived post first wave disease peak
Canada	Yes	Vaccines arrived post first wave disease peak, vaccination uptake rates varied (high early on)

The benefit of analytic induction is that the data analysis began during the data collection phase, and this allowed the researcher to ask additional relevant questions during subsequent country interviews.

3.2.5.2 Thematic analysis

Following the analytic induction approach to hypothesis generation, the next stage was to analyse the qualitative data. When analysing qualitative data, either a deductive or inductive approach can be taken. A deductive approach makes use of a previously prepared framework to analyse the data and by this process the researcher enforces a structure onto the data. In contrast, an inductive approach does not apply framework but examines the data to develop the structure of analysis (Burnard et al., 2008). The deductive approach was inappropriate to use in this research project because it is inflexible and can limit the theme generation. Instead, the inductive approach was time consuming but comprehensive and allowed the interview data to direct the findings. There is a choice of inductive approaches that can be selected to analyse qualitative data: thematic analysis was used in the data analysis of this project.

"Thematic analysis is a method for identifying, analysing, and reporting patterns (themes) within data." (Braun and Clarke, 2006: p.6). The thematic analysis approach outlined by Braun and Clarke (2006) was utilised in this research project.

Braun and Clarke (2006) provide a six stage guide for conducting thematic analysis:

1. Become familiar with your data.
2. Generating initial codes
3. Searching for themes

4. Reviewing themes
5. Defining and naming themes
6. Producing the report

The thematic analysis steps listed were useful in this research. Firstly, the interview data was read and re-read. Fortunately, as all interviews were conducted by the researcher, an initial knowledge of the data was held. Through repeatedly listening to the verbal data in the transcription part of creating the typed data, and by reading the transcripts repeatedly, this formed an active part of data immersion. Although the transcription and repeated reading of the data was time consuming, on reflection it was not time wasted as it formed a firm foundation for data analysis.

Secondly, once the verbal data was heard multiple times, the transcripts were produced and the typed data read repeatedly, the first basic codes were applied. These first codes were initially applied in NVivo, a software programme, which assisted the handling of the data. The researcher also manually applied codes to paper documents to make the process more applied through the use of highlighters and pens. At this stage, all data had simple codes assigned and many parts were coded more than once. The researcher wished to make sure that all data was carried onto the next stages of data analysis and not lost. Instead of coding one sentence, the researcher would often code data either side of the sentence, such as an entire paragraph or section ensuring that the context was not lost. This stage created vast quantities of data.

The third step in the thematic analysis involved examining the codes and attempting to establish order by re-focusing the data into broad themes. This process resulted in several codes placed together to form a central theme. In some instances, there were many codes placed to one theme. The researcher realised at this stage that this was too vast and would likely require sub-themes within them. Also, a small number of codes floated outside of the main themes so these were placed into a temporary 'other' theme in order for the researcher to revisit these at a later date.

Step four is where the themes are reviewed and refined. In this step some of the themes were lost as when the data was re-examined there was not enough data in support. The researcher found that on more than one occasion, two separate themes from the earlier step were actually the same theme. This step required reading the data extracts to evaluate the fit of the themes and to check if any additional themes could be assigned.

Figure 24 provides an example of the thematic analysis approach taken. The example illustrates how the early coding step progressed over time to a final theme.

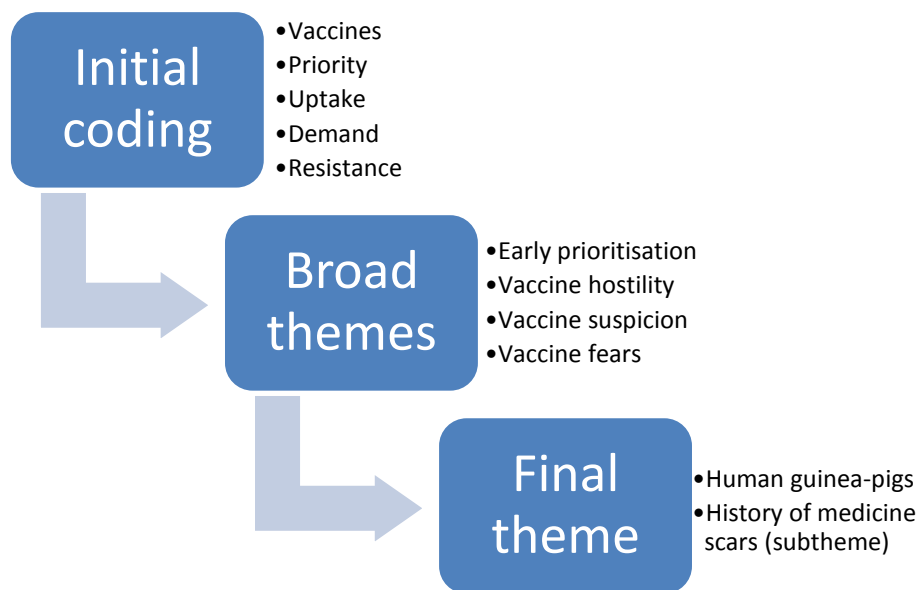


Figure 24. A worked example of thematic analysis.

At this stage the researcher sought support from their supervisor. A section of the data was discussed in relation to the themes to examine if a senior researcher would apply the same or different themes. The researcher was shown how an example theme could be defined and refined. This took the concrete themes to more abstract themes, where the essence of the theme was captured and replaced with an expressive theme. Checking the coding and theme process gave the researcher assurance to progress the data analysis. The fifth step of the thematic analysis concentrates on defining and naming the themes; each theme has a brief explanation attached.

Step six, the final step, relates to the final data analysis and written document; in essence the results chapter presenting the story of the data.

To summarise, thematic analysis involved searching across data to find repeated patterns of meaning. Codes were applied to the transcripts without checking previous research codes on a related topic. Data was repeatedly read, themes reviewed and revised. This has resulted in data driven themes in this research.

3.2.5.3 Handling the data

Interviews in text document format were imported into the program NVivo 8, for coding and thematic analysis. The analysis process was inductive, meaning that themes were identified in the data analysis stage.

The text documents were handled in NVivo for simplistic coding in the first instance. NVivo was favoured for basic organisation and core category coding of the public health measures because frequently the conversation flipped between different measures. As the coding process developed to themes, other approaches were utilised, such as multiple Microsoft Word documents and paper copies: here concepts and categories were utilised (Bryman, 2004).

On reflection, the thematic analysis and analytic induction process were a particularly challenging element of the project. The interview transcription had generated hundreds of thousands of words and the data frequently had multiple codes assigned. The researcher expected the process to reduce the size of the data to themes however initially the coding swelled the data. The researcher was also fearful of losing data that may be of significance later on so nearly the

entire transcripts were coded at first. It was only through reviewing the codes and doing the process several times, that more abstract codes were applied, and themes emerged.

3.2.5.4 Triangulation of data

This research has also benefited from the use of triangulation of data. Triangulation is "*the use of more than one method or source of data in the study of a social phenomenon so that findings may be cross-checked.*" (Bryman, 2004: p.545). The primary benefit of triangulation is that data is cross-referenced, and this provides a higher degree of confidence in the research findings. In this thesis, published pandemic influenza plans and policies, and literature on epidemiological trends and public health response measures in the study countries, have been examined both before interviews were conducted and afterwards in the analysis and write up stages.

The amalgamation of information was always pertinent in this research due to plans, policies and epidemiological reports providing a quantitative research foundation that facilitated qualitative research. As Bryman (2004) explains, the triangulation of data using mixed methods allows for the researcher to fill in the gaps, whereby using one method would not enable the researcher to collect all the information required for analysis. In this thesis, secondary data sources of plans and policies, and literature on the epidemiological trends and public health response methods have provided a platform for the qualitative interviews; the interviews alone would not have allowed for a thorough understanding of study countries

history and experience during the 2009-10 influenza A(H1N1) pandemic. As pointed out in the introduction chapter, the quantitative data published from the pandemic influenza has led to questions that have not been provided in literature elsewhere, and interviews were necessary to explore public health measures in greater depth. Therefore, it is natural that the quantitative basis which has led to the research is examined and included in conjunction with the qualitative data collected. It is felt that this type of research allows for "*...light being shed on relationships between variables derived from quantitative research by a related qualitative one.*" (Bryman, 2004: p.460).

Upon reflection, triangulation in this research has been achieved by using pandemic influenza policies, literature on epidemiological trends and public health response measures during 2009-10 and interviews. An example of the process of triangulation is depicted in Figure 25 where the study countries had vaccine purchasing agreements arranged prior 2009, with the intention of clarifying the number of doses required in the event of an influenza pandemic. The literature demonstrated that for some of the study countries, the vaccination campaigns were implemented after the first wave of disease activity and late implementation was associated with low vaccine uptake. The disease activity and the need to wait for vaccines to be manufactured and delivered, resulted in the participants emphasising that communication messages to the public frequently changed. Each piece of information in the triangulation data led to the identification that there were unforeseen issues with the vaccine supply, which created uncertainty, contradictions and required a lot of resources in

order to implement vaccination campaigns. The triangulation example (Figure 25) demonstrates the improved knowledge that was gained from using multiple sources.

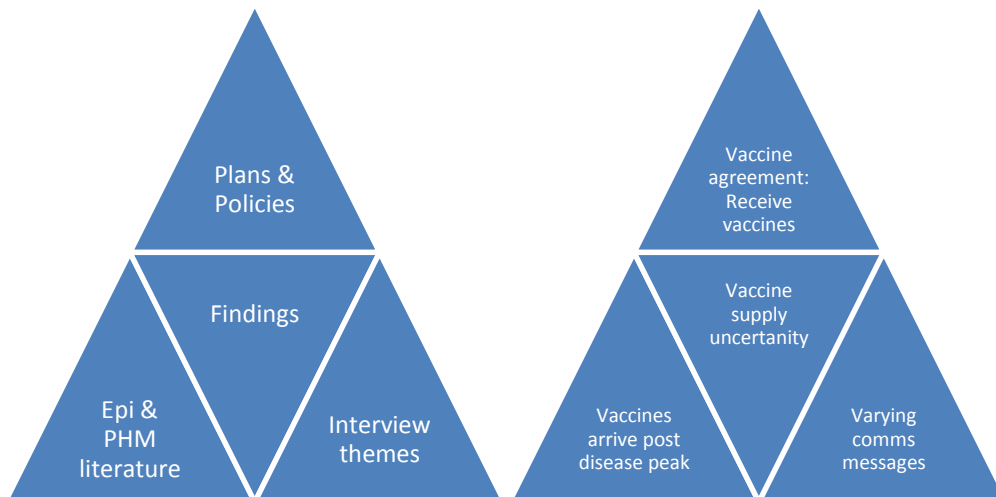


Figure 25. Example of triangulation in practice.

3.2.5.5 Relationship and patterns between categories

After undertaking the coding of interview data, relationships between categories were examined, which helped assemble the results and discussion chapters. The example in Table 19 illustrates the relationship between vaccine uptake in an interpandemic period (thin inner arrows) and a pandemic influenza event (thick outer circle arrows). It highlights the continuous cycle of providing influenza vaccines and how regular experience contributes to high uptake rates.

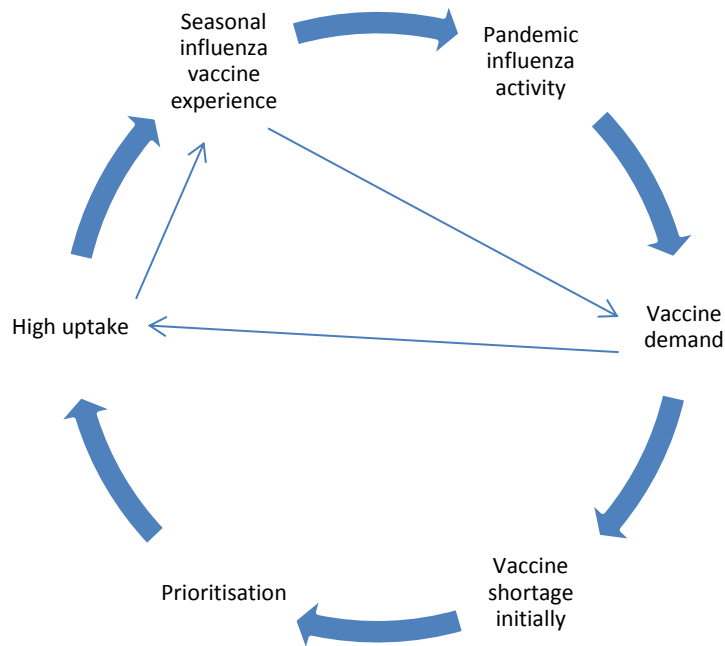


Figure 26. Factors contributing to vaccine uptake.

3.3 Summary of research methodology chapter

This chapter has provided an outline of the research methodology and the study methods. It has explained the thinking behind the research conducted and what indeed occurred in the fieldwork and analysis stages. The chapter explained that this comparative health policy research used qualitative interviews with the support of the documentary analysis of available records, and this has taken an administrative anthropology approach. Countries were sampled by the means outlined, and this resulted in interviews conducted in five study countries to explore the four core policy areas of pandemic influenza response. A qualitative data analysis was undertaken using the strategy of analytic induction process; interviews were transcribed and coded, and thematic analysis was undertaken. This process has led to the

following chapter on the pandemic influenza preparedness prior to 2009 in both the international community and the individual study countries. The discussion then progresses onto countries vaccine agreements and vaccines utilised in the 2009-10 influenza A(H1N1) pandemic.

4 Study 1: Pandemic Influenza Policies

Chapter 2 focused on the three pandemic influenza events of the twentieth century and gave a historical overview of the public health management measures with a particular focus on pandemic vaccines. The chapter moved on to discuss the events of the 2009-10 influenza A(H1N1) pandemic. The previous chapter detailed the research methodology and methods which is a critical precursor to this chapter.

In this chapter, it is now appropriate to examine the national policies regarding influenza pandemics. Firstly, the global importance of planning and policies will be examined with reference to the pandemic preparedness in the years prior to 2009. Secondly, the discussion will progress on to the study countries pandemic influenza plans and the vaccine agreements in place before the pandemic influenza event. The final part of the chapter will examine the actual vaccines ordered and deployed in the 2009-10 influenza A(H1N1) pandemic.

4.1 Pandemic preparedness

Pandemic influenza preparedness activities and investment by nations and international organisations have largely increased over the last 15 years. The pressing need for pandemic preparedness has grown from a greater consciousness that infectious diseases do not observe country borders. Therefore, in order to respond to emerging infectious diseases, such as

pandemic influenza, there is a need to complement national and local government actors with transnational actors to facilitate a coordinated globalised response (Brown and Hegermann-Lindencrone, 2013; Dingwall, Hoffman and Staniland, 2013). Globalised public health risks and uncertainty require not only a country response at the three tiers of national, regional and local levels but also an international involvement. A mixture of these different layers of actors is a vital component for the success of responses, and although this research project has focused on a national level response, it is important to explore the part played by international communities towards pandemic influenza events.

Globalised emerging health threats have notably included the Black Death of the fourteenth century in Europe and more recently HIV from the 1980s. At each time, both were new infectious diseases that required a novel response and caused public panic, fear, stigma and uncertainty at supra-national, national and subnational levels (Dingwall, Hoffman and Staniland, 2013). *"Emerging diseases disturb our assumptions of a known universe of risk. A new hazard disrupts our established strategies for managing our everyday lives. What appears as irrational may be a locally rational response to uncertainty, or at least an attempt to use locally available resources to re-establish sufficient certainty for practical action."* (Dingwall, Hoffman and Staniland, 2013: p.168). Countries varying responses to emerging infectious diseases are understandable given the varying knowledge about what action is politically and culturally appropriate and what is financially feasible. Transnational organisations have

recognised these differences but nevertheless highlighted and encouraged the importance of preparedness activities.

HIV, and in more recent years, Ebola, Middle East respiratory syndrome coronavirus (MERS-CoV), avian influenza virus A(H5N1) and severe acute respiratory syndrome (SARS) infectious diseases outbreaks, as well as the threats of bioterrorism, and susceptibilities generated by ever increasing globalisation, have resulted in intense work towards pandemic preparedness. Transnational organisations are prepared in advance and on stand-by for newly emerging infectious diseases: 'known unknowns' (Brown and Hegermann-Lindencrone, 2013; Dingwall, Hoffman and Staniland, 2013). The United States Secretary of State in 2002, Donald Rumsfeld, stated at a defence meeting that: "*There are known knowns. There are things we know that we know. There are known unknowns. That is to say, there are things that we now know we don't know. But there are also unknown unknowns. There are things we do not know we don't know.*" Substantial investments in surveillance to rapidly detect infectious disease outbreaks, as well as plans and policies, build resilience against these 'known unknowns' have been made at the start of the twenty-first century.

Avian influenza virus A(H5N1) materialised in 1997 in Asia, with further outbreaks appearing in 2003, which highlighted the threats of the animal-to-human route of infection and transmission. This influenza virus was designated 'highly pathogenic' because nearly all infected poultry died; it also happened to be extremely lethal in the limited number of humans infected but this is never the reason why a virus is denoted 'highly pathogenic' by animal health authorities. This

extraordinary outbreak caused worldwide concern about the lethality of this disease and future pandemic influenza potential if the disease evolved to successful human-to-human widespread transmission. Large scale coordinated responses, such as poultry culling throughout Hong Kong, were undertaken and appeared to halt the outbreak (Monto and Sellwood, 2013; Brown and Hegermann-Lindencrone, 2013). Historical impacts of pandemic cases, such as the 1918-19 Spanish influenza, remained well known in the twenty-first century during the time of the Avian influenza outbreaks. Indeed, Taubenberger argues persuasively that the 1918 pandemic probably arose from an avian influenza virus after undertaking analysis of tissue samples from 1918 influenza victims (2006). Although medical care has vastly improved since 1918, unprecedented new risks were apparent, such as the radical change of modern day global interconnectedness and the dense living conditions in vast cities. There were swift flights from one region of the world to another in a matter of hours, and with the incubation period of influenza prior to the display of symptoms contested, it was widely accepted that outbreaks in Asia would not be held back from the global community. It was not so much of a question of 'if' a pandemic influenza would occur but more of 'when'.

At the same time, the 2003 SARS transmission compounded the threat from emerging infectious diseases, and the impact of SARS was extended beyond Asia to various cities across the world (Monto and Sellwood, 2013). The research study countries of Singapore and Canada (Toronto regional area) had the first-hand experience of emerging infectious diseases response to SARS. The timeline of infectious disease events in

the preceding years sharply focused pandemic preparedness across the world.

In 1999, 2005 and 2009, the WHO developed guidance for pandemic influenza preparedness planning; the majority of countries national plans were prepared using the 2005 WHO guidelines. The guidelines outlined pandemic preparations, phases 1-6 and response measures, and contained a number of core areas, one of which included vaccination strategy (Brown and Hegermann-Lindencrone, 2013). At this time, the European Centre for Disease Prevention and Control (ECDC) was established in 2005. Based in Sweden, the "*ECDC's mission is to identify, assess and communicate current and emerging threats to human health posed by infectious diseases.*" (ECDC About Us, 2016). The WHO is concerned with various health conditions across the world, whereas ECDC is a highly specialised infectious disease agency concerned with European health protection; in 2005 pandemic preparedness was ECDC's primary disease priority. The ECDC and European Commission published various documents, such as pandemic surveillance, preparedness assessments and EU reviews, and held workshops prior to 2009. One of the five study countries, Sweden, is based in Europe and the research project was conducted at a UK university. The International Health Regulations (IHR) were implemented in June 2007 and legally binds all 196 countries (including WHO Member States) to report specific diseases to the WHO and the outlines the responsibilities of the WHO. The aim of the IHR is to: "*help the international community prevent and respond to acute public health risks that have the potential to cross borders and threaten people worldwide.*" (WHO, IHR, 2016). Lastly, two

other notable transnational organisations are the United States Centres for Disease Control and Prevention (CDC) and the Pan American Health Organization (PAHO). PAHO is an international health institution covering the Americas (PAHO, 2016). The CDC published pandemic influenza guidelines and played a significant role in the early weeks of the 2009-10 influenza A(H1N1) pandemic due to the emergence of the virus in North America.

4.2 Literature review of study countries pandemic influenza policies and 2009-10 influenza A(H1N1) pandemic events

Documentary methods and a literature review of country-specific literature were conducted ahead of the country visits.

In advance of the data collection, it was important to make use of existing materials in order to prepare the interview aid memoire. As Wrede (2013) explains, documentary methods make use of materials that have been published at a set point in time and *"it is common for researchers to combine documentary materials with other means of acquiring data, such as interviewing"* (Wrede, 2013: p.95). *"Documentary research is a basic source of data for health care policy study in general and comparative analysis in particular."* (Wrede, 2013: p.96). In this research, documents predominately included country pandemic influenza preparedness plans and WHO pandemic influenza guidance in the lead up to the 2009-10 influenza A(H1N1) pandemic. The documentary method enabled the identification of key pandemic influenza response

personnel as well (discussed in the sampling section of the methodology chapter).

A literature review was conducted for the purpose of detailing each study countries pandemic influenza preparedness policies, as well as to develop an epidemiological picture and collation of information about pandemic influenza response and impact in each study country. The literature search was planned using the Population Intervention Comparison Outcome (PICO) search strategy which involves setting an answerable research question and terms to use in a search.

The research question: How was the 2009-10 influenza A(H1N1) pandemic managed in the study countries and what were the outcomes?

Search terms: 2009-10 influenza A(H1N1) pandemic + public health measures + study countries + outcome (the second row are synonyms which contain the various spellings of the keywords).

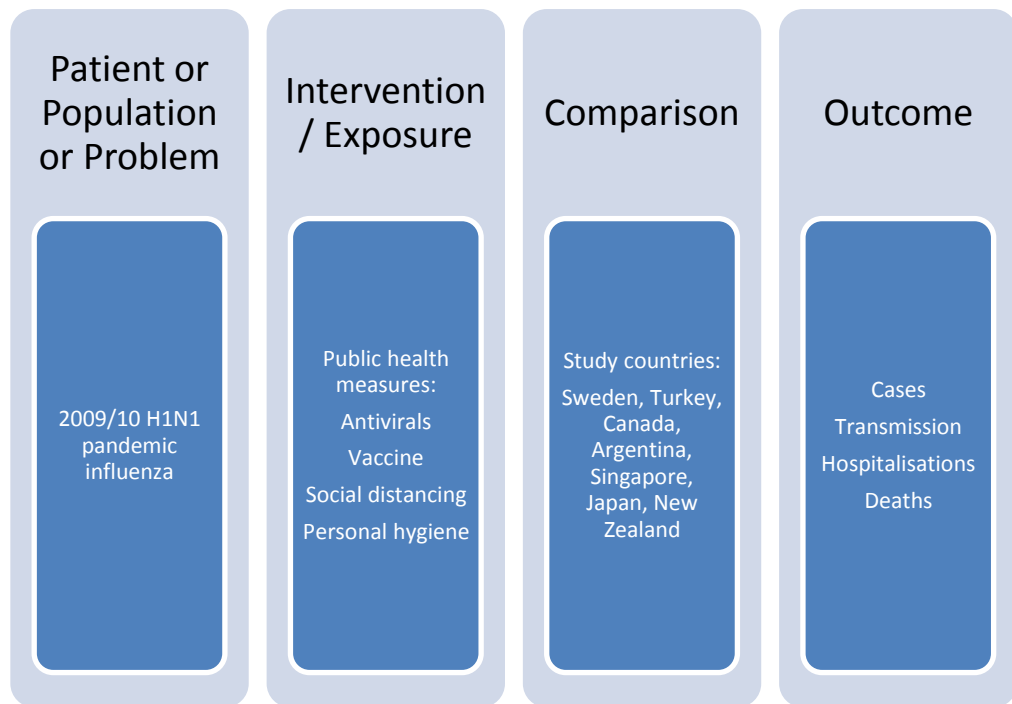


Figure 27. PICO search strategy

The search terms and generated results have been included in Appendix B. References which were not followed up included:

- Specific case studies (e.g. an individual's treatment and experience)
- Other pandemic influenzas (e.g. 1918 Spanish Flu)
- Seasonal influenzas / SARS
- Different word meanings (e.g. Turkey – reference to the bird, not the country)
- Economic focused articles
- A single hospitals' experience (only included if it is the single designated/reference hospital) / very localised experience (e.g. city/town/small region) / a university' experience / highly specialised ICU issues

- Non-study countries (e.g. mention study country in abstract but actually article is focused on another country and their response/experience)

Once abstracts were examined and articles such as the above examples excluded, it was typically found that <25% of articles were appropriate to follow up.

4.3 Pandemic influenza planning

In 2011, the WHO compiled a document with the title '*Comparative Analysis of National Pandemic Plans*', which looked at the pandemic plans of 119 countries and this included a table of national preparedness plans. All five study countries were found in this document, and the information was extracted for inclusion in Table 6.

Table 6: National pandemic plans from study countries

Country	Date	Title	Pages	Language
Canada	2006	The Canadian pandemic influenza plan for the health sector	609	English
Japan	2005	Pandemic Influenza Preparedness Action Plan of the Japanese Government	75	English
New Zealand	2006	New Zealand influenza pandemic action plan	198	English
Singapore	2005	Influenza pandemic readiness and response plan - Draft	26	English
Sweden	2005	Contingency planning for an influenza pandemic - national measures	23	English

Since this document was compiled, all of the study countries have published more recent plans. Japan released an updated version of '*Pandemic Influenza Preparedness Action Plan of the Japanese Government*' in 2007. Singapore also had a revised '*Influenza pandemic readiness and response plan*' released in January 2009. The Public Health Agency of Canada lists all the documents relevant for the '*Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector*' online and each core area is a separate PDF. Therefore, nearly all documents have been updated since 2006 but this process has been conducted over several years. The 2006 New Zealand plan was no longer available and had been superseded by the 2010 '*New Zealand and Influenza Pandemic Plan: A framework for action*'. Likewise, Sweden had a new plan published in 2009: '*National plan for pandemic influenza – including a basis for regional and local planning*'. Both New Zealand and Sweden's country plans were published during the 2009-10 influenza A(H1N1) pandemic at the time of the WHO Phase 6. The following section shall summarise each study country's pandemic influenza plans.

4.3.1 Canada

Canada began pandemic planning early on, in 1983. In 1988, the first draft of the Canadian Contingency Plan for Pandemic Influenza was completed, and redrafts have followed. The plan is for people in the health sector who would be involved in the planning and response to an influenza pandemic (such as health emergency responders, health planners, health care workers, laboratories, pharmaceuticals). As Canada is a

federal country, the responsibility for pandemic influenza planning and response detailed in the plan lies with the provinces and territories to provide health care and essential services. Therefore, the plan specifically focuses on health sector response to a national public health emergency and is intended for guidance in the development of operational plans at provincial and territorial, regional, local and facility level by each government and health care institution (Public Health Agency of Canada, 2010). The Public Health Agency of Canada supplied the provincial and territorial Ministries of Public Health with a framework for organising their preparedness and response activities. National working groups and subcommittees addressed specific issues in the plan and developed guidelines. These were organised into the following components: surveillance, vaccines, antiviral drugs, public health measures, communications and health services. Health services were divided into infection control, clinical care, non-traditional sites and workers and resource management (Public Health Agency of Canada, 2010).

4.3.2 New Zealand

New Zealand has a National Health Emergency Plan (NHEP) to manage emergencies, which is a whole-government approach and includes available expertise and resources. Within the NHEP, the New Zealand Influenza Pandemic Action Plan (NZIPAP) was created in 2002. Prior to this, a response framework for pandemics was developed in 1997. The NZIPAP has undergone several revisions since its creation to include improvements and further understanding since the SARS

outbreak response, and two national response simulation exercises (Exercise Virex 2002; Exercise Cruickshank 2007) which tested the pandemic influenza plan. The Ministry of Health created the Pandemic Influenza Technical Advisory Group to provide advice on matters concerning clinical, virological, epidemiological, infection control and ethics. New Zealand's 21 District Health Boards (DHB) lead the planning and response at local levels (Jennings, 2013; NZIPP, 2010).

4.3.3 Sweden

Following A(H5N1) avian influenza and SARS outbreaks and the WHO calls for pandemic planning and the establishment of the European Centre for Disease Prevention and Control (ECDC) in 2005, the Swedish government instructed the National Board of Health and Welfare to produce the National Pandemic Plan, which was published in 2005 and revisions followed up to 2009. In 2005, the National Pandemic Group (NPG) was established to co-ordinate the planning, implementation and communication of pandemic control measures. The NPG has representatives from the National Board of Health and Welfare (NBHW), the Institute for Communicable Disease Control, the Swedish Civil Contingencies Agency, the Swedish Work Environment Authority, the Medical Products Agency, and the Swedish Association of Local Authorities and Regions (Swedish Civil Contingencies Agency & Socialstyrelsen, 2011). The National Board of Health and Welfare has the responsibility for organising and managing the pandemic influenza contingency planning in Sweden. Strategies cover the legal, medical and

organisational measures against influenza (The National Board of Health and Welfare, 2012). The 2009 'National plan for pandemic influenza – including a basis for regional and local planning' was used by Sweden during the 2009-10 influenza A(H1N1) pandemic and was developed by a working group. This group included representatives from the Swedish Institute for Infectious Disease Control, the Medical Products Agency, the Swedish Civil Contingencies Agency, the Swedish Work Environment Authority, the Swedish Association of Local Authorities and Regions, the County Medical Officers and supervising nurses from some municipalities (Social Services, 2009).

The agencies responsible for containing influenza at the national level in Sweden are managed by the National Board of Health and Welfare (Socialstyrelsen) and the Swedish Civil Contingencies Agency (Myndigheten för samhällsskydd och beredskap). At the regional level, Sweden has County Medical Officers of Communicable Disease Control (*Smittskyddsläkarna*) who manage the surveillance and practical implementation measures employed to alleviate outbreaks in their responsible counties. The Swedish Institute for Communicable Disease Control (Smittskyddsinstitutet, SMI) gathers surveillance data to report epidemiological and microbiological information on infectious diseases in Sweden.

4.3.4 Japan

In 2005, the Ministry of Health, Labour and Welfare of the Japanese Government produced the Pandemic Influenza

Preparedness Action Plan (PIPAP). The Pandemic Influenza Preparedness Action Plan of the Japanese Government was drafted with reference to the WHO Global Influenza Preparedness Plan of 2005. In the estimation of the potential burden of a new influenza pandemic, PIPAP calculated that if 25% of the population were to become infected, then this would result in approximately 17 million medical attendances. Within the Japanese Government, the Inter-ministerial Avian Influenza Committee was established in order to enable collaboration. The Headquarters for Pandemic Influenza Counter-measures was established by the Ministry of Health, Labour and Welfare. The PIPAP would involve local governments, organisations (e.g. health services) and the public (Ministry of Health, Labour and Welfare, 2005). The Japanese PIPAP refers to the six phases of events in pandemics detailed in the WHO Global Influenza Preparedness Plan. The PIPAP separated these WHO phases into two categories of 'no outbreak in Japan' and 'outbreak in Japan'. A revised version of the Pandemic Influenza Preparedness Action Plan of the Japanese Government was released in 2007.

4.3.5 Singapore

The Ministry of Public Health in Singapore released the Influenza Pandemic Readiness and Response Plan in 2007 which detailed public health and medical measures to prevent and manage pandemic influenza within the country. In the plan, the Singaporean Ministry of Public Health would be responsible for leading, coordinating and managing a response to an influenza pandemic. Singapore's response plan expected

that a novel influenza virus would be highly pathogenic, develop outside of the country, spread at a rapid pace and perhaps take a while for it to be laboratory confirmed as a new influenza virus. The plan expected that a new virus would enter the country by infected cases travelling into Singapore very quickly after the novel virus emerged from the South East Asia region and that this would be highly unpreventable. The plan intended the Ministry of Health to work towards delaying the spread of disease within the country (Singapore Ministry of Health, 2009). Singapore's national strategy for pandemic influenza was for the creation of a surveillance system, the reduction of associated consequences of pandemic influenza during the first wave (minimise mortality and morbidity) and then work towards immunising the population of Singapore with the developed vaccine. The Ministry of Health's pandemic influenza preparedness plan specially referred to preparations for the occurrence of avian influenza (A/H5N1). The case definition was sub-categorised into confirmed and suspected cases and would be announced during a pandemic. Clinical criteria were expected to be more frequently utilised for diagnosis of most patients rather than laboratory confirmation because this would involve time delay (Singapore Ministry of Health, 2009).

Table 7. Key characteristics of pandemic preparedness plans.

Study country	Key characteristics
Canada	Pandemic influenza could emerge from country in the world and at any time. There may be no lead in time before arriving within the country. Illness and mortality peaks will occur within weeks of first confirmed cases in Canada. Vulnerable

	populations expected to be most affected.
New Zealand	Creation of Pandemic Influenza Technical Advisory Group. All-of-Government approach to planning and response. Six phases of strategy actions in response to pandemic influenza covering humans, social and economic. Planning model based on 2% CFR. Severe impact of 1918 pandemic influenza in NZ noted.
Sweden	National Pandemic Group Established. Unlikely a vaccine will be available at the start of an influenza pandemic. Expectation of a 2-6 month wait. Knowledge of the uses of antiviral drugs in a pandemic is incomplete.
Japan	Inter-Ministerial Avian Influenza Committee established. If 25% of the Japanese population was infected during an influenza pandemic, then it was calculated that there would be 17 million medical attendances. Pandemic events related to WHO pandemic influenza phases. Expectation of avian influenza.
Singapore	Pandemic influenza expected to originate from outside Singapore and enter country by travellers. Intention to implement measures that would delay the spread of disease within Singapore.

4.4 Summary of plan purposes

The overarching purposes common to the study country pandemic influenza plans were to minimize serious illness and deaths and reduce societal disruption (see Table 8). Each study country pandemic influenza plan purposes are outlined in the below table.

Table 8: Objectives of pandemic plans from study countries

Study country	Purpose of pandemic plan
Canada	<i>"First, to minimize serious illness and overall deaths, and second to minimize societal disruption among Canadians as a result of an influenza pandemic."</i> (Public Health Agency of Canada, 2010: p.n/a).
Japan	The Inter-ministerial Avian Influenza Committee stated that the 2007 PIPAP was developed to <i>"minimize health risks of people and prevent possible damage to social and economic functions"</i> (2007: p.2).
New	The main objective of the NZIPAP is to <i>"minimise deaths,</i>

Zealand	<i>serious illness and serious disruption to communities and the economy arising from an influenza pandemic” (New Zealand Ministry of Health, 2010: p.1).</i>
Singapore	The response plan aimed for three outcomes (Singapore Ministry of Health, 2009: p.8): <ol style="list-style-type: none"> 1. <i>“Maintain essential services in Singapore to limit social and economic disruptions.</i> 2. <i>Reduce morbidity and mortality through treatment of influenza cases.</i> 3. <i>Slow and limit the spread of influenza to reduce the surge on the healthcare system.”</i>
Sweden	The objectives of the Swedish pandemic influenza plan are (Socialstyrelsen, 2009: p.15): <ol style="list-style-type: none"> 1. <i>“That the effect of the influenza on public health is as limited as possible</i> 2. <i>That negative effects on the community are as limited as possible</i> 3. <i>That the resources available to mitigate the effects are used as efficiently as possible.”</i>

4.5 Vaccine-specific policies

Many countries had prepared pandemic influenza national plans prior to the emergence of the novel (H1N1) influenza in April 2009, as outlined in the earlier part of this chapter. International organisations had urged countries to prepare for a new influenza against which people would have very little to no immunity. Events preceding 2009, such as avian influenza virus A(H5N1) and SARS, also played a part in igniting motivation to plan for, as well as enabling countries to test their plans for such a pandemic influenza response. Some countries, including Japan and Singapore, made avian influenza A(H5N1) specific pandemic plans. This is understandable due to the commonplace expectation that A(H5N1) posed a severe pandemic threat, that it was the cause of much pandemic influenza planning and these study countries close proximity to outbreaks in Asia. All five of the

study countries had plans for the event of a future pandemic influenza and all made mention of using vaccines in such an event. The preparedness policy included seeking and securing pandemic influenza vaccine orders with pharmaceutical companies. Therefore, this section shall focus on each study country's vaccine plans.

4.5.1 Sweden

Socialstyrelsen published Sweden's National Plan for Pandemic Influenza (2009) and emphasised the need for vaccines during an influenza pandemic: "*Mass vaccination is currently the only measure which could possibly stop a pandemic, but a vaccine will not be available during the first few months of a pandemic since in all likelihood it will not be possible to produce a vaccine in advance.*" (Socialstyrelsen, 2009: p.39). This statement highlights the belief in the effectiveness of a pandemic vaccine but also the concern of the time delay in vaccine production during the event of a novel influenza.

Socialstyrelsen in Sweden explained the reason for a monovalent, adjuvant and two dose vaccine: "*The vaccine that will be developed for a pandemic virus strain will be different from the vaccine used for the annual influenza. Since the virus in question will be known, the vaccine does not need to be trivalent – instead it will be monovalent, i.e. contain only one virus type. It will likely also contain a smaller quantity of the active substance and include immune-stimulating additives (adjuvants), all to maximise the amount of vaccine available. Two vaccine doses will probably be needed to achieve*

protective immunity, administered with an interval of at least a few weeks. This will require partially new logistics, both for administration and follow-up of the effects and side-effects of the vaccine.” (Socialstyrelsen, 2009: p.40).

In times of seasonal influenza, Sweden runs an annual vaccination campaign against influenza, targeting people deemed at *“an increased medical risk of a serious course of illness and complications, primarily in the form of pneumonia. People in these risk groups more often require hospital care and also represent a considerable proportion of the increased mortality seen in connection with influenza. In Sweden these medical risk groups are defined in the National Board of Health and Welfare general guidelines on vaccination against influenza (SOSFS 1997:21). These apply primarily to people with heart and/or lung disease, as well as people over 65. Together these groups are estimated to make up more than 1.5 million people in Sweden.” (Socialstyrelsen, 2009: p.40).* Sweden considered the annual vaccination programme as a way to learn, develop and prepare for implementing a mass vaccination campaign in the event of pandemic influenza and gain experience in the use of influenza vaccines. However, it was noted that: *“In the face of a threatening pandemic, the vaccination recommendations will differ considerably from those used during normal influenza seasons, for several reasons. The overall ambition will be for everyone to be vaccinated. As the vaccine will be delivered in batches, priorities may have to be made as to which groups should be vaccinated first.” (Socialstyrelsen, 2009: p.40).*

It was recognised that initially the pandemic vaccine would arrive in limited supplies. The reasons given were: *“production*

can only begin after the virus strain has been identified and profiled, and additionally it will probably take two doses to achieve good protection in an immunologically naive population, which implies a need for larger amounts of vaccine. Furthermore, vaccine manufacturer have only a limited capacity to produce large amounts of a new influenza vaccine in a short period of time. This means that countries with no influenza vaccine production of their own must rely on cooperation or agreements to create the conditions for receiving vaccine deliveries when a pandemic threatens or has broken out. Guidelines are already in place for the speedy approval of a new influenza vaccine needed in a pandemic. Talks have also been held with representatives of the European pharmaceuticals industry about the conditions for making production and distribution more efficient in a pandemic.” (Socialstyrelsen, 2009: p.41).

In order to provide guaranteed access to the pandemic vaccine, Sweden’s National Board of Health and Welfare, like many other countries, signed guarantee access agreement in 2007 for a vaccine to be supplied for the Swedish population in the event of an influenza pandemic. The agreement was explained as: *“Under the guarantee agreement, the vaccine manufacturer pledges to reserve a fixed share of its production capacity for Sweden during 3-6 months, which is equivalent to 18 million doses of pandemic vaccine. Production will begin when WHO declares that a pandemic has broken out, or earlier following a possible vote arranged by the manufacturer. The vaccine manufacturer also pledges to have its own preparedness in order to be able to manage production during a pandemic, as well as to give the National*

Board of Health and Welfare feedback on developments and status every quarter. Sweden, for its part, will support the manufacturer financially in its continued work on developing the vaccine. The agreement is valid for three years, with the possibility of a further extension. Under the delivery contract the supplier pledges to deliver the vaccine on a weekly basis during a period of 3-6 months, until the specified volume has been delivered.” (Socialstyrelsen, 2009: p.41).

Ahead of the event of an influenza pandemic, it was envisioned that the vaccine arriving in Sweden would be comprised of two components, antigen and adjuvant, which require mixing prior vaccination and contain enough for 10 doses. The timescale for delivery of the vaccine was estimated to be between three and six months, *“with weekly deliveries of 0.7-1.4 million doses each.”* (Socialstyrelsen, 2009: p.66).

4.5.2 New Zealand

The New Zealand Ministry of Health published the *‘New Zealand Influenza Pandemic Plan: A framework for action’* at the start of 2010 ahead of the arrival of the pandemic vaccine. New Zealand had secured two pandemic vaccine guarantees which would go live from the point of pandemic declaration. It was noted that it would take several months for the pandemic vaccine supplies to arrive in New Zealand after pandemic influenza declaration because in order for the manufacturers to produce a vaccine it is required *“a vaccine that will protect against the pandemic strain cannot be made until that strain*

has developed and is identified.” (New Zealand Influenza Pandemic Plan, 2010: p.142).

It was noted that the numerous aspects would influence the pandemic influenza vaccine order size, campaign strategies and timing of vaccine delivery: *“...including the nature (including the virulence) of the pandemic virus, the size of pandemic waves that may have already affected the population and the probable timing of vaccine deliveries. The process of vaccinating the population may be further complicated if each individual needs to be vaccinated twice because of the novel nature of the pandemic virus: management of this would probably involve administering two vaccinations about three weeks apart.” (New Zealand Influenza Pandemic Plan, 2010: p.142).*

The timing of the vaccine delivery was illustrated as having a prominent impact on the New Zealand response strategy: *“For example, late delivery of a vaccine in a moderate to severe pandemic may mean greater efforts need to be placed on the Keep It Out and Stamp It Out phases to flatten the pandemic curve and spread the impact more evenly over time.” (New Zealand Influenza Pandemic Plan, 2010: p.59).* However, in terms of vaccine delivery timing, it was recognised that New Zealand would need to wait several months for the arrival of vaccines following pandemic influenza declaration: *“A mass vaccination programme is unlikely to start for six months or more after a WHO declaration of a pandemic and production of vaccine. Decisions on the purchase of a vaccine need to be made by the Government, taking into account the costs and benefits to society of reducing the impact of the pandemic. Key decisions will centre on: length and intensity of*

containment measures and measures in the Manage It phase; speed of transition to the recovery phase; immunisation programmes.” (New Zealand Influenza Pandemic Plan, 2010: p.59).

4.5.3 Japan

The '*Pandemic Influenza Preparedness Action Plan of the Japanese Government (2007)*' in Japan was prepared with the expectation of an avian influenza H5N1 virus causing the next pandemic influenza. Therefore, the plans often referred to initial manufacture, stockpiling and use of the pre-pandemic influenza vaccine to provide healthcare workers and public service officials with protection should they wish to have the vaccination. The plan was structured according to distinct pandemic influenza phases with vaccine measures explained according to each phase.

A distinction of Japan in comparison to so many other countries was the intention to produce and supply a domestic pandemic influenza vaccine for the Japanese population. The plans detailed provisions for securing domestic companies to produce the vaccine, isolating the new virus strains, ensuring quality, securing hen eggs, in addition to each prefecture identifying the number of healthcare workers and public service workers for priority vaccination. During the event of pandemic influenza, Japan envisioned that vaccination campaign guidelines and immunisation priority assessments according to epidemiological information and manufacturing capacity would be calculated. Part of the Pharmaceutical

Affairs Law allowed the ability to import vaccines produced and approved outside of Japan should the domestic vaccine supply not be ready or approved.

According to the Japanese Government planning in 2007, it was prepared for all of the Japanese population to be vaccinated using the pandemic influenza vaccines, and for immunisation campaigns to commence as soon as the vaccine supply was received.

4.5.4 Singapore

The Singaporean Ministry of Health published the '*Influenza Pandemic Readiness and Response Plan*' in early 2009 and made mention of the pandemic vaccination policy in the event of an influenza pandemic. As like many other countries, the Singaporean Ministry of Health recognised the manufacturing time required to produce and supply in quantities a pandemic vaccine: "*...it is very likely that vaccines will only be available after 4-6 months. In the initial stages, these will be in short supply. However, vaccination is the key strategy in response to an influenza pandemic.*" (Ministry of Health Singapore, 2009: p.21). Like Sweden, Singapore highlighted the important role of vaccination during an influenza pandemic response, and explained the need for priority groups in the immunisation strategy, as also stated by Japan: "*Initially, when vaccines are in short supply, vaccination will be provided to priority groups, such as those at higher risk of influenza-related complications and essential services. As the vaccines become more readily available, vaccination will be expanded*

to the rest of the population." (Ministry of Health Singapore, 2009: p.21).

4.5.5 Canada

The Public Health Agency of Canada published pandemic influenza plans online and produced a specific pandemic influenza vaccine document titled: '*Preparing for the Pandemic Vaccine Response*' which was published in 2008, although Canadian planning predates this by nearly two decades. The pandemic vaccine aspect of the Canadian response to an event of an influenza pandemic has been held in high regard, for instance, the plan states that: "*Immunization with a safe and effective pandemic vaccine has always been considered the cornerstone of the health response to pandemic influenza in Canada.*" (Public Health Agency of Canada, 2008: p.3).

The Canadian plan explains that the intention is for the Federal Government to obtain enough pandemic vaccines in order for all Canadian people to have the vaccine and to aid swift supply throughout the country: "*The federal government has made a commitment to secure enough pandemic vaccine for every person in Canada in order to help prevent illness due to the pandemic virus. In addition, the federal government is committed to working with the provincial and territorial governments to ensure that the pandemic vaccine is made available to as many people as possible as quickly as possible.*" (Public Health Agency of Canada, 2008: p.3). Although Canada is separated by distinct provinces and territories, the federal government would be involved with and

oversee a pandemic influenza response due to the disease spanning provinces and territories.

Canada was many steps ahead of other countries in respect to pandemic vaccine guarantee contract. In 2001, Canada established a 'pandemic readiness vaccine contract' valid for 10 years with a domestic manufacturer. Canada's preparedness actions and statements emphasise the importance held for pandemic vaccines as reiterated here: *"the need for a safe and effective pandemic vaccine as early as possible in the global outbreak has remained the ultimate means to achieve the goals of reducing morbidity, mortality and societal disruption due to an influenza pandemic."* (Public Health Agency of Canada, 2008: p.4).

Canada outlined their vaccination strategy, which was: *"to provide a safe and effective vaccine for all Canadians as quickly as possible; to allocate, distribute and administer vaccine as efficiently as possible to the appropriate groups of people; to monitor the safety and effectiveness of immunization programs."* (Public Health Agency of Canada, 2008: p.6).

Canada, like so many other countries, produced a pandemic influenza plan based on a set of assumptions for the next pandemic influenza which directly affected vaccine planning. Canada expected the novel influenza to emerge outside of the country and arrive about three months' after identification, although air travel could reduce this estimate. It was recognised that illness from pandemic influenza and deaths would occur and may have a first wave peak prior to obtaining the vaccine. The Pandemic Vaccine Working Group of PIC put

forward these (5 of the 8 mentioned here) vaccine specific assumptions:

- *"A pandemic vaccine will become available in time to have an effect on the impact of the pandemic in Canada. The extent of the effect will largely depend on the timing of vaccine availability in comparison to pandemic activity in Canada.*
- *Two doses of vaccine will be needed in order to optimize protection (i.e. more protection will be provided by a second dose of pandemic vaccine). The two doses would be given approximately one month apart.*
- *The new pandemic vaccine is not likely to be 100% effective, but even a vaccine with relatively low efficacy (e.g. 30%) will help curb the effect of the pandemic.*
- *Concern regarding vaccine safety and reactogenicity will likely be inversely proportional to the severity of the pandemic in Canada.*
- *Depending on the timing of the pandemic and availability of the pandemic vaccine, seasonal influenza immunization programs may not be initiated or completed, as the pandemic vaccine program is the priority." (Public Health Agency of Canada, 2008: p.5).*

Interestingly, Canada identified population groups ahead of the emergence of a novel influenza that progressed into a pandemic influenza; however Canada would not list the order of priority groups because this would only be done once knowledge about the virus had been assessed. The sub-groups discussed were broadly categorised according to age and

profession details. Whilst not setting a priority list order, Canada also had no policy decision in place concerning where the first vaccine doses would be sent within Canada. They explained that a simple per capita approach could be applied in order to be most equitable, however, other factors may influence the decision at the time. For instance, it was explained that in reality, vaccine dose supplies may be considered more important in areas of Canada where the disease activity was accelerating in order to try to suppress the disease in these locations. But then, on the other hand, mass immunisation programmes in areas where the disease had subsided or disease activity was low may provide the preferable situation to deliver an immunisation programme because resources would not be allocated elsewhere. These decisions were planned to be made during the pandemic influenza event and through not formulating this aspect of the plan and setting a policy prior a pandemic influenza, it was explained that this built in an element of flexibility and the ability to respond to current information and knowledge and with technology of the time (Public Health Agency of Canada, 2008).

Table 9. Key vaccine specific content of pandemic influenza preparedness policies.

Study countries	Vaccine specific pandemic influenza preparedness policies
Sweden	In 2007, one guarantee agreement with vaccine manufacturer for pandemic vaccine agreed. "Mass vaccination is currently the only measure which could possibly stop a pandemic..." (P.39) Sweden did not stockpile pre-pandemic vaccines of H5N1 prior 2009 due to the uncertainty surrounding the next pandemic influenza virus. It was planned that the vaccine would be monovalent and would include adjuvants that most likely require two doses

	for immunity. Overall ambition for everyone to be vaccinated. Vaccine would need to be prioritised due to limited initial supply.
NZ	Delay of vaccination for six months initially expected. Supply held of 400,000 doses of pre-pandemic vaccine (H5N1). Prioritised frontline health care workers and people identified as high risk of life threatening complications. Supply amount dependent on pandemic influenza virulence and disease activity in respect to the likely timing of the vaccine delivery. Expectation that two vaccinations spread three weeks apart would most likely be required.
Japan	Japan intended to produce and supply a domestic pandemic influenza vaccine for the Japanese population. Had an interest in pre-pandemic vaccines. Japan wished to vaccinate all of the Japanese population as soon as possible. Japan would identify health care workers and public service workers for vaccination prioritisation.
Singapore	Singapore would be without a vaccine at the start of a pandemic and the waiting time would take at least six months. The initial supply of vaccines will be limited and groups will be prioritised. Vaccination will extend to the entire population in time.
Canada	Developed vaccines will not be available during the first wave of disease activity but it is assumed to be available in enough time to have an overall impact on the pandemic influenza. Immunisation is the most effective strategy to prevent influenza infection and mortality. Vaccination all that wish to reach the vaccine.

4.6 Pandemic influenza vaccines ordered and deployed in 2009-10

All five of the study countries reportedly ordered and deployed pandemic influenza vaccines during the 2009-10 influenza A(H1N1) pandemic according to the published literature.

Sweden and Canada reportedly received the pandemic influenza vaccines first, with the initial batches arriving in October 2009 in small quantities and then increasing to larger quantities over the coming months. This was followed by Singapore and Japan a few weeks later. New Zealand was the last to implement an immunisation campaign due to the southern hemisphere time of year and the availability of the

vaccine. New Zealand launched their immunisation campaign at the start of their autumn; February 2010, almost a year after the emergence of the novel (H1N1) virus.

All countries used the monovalent pandemic influenza vaccine but to varying extents; the differences of vaccine use were multifactorial. The main differences were due to policy, disease activity, vaccine arrival timing, and knowledge during the course of the pandemic influenza. Table 10 shows the quantities of vaccines ordered and product type.

Table 10. Pandemic influenza vaccines purchased in 2009, population size and target immunisation coverage.

Country	Number of doses ordered (million)	Vaccine product	Population size in 2009 (million)	Target population coverage provided
Sweden (The Swedish Institute for Communicable Disease Control, 2011; Statistics Sweden, 2010)	18	Adjuvanted GlaxoSmithKline vaccine Pandemrix®	9.3	Entire Swedish population
New Zealand (Jennings, 2013)	0.3	Non-adjuvanted Celvapan®	4.4	Risk groups and front-line HCWs
Japan (Foreign and Commonwealth Office, 2011; MHLW, 2010; Igari et al., 2010)	9.9 (Novartis 2.5 & GSK 7.4) plus domestic products	Various products: Imported included adjuvant & domestics were inactivated, unadjuvanted	127	Entire Japanese population
Singapore (HAS, 2014; Ministry of Health Singapore, 2009; Vaughan, 2009)	1.3 (1 from CSL Limited, 0.3 from GSK)	CSL Ltd Panvax® H1N1 / Panvax® H1N1 Junior - vaccine inactivated monovalent & GSK Pandemrix®	4.8	Entire Singaporean population in plans
Canada (Eggleton and Ogilvie, 2011; Foreign and Commonwealth Office, 2012)	50.4 (dose order reduced when known that one dose was required)	Adjuvanted GlaxoSmithKline vaccine Pandemrix® and small number of unadjuvanted vaccine for pregnant women	34	Dose order was based on 75% uptake and the need for two doses per person

As shown in Table 10, Sweden ordered enough vaccines to provide each citizen with two doses of the vaccine. This was similar to the approach taken by the United Kingdom. Canada ordered enough vaccines for the majority of the population; when the dose quantity changed from two doses to one, Canada had enough for each citizen. Japan ordered a relatively small number of vaccines to provide coverage to almost all citizens but largely sourced the vaccines domestically. Singapore and New Zealand ordered fewer doses in relation to population coverage. However, New Zealand has an annual agreement for seasonal trivalent vaccines so in April 2010 New Zealand received many more doses.

Table 10 shows national population size and target vaccination coverage. Sweden and Canada reported higher than average pandemic influenza vaccine uptake rates of 60% and 40% respectively.

Table 11 includes the vaccination uptake rate and proportion of ordered vaccines utilised. Sweden and Canada reported higher than average pandemic influenza vaccine uptake rates of 60% and 40% respectively.

Table 11: Vaccination uptake rate and proportion of utilised vaccines in study countries

Country	Vaccine uptake (of population)	Number of vaccines used
Sweden (The Swedish Institute for Communicable)	60%	6,070,604 doses of Pandemrix® were administered. An estimated 5,560,000 of the population

Disease Control, 2011)		received at least on dose
New Zealand (Jennings, 2013; The ANZIC Influenza Investigators, 2011)	24%	One-quarter of the population received monovalent and/or trivalent seasonal influenza vaccine
Japan (Tomizuka and Matsuda, 2010)	17%	22.8 million (Imported: 3,645 doses were dispensed & 541 received the vaccine)
Singapore (Vaughan, 2009)	Not found	405,000 doses had reportedly been used by December 2009
Canada (Eggleton and Ogilvie, 2011)	>40%	Not found

The immunisation schedules varied between the countries in terms of the timing and priority groups. All countries decided to prioritise the vaccine. Japan, Singapore and New Zealand focused on providing it first to healthcare workers whereas Sweden and Canada's first priority group included children, pregnant women and persons with respiratory conditions severely compromised by influenza-like-illness. Japan's subsequent priority groups were pregnant women and high-risk persons, followed by pre-school aged children.

Canada was one of the first countries in the world to receive the pandemic vaccine (Eggleton, 2010), and it was the first study country in this research project. However, the vaccines were not approved for use until 21st October 2009 (Canadian Pharmacists Journal (no author listed), 2009). In Sweden, the vaccines became available on 13th October 2009 for use (Venice II, 2011). Japan's vaccination programme began on 19th October 2009 with foreign produced vaccines, and later domestic vaccines became available (Yasuda and Suzuki, 2009). Singapore was the last northern hemisphere study

country to commence vaccination on the 3rd November 2009: however it was the first South-East Asian country to provide the pandemic influenza vaccine (State of Health, 2012). New Zealand received a limited number of monovalent doses in February 2010 which were reserved for their first priority group of healthcare workers, after which New Zealand moved onto focusing on the seasonal trivalent influenza vaccine which included the 2009-10 influenza A(H1N1) pandemic virus component from April 2010 (Jennings, 2013).

4.7 Country overviews

This section provides a short summary of the key information concerning country specific details of pandemic timing, implemented response strategies and vaccination campaign details. The text boxes are provided for each study country and the information has been reproduced from earlier chapters.

Table 12. Overview of key information for Sweden.

<p><u>Pandemic timing</u>: first confirmed cases early May 2009; three cases by 20th May 2009; first wave during the summer with a peak in epidemiological week 29; second wave peaked in epidemiological week 36: geographical spread of infection north to south of Sweden</p> <p><u>Actual response strategies</u>: notifiable disease on 15th May 2009; surveillance; diagnostic services; health messages; two phases of strategy response (search and contain, mitigation)</p> <p><u>Vaccine deployment timing</u>: October 2009</p>
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Vaccine prioritisation: children with chronic conditions aged between 6 months and 3 years old, all children aged between 6 months and 3 years old; pregnant women; people with respiratory conditions severely compromised by ILI; critical infrastructure employees

Table 13. Overview of key information for New Zealand.

Pandemic timing: first confirmed case 25th April 2009; nine cases by 20th May 2009; cases mainly only reported in city areas by 22nd June 2009; first wave between April and December 2009 and peaked in June; second wave peaked in August 2010; 10 deaths during 2010

Actual response strategies: pandemic plan activated; airport screening; notifiable and quarantinable disease on 30th April 2009; six phases of strategy response (containment and management); antivirals (treatment and prophylaxis); isolation; surveillance; diagnostic services; health messages; Flu Centres; a handful of school closures

Vaccine deployment timing: February 2010 (monovalent doses for healthcare workers); seasonal trivalent influenza vaccine inclusive of H1N1 component from April 2010

Vaccine prioritisation: healthcare workers (monovalent vaccine); annual influenza risk groups including pregnant women (seasonal trivalent vaccine)

Table 14. Overview of key information for Japan.

Pandemic timing: first confirmed cases 9th May 2009; 401 cases in 16 of the 47 prefectures by 4th June 2009; 85 confirmed deaths by 1st December 2009

Actual response strategies: airport screening; quarantine; thousands of school closures; surveillance; diagnostic services; health messages

Vaccine deployment timing: November 2009 (October 2009 for imported

vaccine that was rarely used)

Vaccine prioritisation: health care workers/medical staff; pregnant women; persons with chronic illnesses; children ≤ 5 years old; people aged ≥ 65 years old; available to all.

Table 15. Overview of key information for Singapore.

Pandemic timing: first confirmed case 26th May 2009; first death 18th July 2009

Actual response strategies: notifiable disease on 27th April 2009; airport screening; isolation; contact tracing; antivirals; surveillance; diagnostic services; health messages; three phases of pandemic influenza management; flu centres;

Vaccine deployment timing: November 2009

Vaccine prioritisation: healthcare workers

Table 16. Overview of key information for Canada.

Pandemic timing: first confirmed case 23rd April 2009; six cases by 28th April 2009; 496 cases (one death) by 20th May 2009; cases reported in all provinces and territories by 11th June 2009; first wave during the spring with a peak at the beginning of June 2009; second wave during autumn with a peak at the beginning of November 2009

Actual response strategies: surveillance; diagnostic services; health messages; antivirals

Vaccine deployment timing: October 2009

Vaccine prioritisation: pregnant women; health care workers; persons based in remoted community locations; persons aged < 65 years old with chronic conditions; children aged between 6 months and 5 years

4.8 Development of the interview guide

The examination of the pandemic influenza preparedness policies was extremely helpful in the pursuit of formulating the interview questions ahead of organising the study country visits. It provided an understanding of how long countries had planned for a pandemic influenza event, the assumptions in preparation for a new pandemic (e.g. Avian influenza originating from Asia), and the anticipated response measures (e.g. entire population would be vaccinated; two doses required for immunity).

The literature review, both of pandemic preparedness policies and the history of pandemic influenza in the twentieth century and past response measures, gave the researcher country specific insight into how the study countries have previously experienced pandemic influenza. This context was important ahead of embarking on country visits and upon reflection of the interview data.

4.9 Summary of pandemic influenza policies chapter

This pandemic influenza policies chapter has covered pandemic preparedness, study countries pandemic influenza plans, vaccine agreements prior to 2009 and the (H1N1) vaccines ordered and deployed during the 2009-10 influenza A(H1N1) pandemic. These four aspects of this chapter were an important foundation to build upon before interviews in the field were conducted. The following chapter is concerned with the pandemic vaccine use interview findings.

5 Study 2: Pandemic Influenza Vaccine Interview Findings

This chapter examines the use of vaccines during the 2009-10 influenza A(H1N1) pandemic in five study countries: Sweden, New Zealand, Singapore, Japan and Canada. The emergent themes from the interviews with key pandemic influenza personnel form the discussion.

5.1 Participants characteristics

The interviews were with key pandemic influenza response personnel such as public health officials, policy makers, clinicians, government officials, surveillance and agency staff, all of whom were working at the time of 2009-10 influenza A(H1N1) pandemic in a national role and could comment on antivirals, vaccines, non-pharmaceutical measures and wider societal issues. Whether or not participants had worked across all elements of pandemic response or had a specific role, such as the national vaccination campaign, depended on the structure of services in countries. Typically participants could discuss the uses of antivirals and vaccines but fewer participants were knowledgeable of the non-pharmaceutical measures within their country.

Participant job titles and organisations have not been included here in order to prevent the identification of individuals and breach confidentiality agreements made at time of interview. Some of the highly specialised senior participants held the

only position in their country e.g. Head of Pandemic Influenza within the organisation X in country Y.

The interviewing process has resulted in 36 interviews with 39 people in five study countries, as summarised in Table 17.

Table 17: Summary of number of participants and number of interviews

	Participants	Interviews
Sweden	8	7
New Zealand	10	9
Japan	7	7
Singapore	7	7
Canada	7	6
Total	39	36

One unforeseen issue that arose was that a small number of participants would not be interviewed alone. In one instance the participants explained that they had equal roles and input and that this required them to be both present in an interview at the same time. The researcher was concerned about the effect of this dynamic on the interview process but found that these interviews were positive in that the participants seemed relaxed together, took a longer amount of time to explain points than average and the participants complemented the discussion by adding in extra detail and helped each other recall events. The researcher believed it was more important to secure interviews with the ideal participants rather than be

inflexible about the interview participation or force an interview set-up on reluctant solo participants.

5.2 Interview data

The data collection resulted in 42.5 hours of audio recordings and this equated to just over 300,000 spoken words (both interviewer and participants).

Table 18: Interview data collection summary.

	Audio recording time	Transcript word count
Sweden	7hr 25m	47,018
New Zealand	12hr 25m	94,320
Japan	8hr 48m	41,389
Singapore	6hr 58m	60,910
Canada	6hr 56m	60,953
Total	42hr 32m	304,590

The interview data collection summary table (Table 18) demonstrates that countries such as Sweden and Japan, which have a language other than English, took on average a longer time to conduct and produced fewer spoken words. Nevertheless, the quality of the data from these countries was no less than the other study countries.

5.3 **Pandemic vaccine use focus**

When this research was designed, four core policy areas were proposed to be examined, one of which was the pandemic influenza vaccines. As stated earlier in the thesis, the pandemic influenza vaccine work package focus in this project was:

"...[to] examine the use or non-use of monovalent pandemic influenza vaccines, including timing of deployment and type (inactivated, live, adjuvanted etc.), policy intention (pre-pandemic) versus policy implementation (and reasons for any discordance)."

In other words, the following research question simply covers the proposed above: How and when were the pandemic influenza vaccines used during the 2009-10 influenza A(H1N1) pandemic?

This chapter will refer to the narratives from participants regarding how the pandemic influenza vaccines were used in the reality of a pandemic influenza.

5.4 **Interview themes**

This section forms the central focus of this chapter because it presents the pandemic influenza vaccine findings from the interviews conducted with key response pandemic influenza personnel.

5.4.1 Distribution and Access

5.4.1.1 Access

All of the study countries had a pandemic vaccine procurement agreement in place prior to the 2009-10 influenza A(H1N1) pandemic onset. These vaccine agreements were organised before 2009 so that in the event of an influenza pandemic emerging, countries could have access to a developed pandemic influenza vaccine for their citizens. By formularising an influenza pandemic vaccine agreement, all study countries would have a vaccine to respond to an emerged pandemic influenza threat. The vaccine procurement agreements varied slightly between countries. Singapore and Japan had a multi supplier vaccine agreement, compared to the singular pharmaceutical company supplier route in Sweden, Canada and New Zealand. Both Canada and Japan had facilities within their nations to source a domestically developed vaccine.

Japan had a vaccine agreement to source a vaccine from abroad as it was predicted that they would not be able to produce an adequate supply of domestic vaccine quickly enough during a pandemic influenza scenario. The cost of a dual supply route was significant and the costs were further impacted due to the low uptake rate of the imported vaccine: *"...we cancelled the imported vaccination, but we still paid lots of money maybe, it's quite big money, we can use such a big money for elderly care or for children but yes we have made a contract [....]. First we ordered 37 million doses from GSK and*

212.5 million doses from Novartis, so that's the total amount is equivalent to all the Japanese people to be vaccinated two. In Japan yeah we imported for 99 million persons, so we have 120 million persons, we can produce vaccination for about 20 million people by domestic companies. But for 99, 100 million people, we didn't have the capacity of producing the vaccination." (JA3)

Whilst Japan had the facilities for domestic production of the vaccine in time, Singapore did not. Singapore, like Japan, decided to have a multi supplier for the pandemic vaccine in order to access the pandemic vaccine supply quickly for their population: *"...my guess would be it's to not put your eggs all in one basket because supply, demand and supply, which suppliers would be able to supply you in the first instance. Which supplier would be able to get the, what is that, the regulatory approval for use and things like that so with all these factors coming in I think that's probably how it came about."* (SI2) Another participant commented on the vaccine multi supplier arrangement: *"I think it was just a matter of, because before that, as part of the plan, we already have arrangement with Australian company for pandemic vaccine supply. That's, that was, that's got that as part of our plan, our preparedness plan and though we maintain that so. But at the same time, the people in charge of procurement were also asked us, is there any other supplier who can possibly give the vaccine earlier than the Australians. And then so GSK offered some vaccine earlier."* (SI6)

The multi supplier route in Singapore was due to the logistics of quickly gaining a supply of the pandemic vaccine for Singaporeans: *"I think it was a matter of logistics of our, of*

how much, how many doses can you give to me ASAP and it was X number of those were Australian and then I look at the other company and how many can you give me. In the end it's, so they were not pre-decided, it was better how much, how much doses, how many doses can you give to me." (SI6)

As noted above, the two study countries with multi suppliers (Japan and Singapore) were situated in Asia, which was the region where it was predicted that the next pandemic influenza may emerge from. During the 2009-10 influenza A(H1N1) pandemic, Canada required a small quantity of unadjuvanted vaccines and sourced these from an alternative supplier after discussions with their singular supplier, and thus through the course of the 2009-10 influenza A(H1N1) pandemic became a country with multi suppliers.

Sweden and Canada accessed the monovalent pandemic influenza vaccine but due to the timing of the 2009-10 influenza A(H1N1) pandemic disease activity within the southern hemisphere and time required for the development of the pandemic influenza vaccine, New Zealand received a small quantity of monovalent pandemic influenza vaccines which was soon supplanted by the trivalent annual influenza vaccine containing components against A(H1N1). The monovalent pandemic influenza vaccine was rolled out in limited quantities to first priority groups in January 2010 and then in March the seasonal influenza vaccination programme commenced: *"But the Ministry because there was limited trial information with this Baxter cell culture vaccine, as a whole virus vaccine, the Ministry wanted all the boxes ticked in terms of the relevant information and FDA eventually lead to FDA approval so all the boxes weren't ticked until end of*

January, 21st January or whatever of 2010 [...]. And then in March we started the seasonal vaccination programme which included the new H1N1 pandemic component so that we then moved into the normal seasonal influenza vaccination cycle.”
(NZ4)

Some of the study countries discussed the adjuvant component of the pandemic influenza vaccine as this component would be new to be used (for some countries) during a future pandemic influenza. The adjuvant component would enable the rapid production of large quantities of pandemic influenza vaccines compared to past techniques. A small quantity of unadjuvanted vaccine would be accessed for particular population groups, such as pregnant women. The Canadian pandemic vaccine agreement in place prior to the 2009-10 influenza A(H1N1) pandemic with GSK included the purchase of the adjuvanted monovalent pandemic vaccine in the event of a novel influenza. When describing the adjuvanted vaccine agreement CA2 participant said: *“They had gone, as I say, to an adjuvanted vaccine, for very good reasons, in terms of production capacity and other, I think with H1N1 it wasn’t necessary that, the adjuvant wasn’t necessary in terms of immune response, but for others, with things like H5N1, which was the large concern before 2009, the adjuvanted vaccine really was something that was necessary from everything that I had seen. So GSK did almost exclusively adjuvanted vaccine. They did agree that they would produce a small quantity of unadjuvanted because there was concern at the time about pregnant women, and there just wasn’t enough evidence on the use of the adjuvant in pregnant women. So we did arrange with the, with GSK to*

supply some unadjuvanted vaccine, it was a question of the timing of that. And there was concern that it would not be, the unadjuvanted would not be available in time. So we were told that we needed to find an alternative source, and we ended up contracting for a small, I think 200,000 doses of unadjuvanted vaccine from CSL, and that was done, it was a contract with the company but CSL had to get permission from the Australian government, and there was some dialogue between the Canadian government and the Australian government to allow that to happen. And then the 200,000 doses were brought in and it was allocated across the country based on estimates of pregnant women across the country, and then it was maintained primarily for pregnant women.” (CA2)

5.4.1.2 Distribution

The need for gatekeepers, those forming part of the pandemic influenza response personnel, for the distribution of the pandemic influenza vaccines was discussed by participants from Canada, Japan and Singapore. It was explained that there was a requirement to have “...*gatekeepers for how the vaccine was distributed...*” (CA1), alongside a review of disease activity data for an appropriate response. One participant in Japan spoke of the vaccine distribution plan challenges and the numerous decisions required by response personnel at the time: “...*during the course of vaccination in the Autumn, how to provide vaccine, what is the priority and how to secure the logistics, these are very difficult operation, these two are something that I remember well.*” (JA7)

Sweden and Japan took the decision to provide enough pandemic influenza vaccines for the entire population, Canada and New Zealand purchased for the majority of their national populations (Canada subsequently had enough for the entire population after the one dose revision), whereas Singapore, in contrast, purchased a limited portion of pandemic influenza vaccines. It was explained that in Singapore, influenza vaccine uptake rates had historically been low so would indicate that ordering vaccines for the entire population would be an inappropriate use of resources.

Several participants from Sweden mentioned that the decision taken to purchase enough vaccine for the entire country population was mainly a political decision. Resource allocation for pandemic vaccines was made available to all: *"It was I would say that decision was largely a political decision because from the National Board of Health we went to the government and said of course show the different options on how much to buy, what do you think is reasonable, or what kind of level would you like to go for, and they found it very difficult to, and we said we don't really know what groups go for in this case if we want to give less than to the whole population because for vaccines we really show a chance to affect the disease activity, not only to protect people but also to actually, on the individual, but also to get an impact on disease activity, and we told them quite clearly that at this stage we don't know if there's going to be vulnerable groups we don't know what they're going to look like and how big part of the population that will be so I think, and this is maybe something you should also ask <****> but, what, how the discussion went with the government, but I think they went*

for the National Board of Health's sort of thinking that is very difficult to do anything else than to go for a whole population because how we sort of communicate who's going to get it and who's not going to get it, if there is not enough for everybody I think those it comes down to equitable.....so that part is very very strong in Swedish healthcare there should always be equitable access to healthcare and that's very strong in the law surrounding our healthcare and so on and I think from that sort of, in that kind of culture it was very difficult to say anything else even if, of course technically you could go out and say sure we're never going to reach a level of coverage below or above 70 80% or something that, but that, it's also very difficult to communicate because we know that we have a coverage in childhood diseases of 98%.” (SW5) This equitable access to the vaccine by the entire Swedish population was also discussed by participant SW7:

Interviewer: Do you know they went with the whole population instead of just...

SW7: "Just to avoid the discussions I think. And we had the vaccine for the whole population."

Interviewer: In the agreement? Did you have that in the plan?

SW7: "Yeah. And they were able to distribute it too, at that time, so I think to make it more fair, Sweden is a fair country isn't it?"

Interviewer: Yeah. So for equality and access?

SW7: "Yeah, for everybody. Why should special groups have it, and so on. I think this part of you know, I think that people

in Sweden the public think that the government is supposed to take care of them and that the government is supposed to be fair, and I think that's part of it."

The vaccination campaign formed the backbone of Sweden's pandemic influenza response in 2009: *"The biggest event was the vaccination campaign, because we took the decision that we should offer everyone in the country the vaccination, that was the biggest issue and when we started the campaign it was all over the papers and then in some cities people were queuing up and I think Sweden in the end, we had the highest coverage of people being vaccinated. We had the highest. So, and that was of course, after the pandemic it has been thorough decision in media and amongst people, 'was it necessary to vaccinate the whole country' and things like that so it has been many decisions about this, many articles in the papers."* (SW6)

Interviewer: Do you know why Sweden chose to get enough for the entire population?

"Well, as you will never know the severity of a new virus, this you have to, you have to prepare yourself for the worst case so that's why. It was a preparation, it is a preparedness preparation for the worst case, so, but on that issue, I'm not sure whether there were more countries with the planning to vaccinate the whole population, there was certainly more countries but they didn't achieve. And it's also of course a political issue because if this was to be a very very severe pandemic, how do you choose between people." (SW6)

Once the vaccine began arriving into Japan, it arrived in batches and this supply required priority groups to be arranged: *"I do not remember quite well but I presume Japan, as a government, intended to provide the vaccination for all the population but we couldn't do it all at once as the productions are coming step by step so we ultimately wanted to vaccinate everybody but we certainly had to set a priority who should be vaccinated first and then second and third and fourth and going down."* (JA7)

The discussions on the distribution of the pandemic influenza vaccines referred to the subject of the equitable allocation of vaccines. Key pandemic influenza response personnel presented the need to provide equitable access and distribute the vaccines fairly but the pressures of 2009-10 influenza A(H1N1) pandemic demanded that vaccines would not initially be available to the entire country population. Therefore, the intentions of the plans were to provide equitable access and distribution of pandemic influenza vaccines but the reality of pandemic influenza response threatened the desired equitable allocation. Participants discussed this challenging area of the pandemic influenza response, such as when the vaccines become available it was necessary *"...to agree on an equitable allocation of the vaccine."* (CA2). However, even though a distribution plan was agreed, in reality the pandemic influenza disease activity required changes to be made to the vaccine distribution plans: *"And in theory what we were going to do and then in practice was a little bit different, but, because the vaccine was not really coming out in the same, at the same rate or as much, as quickly as we'd hoped it was going to be. So it was a question of organising an appropriate allocation on*

a weekly basis, is what it came down to. And then later we ended up having to, or the decision was taken to access a small quantity of an alternative vaccine.” (CA2)

Frequently the pandemic influenza vaccine supply arrived later than anticipated which interrupted the planned vaccination campaigns within the study countries. The changing supply timeframe and vaccine quotas caused uncertainty and required pandemic influenza response personnel to make amendments to intended vaccination programmes. The supply of the pandemic influenza vaccine in Canada arrived slightly later than anticipated: *“...I know that the dates kept getting moved up, we thought it was going to be a certain time and then there were some issues with the distributors and I think that was globally, and there was some messaging around then...” (CA1).*

Sweden had secured a pandemic vaccine supply before the 2009-10 influenza A(H1N1) pandemic emerged. Participants discussed the challenge of waiting for the supply to arrive and dealing with the fluctuating doses reportedly arriving in to Sweden: *“...it was very frustrating with the lack of vaccine, and it was so changing all the time. The deliveries, the information would change several times a week, we had one week were it could be changed seven times, in a few days, and we had to recalculate all the time, and inform all these 700 places that you won’t get what you were expecting, so you had to tell people to wait, and I think that was the hardest thing, to communicate how much vaccine they would have and how many people they could vaccinate, and then they were in turn, discussing with all the patients who were waiting for the vaccination, so that was frustrating.” (SW2)*

Sweden's pandemic influenza vaccine supply, Pandemrix®, was sourced from GSK. Sweden's pandemic influenza distribution plan was in place before the vaccine batches began arriving: *"....we were prepared to start several weeks earlier, and we were waiting but in the end there was problems and we were promised delivery at least a couple of two three weeks earlier, everybody stood ready to start vaccinating but they had some technical problems with the vaccines and they had a delay in the delivery of them."* (SW5) *"The main problem with the vaccine was lack of access for a long time, and that the deliveries were so uncertain we never really knew how much, how much vaccines we would get until it actually arrived, apparently the production process in the beginning was not very easy to [MUFFLED] so the amount, and that caused quite a lot of irritation because it was very difficult to plan how much vaccines to offer when we never really knew how much vaccines there was going to be available."* (SW5) *"Well we hadn't really prepared for, and I don't know if the companies had before, but they had never told us about it, was the irregular distribution, we had, we knew that we were going to get vaccines during a number of weeks, weekly deliveries and somehow we had assumed of course we were going to get equal amounts each week but that was not true at all, in the first weeks we got comparatively little and then it became more and more and that was something we missed, or miscalculated, I don't know who really is to blame about that, but that's something we didn't understand."* (SW5) Even with a vaccine arrangement in place, there was concern about when the first batch would arrive: *"Yeah I think there was a lot of fear whether they can deliver it, whether they can honour the contract and were*

indeed able to deliver the vaccine and then the problems in actual fact the take up rate was low for everyone.” (SI3)

The participants discussed the quantity of vaccines and cost when making supply decisions. Initially many countries factored in the need for two doses per person into the quantity and cost calculations, which subsequently was altered to one dose per person after further knowledge was gained during the 2009-10 influenza A(H1N1) pandemic.

Singapore ordered approximately 1 million doses of pandemic influenza vaccine (700,000 from the Australian manufacturer and 300,000 from GSK) and this supply covered approximately one quarter of Singapore’s population. Other countries, such as Sweden, ordered enough vaccines to cover their national population, however Singapore ordered less based on the reasoning: *“My understanding, which could be wrong, but my understanding is that the vaccines were expensive, I mean there is a certain cost and there’s also a concern not to waste things, but we also weren’t sure that people would actually take the vaccine. If you remember, I mean there are issues with adjuvant, there was a small adjuvanted vaccines, and adjuvanted vaccines have not been used in the United States because of concerns about the adjuvant and effects from it. So I think in the beginning when we were looking at it, we were looking at whether even if we bought vaccine for every man, women and child in Singapore, whether it would actually get deployed, because you know you only have a certain amount of period of time to give the vaccine, if you really want to make a dent on what’s happening, it doesn’t make sense to give vaccine to people who have already got the disease, kind of like shutting the*

barn door after the horse is out. So in a sense you are in a race between the actual disease and preventing the disease with vaccine. So we know the way flu works is that, the attack rate for flu can be 20 to 30% in your conventional flu, okay, and it's kind of like putting a drop of ink in water and you watch it diffuse, right. So you know in the first season it's going to get X number of people in the transmission, whether it's 20% or 30%, in the second season it will spread a little further but the people who got it in the first season are less likely to get it in the second season right, but your job is that, you don't necessarily know who's had it because you are not testing everybody because it's too expensive and it's just not feasible to test everybody, especially when the testing is so poor, that we talked about. So now you've got to give the vaccine to all these people that haven't had it, but you don't necessarily know who had it and who didn't have it, and you have to do it ahead of them catching the disease for it to make any difference at all. So but in terms of looking at all that stuff, you know we basically decided it probably makes most sense to do it for the most vulnerable people, the people who are in the essential services people, people in the front line, so healthcare workers etc and people who are willing to take it because in the end we bought it and people didn't want it. And then that was also tied to some funding issues, we had to price it so that it wasn't just free but it wasn't hideously expensive either." (SI4) Ultimately, securing a supply of pandemic vaccine was more important than the live/inactive/adjuvant type vaccine components: "Yeah we were comfortable whether it was, whether it contained adjuvant, did not contain adjuvant, it didn't matter as long as it was a vaccine against H1N1 yeah." (SI6)

Interviewer: Do you know where that number's from? Because I heard, you know the pandemic vaccine, it was about 25% coverage, is that based on expected uptake?

SI5: "No, pandemic, a vaccine, you're looking at, pandemic vaccine, you're looking at whole population."

Interviewer: But in H1N1 you didn't order enough for the whole population.

SI5: "Again we can order more. Again, when the vaccine was available, people also know the H1N1 is not that serious. In my opinion, you know?"

The experience of the initial cases in Singapore aided decision makers to decide how many doses of the pandemic influenza vaccine would be ordered: *"So we accepted that first wave is mild but we were not sure that a second wave would be equally mild, it may be more severe and we were therefore that factored into our decision to get quantity of pandemic vaccine. So we decided, OK let's get quantity of pandemic vaccine and try to get people vaccinated before the second wave. Because if we had not, if we were not worried about that second wave and we were, we were very sure that the second wave would be equally mild, I think we would not have got the pandemic vaccine. But there was no way you could know. There was no way you could predict that and nobody would dare to predict that, so that's why we did get the pandemic vaccine and we push it out to the public. So that was the, so the next thing we were worried about, but after that when the second wave came and it was equally mild, but it was OK. We had no further worries after that."* (SI6) The

pandemic vaccine was free to the targeted population group of healthcare workers in Singapore: *"I don't think it was entirely free in Singapore. It was provided free to the healthcare workers via the institutions, for example, Tan Tock Seng will pay for me for free but I don't think it was for free for the public. But it was for free for some of the institutions like some of the long term care facilities, nursing home and community home."* (SI3) The other study countries included free healthcare worker vaccination or at a very low cost.

Singapore reportedly ordered one million monovalent vaccines against A(H1N1) (700,000 from and Australian supplier and 300,000 from GSK) for a population of about 4 million at the time. The reason for this quantity and the use of the dual supplier was explained as: *"I think we are just buying insurance for Singapore. So first of all we don't have vaccine manufacturing capacity in Singapore and with a population of 5,000,000 it doesn't sound practical for us to have ... of the vaccine producing capability. So then we can only rely on our friendly neighbour to extend assistance. So we have existing contracts with Australia, CSL, in producing vaccine for us and that happened, they did supply the vaccine to Singapore ... 25%, a quarter, of the population how do we come to the calculations. I think this is nothing atypical because if you look at the outbreak preparedness in fact you have to depend on the national strategy who are the individuals you would like to protect, right? So it would be the key service delivery persons so that your country can continue to run and function. By looking at this kind of distributions and using this kind of strategy we then decided perhaps we need to cover at least a quarter of the population."* (SI3)

"Yeah although we were lucky we didn't order for the whole population. So our population is five million and we took the provision that each person needs two doses and so potentially we should have over ten million doses but at the end we only ordered one million doses. But then there was only enough for 500,000 people or 10% of the population and, but that decision was influenced by the mild nature of the pandemic, OK soon there was a ... prediction that because of the mild nature and people's perceptions, the vaccine that you buy and you offer will not be, people will not be scrambling for it." (SI6)

It was further explained that following the pandemic influenza announcement, there was a need in Canada to order the adjuvanted version of the vaccine because there had been developments in the field of influenza vaccination since the agreement had been set up: *"So in the pandemic 2009 we had to, although we had a contract that had an option to allow us to purchase pandemic vaccine, we had to actually negotiate the terms of the amendment to actually exercise the option. So we had to negotiate with our supplier the quantity of vaccine that we were going to get, even the price, because the technology that we were getting, we were getting an adjuvanted vaccine, whereas at the time the contract was put in place in 2000 that wasn't a possibility, we were planning to get an adjuvanted vaccine in 2000 so we had a price structure in the contract but that didn't apply to an adjuvant, so we had to negotiate the contract amendment."* (CA2) And even though the agreement was explained well, there was still some doubt in the past about the necessity of the pandemic vaccine contract for a future pandemic influenza event: *"...I*

think our, we, in terms of the vaccine supply itself we had, there were early issues that were really kind of growing pains, putting into place a contract that no one really anticipated we would ever use, to be honest, but I think the pandemic vaccine response went, overall was, to me it was a highlight.” (CA2)

The vaccine supply order covered enough for two doses for 75% of the Canadian population. However, this generated discussion on what the appropriate order should be and required estimating a reasonable expectation of immunisation and ordering beyond this number in order for supply to exceed demand. Once the order was placed, information about the disease activity and further knowledge is continuously gained, for instance: *“...so the order was in, and then you’re right, it was based on two doses for 75% of the population. And we did have some leeway after placing the order in order to adjust it downwards, and we were really waiting as long as we could for additional data from the clinical trials that the company was doing in terms of whether or not there was reasonable expectation that one dose would be sufficient, and there was, that comfort level did arrive. It wasn’t completely verified but it was a high enough comfort level to suggest that we would only need to worry about one dose.”* (CA2) After receiving news that one dose would suffice, vaccination plans were amended with this knowledge.

A cost sharing arrangement was put in place in Canada to enable the cost of the pandemic vaccine supplies to be shared between the federal government and provincial government with a 60/40 split, with the provinces providing decisions on the number of doses required in their localities. In addition,

the federal government purchased a second supply that was held as reserve stock *"...and it was there if was needed, and it turned out it wasn't need, but it was, the feeling was that we were, again, better to overact rather than under respond, so..."* (CA2)

Canadian provinces and territories are part of a voluntary collective vaccine procurement agreement whereby the cost of vaccines is shared. This is not compulsory due to the Canadian federation structure maintaining provinces and territories in charge of healthcare in their localities. This agreement was applied to the A(H1N1) pandemic vaccine *"there was an agreement negotiated between the federal government and the provinces that there would be cost sharing for the vaccine"* (CA2) and now the Pan-Canadian Public Health Network has been formed to span across Canada and circumvent the federal, provincial and territorial committee division.

As explained by participant NZ4, New Zealand purchased some monovalent pandemic vaccine but soon used seasonal trivalent influenza vaccine: *"...we purchased some but actually we only had it for a very short amount of time before the trivalent seasonal one became available and that gave protection against a wider range of viruses that were circulating in the world and that we assumed would be here. So actually it was available and it was used, but it was supplanted really by something that was more useful."* (NZ4) During both the seasonal influenza vaccine campaign and the pandemic influenza campaign, the vaccine was offered free of charge to risk groups: *".....that's the same with our seasonal influenza, so that now, seasonal influenza, again this is all on the website, if you are immuno-compromised, if you are over*

65, if you have other conditions that make you a higher risk so asthma, respiratory, then you can get it free of charge, and that's the same for seasonal influenza, you know, that's our normal policy and there are obviously a number of workplaces that subsidise it as well and it's quite broadly pushed nationally..." (NZ6).

In Japan, the pandemic influenza vaccine supply was mostly from a domestic manufacturer as explained: *"...that's what we are going to ask in the new research. Do Japanese people really do not have the vaccination made by foreign companies? But media, mass media, criticised the vaccination, imported from other countries, some media said that, that influenza vaccination, imported vaccination, has adjuvant, do you know adjuvant? Adjuvant is a component of vaccination which simulates immunity, yeah and that makes a strong immunity reaction for us and it's already contained in like Human Papilloma Virus vaccination, something like that. We have already had a vaccination containing adjuvant but some media said imported vaccination has adjuvant, we don't know what's happening if we have adjuvant vaccination something like that, and it's not really evidence based. But some people, I think it's quite political things, some people didn't want to, some people really disagree with importing vaccination from other countries."* (JA3) For other vaccines, Japan typically produces them within their country so the population is used to and trusts a Japanese product.

5.4.1.3 Delivery

All the study countries provided the 2009-10 influenza A(H1N1) pandemic vaccination programme through both primary care and/or hospital healthcare facilities, with some country's placing on specialist venues to provide mass immunisation.

Sweden, Canada and New Zealand provided the 2009-10 influenza A(H1N1) pandemic vaccination programme through both primary care facilities and placed on specialist venues to varying degrees, with delivery differing by regional approaches. Sweden provided the pandemic vaccine in typical venues such as primary health care as well as putting on specialised organised venues for this event such as schools. As explained, the pandemic vaccine was provided in: *"...they were both in the primary health care centre, the maternity centres I think they vaccinated the pregnant women, the centres for infants at school, so various places..."* (SW2) And: *"...as a principle the counties did set up their own ways of distributing to their citizens. Some counties used the existing system, some set up specific vaccination centres in schools or things like that, it differed, but that is an issue that National Board of Health and Welfare are more familiar with it but not practice."* (SW6)

In Canada, there were differences in approaches in the method of how the pandemic influenza vaccine was delivered. In some instances, an individual's usual physician would provide the immunisation, in other areas specific clinics were provided. The open clinics were considered accessible for all the family / small community to attend at the same time. This

is exemplified in the following interviewee accounts: *"You could, and you could go to your physicians, your primary care practitioners, but they did run these big open clinics run by Ottawa Public Health. Now they always do vaccination campaigns to make it accessible, because not everybody has a family doctor in Ontario and, so you had a choice, but it was just as easy to take your whole family and go to the school gym, it was, it was to make it accessible."* (CA1)

"...some jurisdictions used their normal routes, right? So the public health offices, family physician offices, so forth. Other jurisdictions went with mass immunisation clinics or pharmacists taking on, we have, excuse me, pharmacists taking on more and more of the role now with influenza vaccine which is a really positive thing in terms of preparedness, right? Getting the population to accept vaccine from, yeah. So we had some challenges around that because we were asking people not only to get vaccinated and get vaccinated within a very short time frame we were asking them to go about it differently, right? Whereas most Canadians are sure that they're, their family doctor's office or some clinic to get their vaccine in a fairly laissez faire way in the fall, now we were asking them to do this quickly and you weren't going to go to your family doctor's office, you were going to go and line up at the community centre for three hours, right? Or some, you're going to make an appointment. Some had some really interesting models of delivery particularly in Ontario around scheduling appointments and things like that. There was also the challenges, the technological challenges, right, of just recording and monitoring all of these, tracking all of those vaccines. So

everybody filling out forms, and then how we keep track of all these forms and then who's going to, sure you're doing it on paper then who's going to enter all this paper and so some were working from electronic, they were trying to do this in an electronic fashion. So there were some really important and interesting lessons learned and I think some real process improvements, yeah, that will come out of it." (CA5)

In the remote northern communities of Canada, it was not possible for the local populations to visit their physicians for the vaccination, so a mass vaccination approach was taken instead: *"No, we can't in our, in our northern communities, it just doesn't work that way. Yeah, you really have to do a targeted, and, yeah."* (CA3a / CA3b)

"Yeah, yeah, and that's what, the same story was found in Nunavut, so we provided Nunavut with draft model of conducting, for conducting a protocol for mass vaccinations, and they used that. And their uptake again I think it was in the 90%s. Yeah, so, and then I heard another, at one of our meetings that we had after, the, the special populations meetings group that we had, we heard from them that targeted programmes that were targeting street people or, or whatever, were really, really high uptake there. And then I think at a, at a meeting I was at in Europe last spring they were saying the same thing, the same was found, the targeted programmes seemed to be what really works best." (CA3a / CA3b) The challenge was to rapidly vaccinate an entire community by the resource of nursing station staff within just a few days, and then fly the nurses/nurse practitioners onto another remote community to repeat the process: *"That's right, yeah, so we were targeting to do entire communities*

within three days. So we'd get up, ship a bunch of nurses up, get everybody in the community, of a community of like 500 people, within 3 days we would have them working like 7.00 am to 11.00 pm at night." (CA3a / CA3b)

The way the immunisation programme was delivered in Canada was down to the population, demographics and geography: "It's just population, the demographics." (CA5)

When the public received the vaccine, it was free: *"It was, yes, yeah, it was free to the entire population."* (CA1)

Japan and Singapore provided A(H1N1) vaccination programmes through existing healthcare service of primary care and/or hospital facilities. In Singapore the hospital healthcare facilities provided the vaccination clinic, which included a specific fever tent where by patients with fevers attended. *"Well in the hospital, in the healthcare facilities, it's all provided from the Ministry of Health to the healthcare facilities. So we did not set up a specific vaccination clinic for people to queue up, no."* (SI3) Japan provided the pandemic influenza vaccination within the existing healthcare service: *"We designated a special place within the existing health care facilities, so it's not gymnasium turned into a makeshift hospital, it's not that hassle, but we set up in existing health authorities as vaccination centres."* (JA7)

5.4.2 Uptake Rates and Demand

5.4.2.1 Appraisal of uptake rates

Canada, Sweden and New Zealand spoke positively of their pandemic influenza vaccination uptake rates. There was the estimation that Canada achieved uptake rates in the highest band worldwide: *"...I think our uptake was pretty high, probably amongst the highest in the world. In terms of getting a vaccine for the population we were probably amongst the highest as well."* (CA2) Sweden reported a national uptake of 60% of pandemic vaccines by December 2009. It was expected that Sweden would have a high uptake of the pandemic vaccine: *"...we believed we were going to arrive somewhere there, maybe even more because we do have a high uptake of vaccines normally so there is a big tradition of high uptake of vaccines and then of course we got a bit worried when we got reports from many other countries where the uptake was very very low, but, so I don't think, if you asked people beforehand I think many of them would have said sure, no 60 70 80% is not impossible."* (SW5) Some of the New Zealand participants struggled to clearly remember the vaccination against A(H1N1) campaign due to the incorporation of A(H1N1) into the seasonal vaccination programme. However, in New Zealand it has been noted that uptake rates for the influenza vaccine have increased each year since 2009:

NZ9: "So it was in the seasonal vaccine, sorry our seasonal vaccine starts sometime in March, seasonal vaccine delivery and runs through to the end of July most years, and I'm pretty sure it was in the seasonal, well I'm definite it was in the seasonal vaccine for 2010. I know we got some of the

monovalent supply, but I honestly can't remember who got it."

Interviewer: I read that it was healthcare workers, I think.

NZ9: "I think it was probably even a subset of healthcare workers, and I can't honestly remember if I had it or not. I get a seasonal flu every year anyway, I don't think I got the pandemic strain, I don't think I regarded myself as high risk because, there was the kind of high risk and then there was the essential work force, possibly I fitted into that latter category, but honestly I can't remember whether I had it or not. If I had we would have delivered it here, we have a bunch of nurses who run the vaccine programmes for us."

Interviewer: So would it have fallen into the yearly vaccine programme?

NZ9: "Yeah, it was a major promotion point for the 2010 seasonal influenza vaccine which included the pandemic strain and we knew by then from the serosurvey, I think, 30 odd percent of people had already had antigens to A(H1N1), I can't remember the percentages but there was a study published and so we realised that it was going to be a major component of the seasonal influenza given that it was still circulating broadly in the northern hemisphere, if we were going to get a reintroduction we would still have about two thirds of the population susceptible so we knew that it would be a predominant part of our seasonal patent and we promoted it on that basis."

Interviewer: I read that about one million people had the vaccine, was this about what was expected in terms of the seasonal numbers?

NZ9: "Yeah so we'd struggled to make a million, so New Zealand's got a population of just over four million and it did have then, I can't remember when we passed that milestone but it wasn't long ago, and we had progressively kind of I guess with free seasonal flu vaccine for at risk groups was introduced in 1997 we kind of got 3 or 400,000 people and then it's been slowly going up. And we would have expected probably about 800,000 in 2009 or 2010, and we got a big jump, not all, a lot of those people paid for it, it's not a million people eligible on the basis of age or risk. But as I say, it's gone up every year and it was a good number above a million for the year that's just finished in terms of the seasonal campaign."

The uptake of the 2009-10 influenza A(H1N1) pandemic vaccine was reported as about one million people receiving the vaccine in New Zealand. When asked about the expected uptake one participant said: *"Well we probably would have thought more people would have been interested in it but we'd have a period of flat where the vaccine uptake had plateaued and that was something that was unique to most countries, same in Australia, we'd got to the point where we couldn't really improve the uptake nationally. Some countries post SARS, Korea for example sort of had big, as part of the SARS strategy the following year, so they could separate out SARS from influenza cases, sort of had massive substantial uptake, increases. Whereas we didn't in New Zealand, didn't manage that and really it's only over the last year that there have*

been substantial increases and got sort of pre-empted the H7 outbreak so just a level of awareness that things have moved on, but no I would have liked to have seen far more after the pandemic.” (NZ4)

Uptake rates of the pandemic influenza vaccine were discussed in terms of suboptimal uptake rates in Canada, Japan and Singapore. The reasoning given for lower than anticipated uptake rates included mild pandemic influenza event which reduced the request for vaccination and vaccine safety. Lower than anticipated uptake rates left study countries open to broader criticism over wasted public health resources.

Overall, the lower than anticipated uptakes rates in Canada (in comparison to the volume of doses ordered during the pandemic influenza) has become seen as an over-reaction to an event that turned out to be less than originally thought. One participant explained how the volume of doses ordered made sense at a government level and working in a position specialising in pandemic influenza, however the general public opinion, which they could empathise with was focused on the waste of resources, doubt in those responsible for events and since 2009, seasonal influenza vaccinations rates have fallen below expectation levels: *“...the general public, my, and I don’t base this on anything but just conversations you have at cocktail parties and so on, is people think that it was so overblown that we wasted mass amounts of, of resources for a non event, and so on and so forth. And I think, seeing what a nosedive our already poor flu vaccine uptake rates, they, they took a further nosedive in the years after H1N1. And it’s just this past season where we’re having more severe illness and,*

and that sort of thing again, that people are, are starting to come around a bit. But we saw a big hit like that in credibility from the general population.” (CA3a/CA3b) Also: “I think for sure, like in 10/11, 11/12, that people were pandemic'd out. It was kind of like OK, stop talking about it, because then after, like we spent the entire 2009 dealing with it, and the entire 2010 dealing with lessons learned.” (CA3a/CA3b)

Japan reported an uptake of the pandemic vaccine of about 20% in the population. The foreign produced vaccine was barely used in comparison to the amount purchased and the amount of domestic vaccine utilised: *“22.8 million domestic doses were injected into Japanese persons, so we have 120 million people so only 20 percent or something. But of course it depends on the age, maybe older people tend to have more vaccination, maybe 40, 50 percent. We imported lots of vaccination from GSK or Novartis but we only used 1,350 doses from GlaxoSmithKline vaccination so maybe 0.1%.” (JA3)*

Interviewer: Right, not very many?

JA3: “We didn’t use. Yeah because many people did not want to have vaccination made by other companies other foreign companies.”

Interviewer: Oh really?

JA3: “Yeah and for Novartis vaccination we just used 2,285 doses so we totally ignored the imported vaccination because we have already had enough vaccination and many people didn’t want to be vaccine because there are so many who

have already infected H1N1 when we had the vaccination in December, or in January. "

Japan's population received more than 20 million doses of the pandemic influenza vaccine: *"More than 20 million, I can't remember the exact number, maybe more than 20 million people. [...] Oh we expected more people, we provided for all population."* (JA6)

When asked about the possible reason for the difference between the uptake of about 20% of the population compared to the provision for the whole Japanese population: *"I don't know why, maybe mass media's announcement maybe it was effective, but it's quite interesting that Japan is said that our vaccination strategy was very delayed compared with other countries. [...] because we had, I mean for example number of vaccinations were very limited in Japan, I mean measles or polio these kind of vaccines, maybe in your country for example Hib what else chicken pox, [mumps, not as a public service...] ...because a very long time ago, twenty years ago we had very severe cases of health damage after vaccination and they sued our government and they won, so we lost many cases in court and then we changed the law and we reduced some kind of vaccines as a public service and since then we had a very dark image against vaccination, so even if new vaccine was developed and other countries introduced it as a public services, in Japan it's impossible, so what we call a vaccination gap occurred. Anyway so totally seven vaccinations, other countries have already introduced several new vaccines, but in Japan we didn't. But very luckily after this pandemic happened, at that time many Japanese people noticed that there is a vaccination gap and our vaccination*

policy is very delayed compared with other advanced countries so now we have a movement, tried to increase the kind of vaccination. [...] the kinds of vaccination and just a half year ago we succeeded in changing the immunisation law and we succeeded in the increase in three vaccinations. So HPV vaccine and the Hib and [nemonitis] and now we are trying to increase another four vaccinations.” (JA6)

Table 19. Example of triangulation of data in regards to vaccine uptake rates.

Key interview themes	Epidemiological data	Pandemic preparedness plans
Vaccine uptake rates: <ul style="list-style-type: none"> • Suboptimal • Lower than anticipated 	Immunisation coverage e.g. <20% in Japan Mild pandemic event for the majority of people Early first waves of infection arrived before vaccine	Severe pandemic influenza planned for, with the expectation of high vaccination demand Inflexible plans Vaccines arrive before disease peak

5.4.2.2 Uptake rates in distinctive population groups and localities

Canada, Sweden and Japan participants spoke about pandemic vaccine uptake rates relating to specific population groups. The specific population group of aboriginal populations was associated with high uptake rates whereas low uptake was reported for the specific population groups of healthcare workers, religious groups and young adults.

The pandemic influenza vaccine uptake was considered to be very high in the specific population group of First Nations

persons in Canada and this was considered to be the result of a well-planned mass immunisation programme of delivering vaccines through clinics. For instance: *"we knew that the vaccine was going to be rolled out the week of October 26th, so we started planning this in the summer about how we were going to roll out the vaccine and do these clinics within a four week. So how are we going to get everybody immunized in a four week period? And so we had to take nurses that you know, hadn't been necessarily working with clients because they were doing more policy work, and get them recertified, and we sent out an extra 40 staff from headquarters that normally don't work in northern reserves, and shipped them out. That was a huge organisational challenge, because oftentimes it's weather dependent"* (CA3a/CA3b) This hard work paid off because it resulted in very high uptake rates in these parts of northern and remote Canada: *"Yeah, so it was a big, it was a big endeavour, but we planned very, very well, and so we got a, a very large uptake of the, higher, higher than the Canadian average."* (CA3a/CA3b) Achieving an uptake of approximately 90% in the First Nations and aboriginal population was challenging and resource intensive: *"...so the face to face meeting with the people, it's not big government says you got to do it and so they're all going to come out and get it, no, it's the relationships. And that's why it has to happen at a community level and at population bases, you know, where the trust has been established."* (CA3a/CA3b) This incredible uptake rate was compared to the Canadian overall uptake rate of 42%.

On the other hand, healthcare workers, as per seasonal influenza uptake rates, had low uptake rates of the pandemic

influenza vaccine in Canada: *"...healthcare workers historically are one of the lower compliance groups with getting immunised for flu and unless you have a physician champion in your organisation who is actively promoting and engaged in the programme, that's, sometimes it doesn't work. Long term care I think there's better uptake, because people see that population at risk with the flu and I know BC has recently passed legislation for mandatory immunisation of healthcare workers. And if they don't then they have to wear a mask. So, and that's been challenged, but that's the first province to actually take that step. So, but even in my own office, and people work with this and I said, did you get your flu shot, 'I, I'm not, I'm not convinced,' so it's kind of interesting that it's, there's scepticism around the flu vaccine."* (CA1) It was presumed that the reason for this may be due to effectiveness concerns or adverse effects from the vaccine or lack of education on the matter: *"I only had it once and I got really sick, that seems to be the thing, there's a lot of, a lot of misconceptions and, but we have a lot of work to be doing in terms of improving vaccination among healthcare workers in particular, yeah."* (CA1)

It was reported that the uptake in the Swedish Muslim community was less than the national average because of concern about pig components of the vaccine as it would protect against swine flu. Therefore, public health professionals charged with the delivery of the vaccination campaign engaged with religious leaders to communicate about the vaccine and alleviate fears: *"...we had a large group of Muslim community here, and they were afraid of the vaccine since it was the swine flu and so they responded to that, and*

didn't want to have the vaccination. So I think we had to, when they had their Friday sermons, do you say that, we went there and with some spokesman, we tried to inform them. [.....] they thought it was just some kind of link with swine so they didn't want to have it." (SW2)

The uptake of the pandemic vaccine within the group of young adults was limited and it was thought that communications to this population could have been more effective: *"...I think that one of our weaknesses that was you know, the groups that are, was heavily affected was the young people, and they didn't get the message, it was older people, families, that got the message, they younger people they didn't care much, and that was one of the problems because they died, the young people died, but I think we could have been a lot more effective in our communications to the youngest."* (SW7)

Countries discussed regional differences in pandemic influenza vaccine campaign provision and uptake rates. In particular, Canada experienced regional differences which were explained by differences in Canadian geography, and ethnical and socio economic diversity. 2009 saw the highest purchase for influenza vaccination in Canada since records began, counting both before the pandemic and post it, with a figure of 13 million doses. There were differences between provinces on whether seasonal influenza vaccines were held back until after all pandemic influenza vaccines had been administered or to just the pandemic influenza immunisation programme in conjunction with the seasonal influenza programme. As explained: *"I think this, it's an example of where the provinces did things differently, there were a number of provinces, maybe five or six, that held off on their seasonal programme*

until they rolled out, pretty much rolled out H1N1 completely, there were other jurisdictions that went ahead as normal and put H1N1 in where it, when it was available. So at the end of the day I don't think we came close to actually using the 13.5 million but in terms of demand it was, certainly was the highest that we've had." (CA2)

It was explained that demand varied both between and within provinces of Canada, some of this surge demand was unforeseeable whereas some demand came down to the way in which the immunisation campaign had been organised locally: *"...it came down to some provinces did a better job, from what I understand, of allocating the vaccine within their jurisdiction to avoid that kind of issues, others did run into problems with clinics being just overwhelmed basically with the demand, unexpected demand. But again, I think it varied across the country, even within jurisdictions it probably varied in terms of their capacity to deliver the vaccine."* (CA2) The variable pandemic influenza vaccine uptake rates throughout Canada were also discussed by this participant: *"Yeah. There was a real demand. It was hugely variable across the country again because the country is so diverse. That's the one thing about Canada is that geographically, ethnically, socio economic, like the diversity is just really something. [.....] And different parts of the country there would be different demand and certainly different parts of the country different uptake. [...] And differential uptake with the different models that were used for programmes, differential uptake in, some of our first nations were aboriginal communities. Because our aboriginal communities really did get hit fairly hard in the first wave they certainly were aware of their vulnerability in terms and so*

uptake in our aboriginal communities was quite good for vaccine. So that was quite positive.” (CA5)

5.4.2.3 Demand and motivation for obtaining the pandemic influenza vaccine

Sweden and Canada spoke of a surge in demand for the pandemic vaccine at the start of the pandemic influenza vaccination campaigns and experienced demand for the vaccine out stripping initial supply. This was an inverse relationship between demand and supply. Both Sweden and Singapore noted that a decrease in demand for the vaccine coincided with a drop in pandemic influenza disease activity.

Some of the Canadian interviewees spoke about the surge of demand seen for the pandemic vaccine. Frequently, members of the public queued outside healthcare centres waiting for the pandemic vaccine, even though additional staff had been laid on to meet the extra anticipated demand. With the extra staff working on the mass immunisation programme, it would still require many days to vaccinate the population. *“...for example, I can talk about Ottawa, where people lined up and it, they were in clinics every day, but it’s a big resource thing for just Ottawa Public Health, so they were having to bring in other nurses and other people to assist, volunteers and, so the demand was just more, they couldn’t possibly deliver all the vaccines in one day to meet, to match the people lined up outside, so they actually started giving people numbers and saying, no you’re not going to get in before the next two hours.” (CA1)*

The demand for the pandemic influenza vaccine from the public exceeded supply because at the start the vaccine arrived in limited batches from pharmaceutical companies: *"Yeah, the demand from public was much much bigger than the amount of vaccines available for quite a long time."* (SW5) At the beginning of the pandemic influenza vaccination campaign, the Swedish population demand for vaccines outstripped supply: *"...from the beginning, the people were very motivated and asked for the vaccine and got no vaccine."* (SW4)

Interviewer: They were asking for the vaccine before it had actually arrived?

"Yes, you had the decision that we should start this campaign and then people started to demand, why can't I be vaccinated? And of course we, even when the campaign started, we didn't get enough in, and then there was another role for us, of course it was to have the contact with the drug company for example, because they couldn't have the contact with 21 either, and then we were extremely criticised by the media, why don't we get the...? Media, television, radio, why don't we get the vaccine? And you know the main problem was that we didn't get the vaccine fast enough, which is very very interesting which we are discussing for the future. That there are very much, I think that is one of the main problems that the epidemic has already started when we received the vaccine and we didn't get vaccine, we get 100,000 doses or half a million doses but from the beginning there was an enormous demand for more, television reporters where are the ...? And the drug companies, of course they tried but there were other countries also. So that was a very, if you ask for

the concern from them from the beginning, how could we vaccinate all those people, I think they did it excellently, the organisation was excellent in those county councils, but then it changed to why don't we get enough vaccine and then it just dropped off of course with the epidemic." (SW4)

Interviewer: What the disease activity or the demand?

"The demand dropped of course when the disease activity dropped, and I think there was many people, there was still some people who had planned to be vaccinated but, for example, this place we should have the visit of, we should be vaccinated, but when it was the time, the epidemic was already faded away." (SW4)

An inverse relationship was seen in terms of demand and roll out of the vaccines. At the beginning of the campaign, the number of doses of vaccines was limited and demand was high, over time more vaccine doses became available and demand decreased. As explained: *"...the roll out of the vaccine was, and again in retrospect it was, it probably was predictable that it would, the roll out was slow. As the company ramped up production, and they were going with a fill line for example, and we're now actually investing in, we have a new long term contract also with GSK and we're investing in expanded filling capacity because that was identified as one of the bottlenecks in production the last time round. But as they ramped up, production ramped up, filling, any issues that were going to arise were going to arise early. So the vaccine came out slowly at first and then the weekly picked up over time so that we were getting more, and demand, well obviously was heaviest at the beginning..."* (CA2)

The amount of vaccine to order was calculated following an assessment of the disease characteristics of the pandemic influenza circulating: *"...of the influenza vaccines to be put into their calculations because we reckon that under unusual circumstances the take up rate, the coverage, will go up, people will actually fight for the vaccines in order to, which is what happened in America a few times with the vaccines dropping."* (SI3)

By the time the vaccines had arrived in Singapore, the demand had waned and there was not the reported incidences of queues outside surgeries for the vaccine because: *"...during the last pandemic for the reason because, as I mentioned, we don't have the vaccine producing capability over here, we can only rely on our neighbours and our neighbours need to protect their own interest so in other words they will only start to manufacture for us after they have met their own internal need, right? You know ideally you take care of your own country first before you can extend your help to your neighbour. So by the time the vaccines became available to Singapore it was relatively late and by that time most of the Singaporeans are well informed enough that it was not a fantastically severe disease. So similarly for the healthcare workers, not all the healthcare workers decided to go ahead and take up the vaccine."* (SI3)

The motivation for obtaining the pandemic influenza vaccination was described in Sweden as an individual level of fear regarding contracting the disease and on a societal level of collective responsibility as citizens to all contribute which arguably played a role in achieving high vaccine uptake rates. In Singapore, there was a low uptake of the pandemic

influenza vaccine which corresponds to the typical low motivation for seasonal influenza vaccination.

In Sweden, the motivation for vaccination was described as a fear of contracting pandemic influenza at an individual level but also a sense of collective responsibility felt by the population to get vaccinated: *"...the reason to vaccinate is fear, but it's also some kind of course, many people, get out the message, it's a matter of loyalty, you should vaccinate because then you contribute to less spread in society, and then you are, I don't know what you call it, it's not just for yourself, it's for many other people, you decrease the risk with people with underlying conditions and so if you go to vaccinate."* (SW4)

The uptake of the influenza vaccine was reported as low in Singapore normally during the seasonal influenza period (twice a year peaks due to the tropics location) and this was the same experience during the pandemic influenza vaccination campaign. *"So every winter you have upsurge in all your flu cases and that, but we don't have that, we have influenza throughout the year and then there's no definite season. And the, so if people have incorporated it into their lives, it's taken as something, it's, the symptoms because it, the way it manifests, the clinical features of it, it's just basically fever and cough basically. And people get respiratory infections quite often and people get something like the common cold almost. And something that is not serious, and that's why even the uptake of seasonal flu vaccine is not very high, even with a lot education and we try to get people who are at higher risk to be vaccinated. But they're not, the uptake is quite low still. Yeah the, the*

perception is that it's, is not something coming or serious. Yeah and actually the 2009 pandemic reinforced the public belief in that influenza is not serious. Yeah because from the general public's experience with the 2009 pandemic was, you don't, people were not like dying and a lot of people were ICU and that's why when the pandemic vaccine was rolled up there was a hoopla uptake. So that's what, not, it's not surprising then that for that seasonal influenza, the general public continues to think that it's not very serious." (SI6)

The pandemic influenza vaccine arrived into Singapore in October 2009: *"End of October but the, that was the first supplies coming into Singapore but by the time you actually roll out to the public, make it available to the public, it was the first week of November."* (SI6)

The pandemic vaccine uptake was lower than expected due to the perception that this flu was characterised by mild symptoms and the concern for the safety of a vaccine developed rapidly, as explained: *"Yeah because, there, it was quite interesting that because of the disease, the disease and the perception that the disease is mild, there were a lot of, they were concerned by some parties and groups of people that this is a, this vaccine is not so safe, it's not properly tested. It's a rush and it's developed in a hurry and things go through the internet and they says, no so there's no need to be vaccinated, the disease is mild and you will get all kinds of side effects. So we had to counter that through public education and say that, if you belong to this group A, B, C then it's better for you to be vaccinated, don't worry either way the vaccine is safe and so forth, we had to reassure the public. But still because of the overriding perception and*

based on the actual fact that the disease was quite mild. And not very different or actually quite similar to seasonal flu, most people said, there's no need to be vaccinated. Yeah so we had a lot of unused vaccine.” (SI6)

5.4.2.4 Implications of vaccine uptake rates on other public health measures

The high reported uptake of vaccines in Sweden might have reduced the need for other public health measures, such as antivirals: *“I think, I believe, that since so many people were vaccinated, that contributed to that fewer people taking antivirals, that's my impression without knowing.” (SW3a)*

5.4.3 Prioritisation

The study countries Japan, Canada and Sweden discussed how the initial batches of pandemic influenza vaccines were required to be prioritised but over the course of the vaccination campaign would be available to everyone. Singapore set aside vaccines for healthcare workers but did not have priority groups or enough purchased for the entire population. New Zealand had a small batch of monovalent A(H1N1) influenza vaccine, with which healthcare workers were prioritised. The monovalent vaccine was replaced in a few weeks by the seasonal influenza trivalent vaccine containing A(H1N1) influenza.

Canada planned to have vaccines available to all and on equitable terms however, the nature of pandemic influenza vaccine production meant that a discussion of priority of vaccines would need to occur before the roll out of the vaccination campaign. However, for some of the Canadian interviewees, the term 'priority groups' sat uncomfortably and instead the preferred term was 'allocation of vaccines' because *"...within a month there was enough vaccine for everybody in Canada who wanted it..."* (CA3b), as illustrated: *"We worked really closely with our FPT colleagues around vaccine prioritisation, so when Canada was developing the pandemic vaccine there was a series of discussions around the roll out of the vaccine, because you knew we were only going to get a certain amount of doses each week, and how were we as a country going to prioritise those doses?"* (CA3a)

The uptake of the pandemic influenza vaccine against A(H1N1) in Singapore was reportedly lower than expected so there was no need to strictly prioritise it: *"...I mean in an ideal situation if let's say the uptake was very high then obviously it would be shunted to the people at high risk or complications first but I think in this case the uptake was actually quite low so there was enough to go round."* (SI2)

Whilst other participants said that in reality Sweden did not prioritise the pandemic influenza vaccine for specific population groups: *"And then they started to identify the key functions, key competences, and then they started to see, the questions that were raised at that time when they had more clear picture was if they had antiviral medicine who could get that to make that they wasn't infection and so on, should we prioritise the vaccine and so on, it connected with that. But at*

that time we decided that it was no positive, no one could get before the other one in the line, it was mass vaccination, instead of just a few groups.” (SW7) However, some participants from Sweden did explain that vaccines in the initial weeks were only available to specified priority groups.

5.4.3.1 Priority vaccination groups

Sweden, New Zealand, Singapore and Japan prioritised healthcare workers and/or critical infrastructure employees as the first group to be eligible for the initial supply of pandemic influenza vaccines. The risk of healthcare workers contracting pandemic influenza and contributing to the spread of disease through employment was an important risk to mitigate against, as well as prioritising the maintenance of healthcare services and critical infrastructure through providing the vaccine to key employees. Canada took a different approach which was organised by the geographical challenges of the vast country: starting in the northern remote and isolated communities where healthcare is provided in mostly nursing stations and spread out across sparsely populated land. The risk of remote and isolated individuals contracting pandemic influenza may have left them vulnerable to severe outcomes and medical access issues.

CA3a: “And so after many meetings and much discussion and much look at the science, it was decided that pregnant women, First Nations in remote and isolated communities and, who else were designated priority groups?”

CA3b: “Well we weren’t using the term priority groups.”

CA3a: "Oh no, sorry."

CA3b: "That was, yeah, that was taken off the table. Because, because it was a matter of allocation, not that there wasn't enough vaccine, and so priority did have to be set. There would be, in a matter of weeks, enough vaccine for everybody, so then these other risk groups were allocated the, the, had their allotment or their, so yeah. [.....] And as usually the case with vaccine allocation in this country the smaller jurisdictions, including the northern territories, are often given the first allocation, and just because it's easy, there's what 35,000 people? Something like that in, in Nunavut, in the whole territory, and so it's easy just to knock those off, get them done and then, then start doing the logistics with the larger jurisdictions like Ontario BC, that sort of thing. During H1N1 Manitoba was first hit, but then Nunavut..."

In some areas of Sweden, they tried to prioritise particular key workers, e.g. health care professionals, to get the vaccine first but this was difficult to enact due to equal access arrangements in Sweden (Note MSB is the Swedish Civil Contingencies Agency): "...but then there are key positions in society that you should, people working in health care and so on. MSB tried, but it never worked out, it was very difficult to, in some places they tried to vaccinate people in key positions, but it's very difficult to do because it's a matter of equity, why should...? It's also political, extremely difficult." (SW4)

Interviewer: So that's the prioritisation of, is it critical infrastructure?

"Yeah, it's the critical infrastructure. To me it's not the average healthcare worker, it's probably the technician at the hospital, who is responsible for IT and so on, but it never worked out." (SW4)

Interviewer: Trying to define that group?

"Yeah, of key positions, that's very few people, usually infrastructure as you said." (SW4)

New Zealand did not have the vaccine to use until 2010 due to the timing of the disease activity and the production of the pandemic influenza vaccine. Initially the pandemic vaccine against H1N1 was prioritised by only being offered to healthcare staff: *"...it came later, and we, we're obviously aware of the potential second wave which can be bigger than the first wave [.....] we were mindful of this potential second wave so we offered that to hospital staff and then the rest of it was made available, that staggered introduction was something that had to be managed very carefully." (NZ1)* It was explained that due to the nature of the monovalent pandemic vaccine being scarce in the first instance, it was necessary to prioritise it at the beginning and therefore it was necessary to explain the reason for prioritisation of one group before another: *"Well in terms of you know, people's perception of what we were doing, are you just trying to protect your staff first instead of us, why can't we have it too, well there wasn't enough to go round that monovalent stuff, so what we said was look, if a health worker gets sick they can spread it to many many other people, so that's why we'll offer this, but we'd still guarantee and succeeded in delivering*

trivalent vaccine to people well before the season started.”
(NZ1)

The monovalent vaccine against pandemic influenza H1N1 was prioritised for healthcare workers and offered free of charge in New Zealand: *“We’re talking about the monovalent vaccine was free was only offered to the healthcare workers, was only offered through the healthcare system. Seasonal influenza vaccine is 2010 when that was rolled out was free to those at greatest risk from influenza and the guidelines was extended then to include pregnant women.”* (NZ4) Typically the annual flu vaccine is available free of charge to vulnerable groups in New Zealand, such as people from deprived backgrounds, Maori Pacific persons.

The pandemic influenza vaccine was available to everyone in Singapore, however, initially it was prioritised for healthcare workers to obtain the vaccine: *“In terms of prioritising vaccine, of course we, when we, one of the priority groups to be vaccinated were healthcare workers. So we set aside vaccine for them so that they would not have to compete with the public, so it was reserved for them. But it wasn’t also very like, some healthcare workers still, there’s no need to get vaccine.”* (SI6) The vaccine was initially prioritised for key essential workers.

The pandemic vaccination campaign commenced in October 2009 in Japan which coincided the first wave of disease activity. One participant discussed the gradual availability of vaccine doses which corresponded to the need to initially prioritise the vaccine: *“The first vaccination project was October 19th, just during the pandemic first wave and we*

provided it gradually so first one week we only two million [doses]. Second week, third week, another two million, another three million, so gradually gradually we could provide. So we had to decide a priority, so first priority group was medical staff.” (JA6)

The first priority group at the beginning of the vaccination campaign in Japan was medical staff: *“There’s a priority for vaccination in 2009, the first of all from end of October 2009, only for medical staff but only for one million doses.” (JA5)* Individual medical centres received allocated vaccines, e.g. 500 and these needed to decide their own allocation groups: *“We should decide who to give this 500 vaccine to. It was very difficult.” (JA5)* Some hospitals would have liked more than their individual allocated vaccines: *“There were few, they wanted more, we wanted more doses because increasingly for us in this hospital we received if I remember 200, 300 doses so all paediatric doctors and all doctors of emergency and all nurses of paediatric ward and all nurses from emergency, but in some hospitals all staff could be immunised with the vaccine so very different, so depends which hospital you work.” (JA5)* There was a demand from medical staff to have the vaccination.

The subsequent priority groups in Japan were pregnant women, high risk persons and infants: *“In the beginning of November the priorities goes to pregnant and high risk persons, with some immunocompromised or patient with cardiac disease or something like that. And then preschool aged healthy children and there’s something like that. [...] You see this is Japan’s priority, written in Japanese, this is for medical staff, next one is pregnant women, first medical staff,*

two pregnant women. This pregnant women, this is people with underlying diseases, at preschool, primary school and elementary school. There are many stages, it's very difficult." (JA5)

5.4.3.2 Pandemic vaccine prioritisation challenges

The prioritisation of the vaccine during the pandemic influenza was challenging work for key response pandemic influenza personnel: *"...dealing with the different issues that came up there in terms of prioritisation and challenges around prioritisation because although we have contracts that really do allow us to provide vaccine for all of our population, well, everyone who will take it for sure it comes off in allotments, right? And so it's not, we're not going to wait until we have enough for everybody so we have to roll it out in a progressive fashion. So there was a lot of work around that prioritisation..."* (CA5)

Deciding on the prioritisation order was morally difficult, and remains difficult to this day, with no clear cut answer as to what the correct action is: *"...and I've had discussions with people, OK, like if I have ten doses of vaccine and does the big burly policeman want to get in line in front of the one year old child or in front of the elderly grandmother or the pregnant woman? Which one are you knocking off line? Do you know? So these are very, very tense issues and they will continue to be because we will never have the kind of resources that are infinite, right?"* (CA5) Considering and defining consistent categories of who belonged to priority groups was difficult to

do, particularly during a time pressured environment of a pandemic influenza: *"It, with first responders it's the question of also defining adequately who first responders are. And in critical infrastructure, a worker is someone that, everyone has a different view of what's critical infrastructure that needs to be maintained, so..."* (CA2)

The prioritisation of the pandemic vaccine was challenging to determine in Japan: *"...and then if a vaccine is produced it will be given to the, it is necessary to think of one by one and who is a priority and who is a second priority this is another difficult issue but this is needed to think about the priority, the prioritisation. And the policy in Japan the vaccine should be produced to cover most of the, almost all the people."* (JA2) Japan discussed the need to prioritise a pandemic vaccine in the inter-pandemic planning period: *"Several years, maybe three before 2009, 2007 or 2008, we had a decision about that, about priority and we had decided very roughly, for example for the children. [...] before 2009 we had a discussion and we had decided roughly the priority and then from August until September we had a very serious discussion, we had a meeting consisting of researchers, experts and the anti-vaccine group, anyway so many kinds of people we welcomed and we had a serious discussion, more than 10 times, 20 times."* (JA6)

Interviewer: Really, it took that long to decide?

"Yeah, every two days we had these kind of expert committee from mid-August to mid-September, so one month, and finally we had consensus, and then we published to the people, Japanese people, public comments, we received 3,000 public

comments we received and we analysed. Yeah using these public comments and experts discussion we had decided the priority. First priority was medical staff, and then next one was pregnant women.” (JA6) [Document shown in interview]

Interviewer: People with underlying diseases.

“Yes, and for small children.” (JA6)

Interviewer: Is it based on information such as what you know about the virus, who you knew it was affecting?

“Yes right.” (JA6)

Interviewer: The WHO said about pregnant women and very young children.

“We used information from the WHO and from United States, from Mexico so in August or September some journal published the data so we used that data and WHO recommended that the first group should be medical staff so we used that idea, and one of the paper announced that pregnant women were high risk so we decided to prioritise pregnant women and underlying people.” (JA6)

Overall, the immunisation programme, in terms of roll out and vaccine type, was considered to be one of the most major components of the Canadian pandemic influenza response: “I would say probably one of the major elements would be the rollout of the vaccine and the need to prioritise who was going to get vaccine first just because of our, the progressive supply. I would say the vaccine as well because we introduced an adjuvanted product for the first time and so that

was a really challenging exercise trying to ensure people felt comfortable with the safety and efficacy of a new type of product in a pandemic situation. So the vaccine rollout was really one of the major, major elements.” (CA5)

“We did that for our primary care partners as well as our acute care partners, and we had instruction sheets for staff, and we set up vaccination for health care workers that were going to be working in these flu assessment centres as key prioritised groups for vaccination when and if it became available.” (CA6)

5.4.4 Risk Groups equated to priority groups

Frequently, the priority groups translated to the risk groups identified as most vulnerable to severe outcomes from the 2009-10 pandemic A/H1N1 influenza, although if the vaccine doses had arrived in large enough quantities then these priority groups may not have been required: *“...we had expectation that we would get sufficient vaccine early enough, that it may not be necessary, but it was a precautionary measure to ensure that there was a plan in place if the vaccine was not coming at the rate that it was, it could be administered to the general public, that there needed to be some kind of a plan in place that, again, that provinces could follow or not depending on their own decisions, but in terms of how they should, or guidelines for how they could prioritise based on the best available science.” (CA2)*

When determining the priority during the pandemic influenza, information was required about the risk groups: *“...if the pandemic come, we need information which population is most*

severe or which population is needed, and also we have to save the severe older person or we have to save not so severe young infant for our future, it is very difficult decision but we say the people and also the policy maker this time we have to decide on this, sometimes it's a very cruel decision. But at the moment we don't have any pandemic so nobody knows which one is the best scenario." (JA2) [In regards to the 2009pdmH1N1]: *"Actually the consensus has been made that a medical person is the first priority because they had to be immunised and they have to watch the patient, and the second priority is the related people, not only for the doctor, but nurse, laboratory people, that's all medical people."* (JA2)

Interviewer: So keeping the health system running?

"Yes, yes, and also the next rank is the people who work for, the term of the life line, to keep the minimum people alive for example food." (JA2)

Interviewer: So like your essential workers?

"Yes, yes, some workers." (JA2)

Interviewer: So that could be anything, not just healthcare workers?

"For example, traffic workers, and also medicine producer companies, and also people who work in Ministry etc yeah." (JA2)

Interviewer: So your essential workers, to minimise societal disruption?

"Yeah." (JA2)

5.4.5 Locality prioritisation

Even though prioritisation was introduced across Canada, different provinces and territories implemented their own priority groups, which occasionally varied and led to questions as to why it was available to specific groups in one area of the country and not other areas: *"One of the other issues was around, in terms of pandemic vaccine in particular, is that, because we plan that, our planning would allow for all Canadians to have access to vaccine over time, like we can't give vaccine to everybody all at the same time, it won't become available all at the same time. So there's a need, [...] to prioritise who would, the, how the first batches of vaccine would be rolled out, and so of course each province and territory would get their allocation of vaccine. [...] it would have been in batches, so there would have been like a first supply and then further, subsequent production, more supply, so the initial availability of vaccine required prioritisation and so there's, along with that there were some issues with inconsistent, consistency that there was some differences of implementation. You've probably heard that as well across the country, which also can lead to confusion and why do people in this province get, why do certain people, certain groups within this province get it and other provinces weren't doing it the same way, so there were some issues around that. And again it was about communicating who the, why there was a need for prioritisation that eventually there would be vaccine for everybody, but that because there was a limited supply there was a need to determine who should get*

it, who really needed to be in that first line of, that first tier of first targeted groups, yeah.” (CA4)

5.4.6 Timing of pandemic influenza vaccination campaign

5.4.6.1 Disease activity and vaccine arrival

In terms of disease activity, the necessary production time required meant that the vaccines arrived after Canada had experienced their first wave of novel influenza: *“The other challenge with vaccine was we got our vaccine, just the timelines to produce vaccine and our vaccine came in just as we were going into our second wave and so we were playing catch up at that point and that has a lot to do with your strategies, right? If you know you’re going to be in the middle of, you know you’re going to be in a pandemic wave you have to treat people who are most at risk of complications or, yeah, they get big, bad outcomes whereas if we’d been a little bit ahead of that wave we might have tried to hit the transmission, get those kids vaccinated before they were too sick.” (CA5)* The vaccination campaign timing in reference to the disease activity meant that there was a real focus on delivering the vaccine to persons who may be at risk of the most severe outcomes. The strategy switched from trying to vaccinate transmitters (e.g. children) to vaccinating those most likely to require hospital care and may die (e.g. risk groups).

In Japan, the vaccines began arriving in November which was after the peak of pdm09H1N1 disease activity: *"We didn't get the vaccine, it wasn't available until after the peak of the pandemic so the vaccine was a little bit late."* (JA4) The disease activity was earlier than the vaccine arrival: *"...the peak was in September or October, it was a little bit earlier."* (JA3)

5.4.6.2 Portion of pandemic influenza response

In Japan and Singapore, the pandemic influenza response using vaccines was limited due to the timing of the vaccination campaigns in relation to disease activity and the number of vaccines used. The vaccines had arrived after these countries had experienced their first pandemic influenza waves.

"...vaccination is, was very limited, vaccination for pandemic 2009 is, was very limited, only vaccination only began in November or December and at that time the peak in most areas in Japan, pandemic influenza has, had been finished at that time, so very limited but, so, but of course please ask doctor, please ask a practitioner, they vaccinated many patients with pandemic H1N109 after the peak of epidemic, so vaccination is not, has not main role for decreasing Japanese fatality." (JA1)

"Vaccine campaign started in November or early December, that was already just after the peak of the pandemic influenza and before the peak come in the government decided to import the overseas produced influenza vaccine, urgently. But almost at the same time, the domestic vaccine is produced but

that was the time of the peak of the pandemic influenza. Of course, many people wished to be immunised but also total number is decreasing down and the people [forget].” (JA2)

Japan did not experience a demand for the vaccines due to the timing of the first wave of disease activity: *“No because the peak of the epidemic had already passed at the time when the vaccine was widely available. So this is October and November and many children could be immunised, could not be immunised until December, so many patients have already caught influenza during this so [...] very late for these patients.” (JA5)* Also: *“So now people were realising that this is not a severe pandemic and also there is plenty of vaccine coming so a sense of scarceness rapidly disappearing at the end of November to December which was apparent in January so the issue was gradually shifting, atmosphere gradually shifting from October November December January and actually January it was apparent for everybody that the vaccine was actually oversupplied and next is how to return the vaccine because at the time of November or early December each medical facilities ordered a lot of vaccine which is coming end of December or January for general vaccination but in October or in January and February there was not that much appetite among the general population for vaccination because the pandemic is gradually ending so that many health facilities are facing a lot of stockpile of vaccine which they’re supposed to buy so there was the issue of how to return the vaccine or who is actually paying for the vaccine not used so the nature of the issue was shifting from the early phase to middle phase to later phases.” (JA7)*

Naturally there was a desire for the disease activity to be held back until the vaccines had arrived and the campaign had started: *"Clearly we wanted it to start October, mid-October, because that's when we anticipated having vaccine available and at a local health agency level, you're responsible for local surveillance, local response, but also local vaccine strategy."* (CA6)

5.4.6.3 Perceived effectiveness of vaccines during the pandemic influenza response

The interviewees discussed the perceived effectiveness of the vaccines contribution to the pandemic influenza response. Sweden interviewees felt that the vaccines could have played a role in reducing the burden of pandemic influenza, whereas Japan, New Zealand and Singapore felt that vaccines would not have played a major role. Canada, Japan and Sweden noted that no third wave of disease activity occurred and the role of vaccines in relation to this was unknown.

The immunisation programme effectiveness was considered to have been limited due to the campaign timing occurring after a peak influenza activity, but at the same time the effectiveness was difficult to assess because immunisation was rolled out throughout the country: *"We had that in our epi curve and you'll see that when you'll get the epi curve. But the problem was is that we, our vaccine rolled out just as we were peaking and so, yes, it went down and maybe it wouldn't have. But public health is, you never get to see what would have happened if you didn't do, you know. And in public*

health your successes are the things that don't ... So you'll see that, but there's a lot of discussion about whether the vaccine really had an impact or didn't have an impact because it would have taken its course anyway, but. And those kind of decisions are the, or those kind of discussions are the very thing that are so challenging at the time that you're rolling out a vaccine. Yeah, because you have experts saying, oh, there's no point to this or people just don't bother and on an esoteric level talking at a population and if you're feeling lucky and you're the one, but on the other hand the peak is a lot of very substantial illness, right? So, yeah." (CA5)

"Here, with that same curve they said that the waning of disease activity was to happen too early for the vaccine to have had a significant effect, to explain that curve. And more likely was the prevalence of disease in the first wave that immunity was developed. And those who were going to be more severely affected were affected in the first wave. But that's what was said here, that, that our vaccine was, with that curve, because we had the same kind of curve, but when our vaccine started and, and when the disease activity dropped off, it was too close together for that to be a causative factor, yeah." (CA3a / CA3b)

Canada didn't have a third wave of disease activity so it was possible that the vaccination campaign played a part in this: *"But then it's hard to say would we have had a third wave, had we not had?"* (CA3a / CA3b) Canada's disease activity dropped off in December 2009.

The effectiveness of the pandemic vaccine in individuals was only briefly discussed by a few interviewees in Japan: *"In*

Japan the pandemic vaccine effectiveness was 70%, that was very high. That was 89% for pregnant women, this is what was reported in this journal, I mean 0.2224% of pregnant women with vaccination and 2.08% in pregnant women without vaccination so the effectiveness was about 90%.”
(JA5)

5.4.7 Side effects

5.4.7.1 Promoting safety of new vaccine

Resources were invested both before and during country's pandemic influenza vaccination campaigns to promote the safety of the new influenza vaccine and encourage vaccination. National campaigns were launched, as well as targeted programmes towards specific population groups, and particular aspects of the vaccination campaign were addressed such as the adjuvant component of the vaccine because this was an alteration to previous campaigns.

Before the immunisation campaign was launched and the vaccination clinics were opened, a lot of resources were invested in promoting the safeness of the new influenza vaccine to Canadian public. For instance, interviewees spoke about the work which involved responding to public anxious that the vaccine may cause injury to them or their children. Responding to these concerns was particularly important because children were a risk group and specifically targeted in the immunisation campaign: "*Safety concerns that somehow*

the vaccine was going to cause injury and particularly as children were identified as a real population of concern for us there was a lot of concern about the safety of the vaccine.”
(CA5)

One participant discussed their focused work with persons, such as First Nations and Inuit people, living in territories of Canada:

CA3a: “Well there was a lot of work that we had to do prior to the mass immunization clinic, was the fact that it was a safe vaccine. So aboriginals, they’re more of a holistic, they look at medicine more holistically than we do, and vaccine is not always something that they would go to first. And so we really had to work with our Grand Chiefs, for them to demonstrate, and they did it on, in the media that they got their, their shot to show that it is safe and no one’s trying to hurt you by giving you this vaccine and...”

CA3b: “And you’re not, you’re not the guinea pigs.”

CA3a: “Yes.”

CA3b: “Because that was another perception, since aboriginal groups were prioritised to have the first allocation of vaccine, that was at times perceived as oh yeah, sure, you’re going to give it to us first before you give it to the white people, because if it hurts us then you won’t give it to the white people, so.”

Interviewer: So the reason, you said that normally the vaccine would first go to the northern territories and so is that because the flu hit there first, or is it a delivery thing?

CA3b: “That, it is just strictly based on numbers of, of vaccines, it’s just easier just to knock off those, get them out of the, low hanging fruit, right? So yeah.”

Interviewer: *I wouldn't have thought that would be construed the other way, that it's like being tested on us first, but it's just something I wouldn't consider, because I never worked in the area, so.*

CA3b: *"Yeah, but there's some long standing trust issues between the government and First Nations in this country, and so we didn't..."*

CA3a: *"And Inuit, not just First Nations."*

CA3b: *"And Inuit, yeah that's right, for aboriginal, so."*

Canada, like many other countries, has a group within the population who do not wish to have vaccinations against diseases primarily due to reported safety concerns and so this became an issue when delivering the vaccination campaign. As could be expected, infectious disease public health personnel found this low vaccine confidence challenging because they are knowledgeable about the impact of infectious diseases in history when public health measures such as vaccines were not available to the infected: *"And then there's the whole challenges around the anti-vaccine movement and how to deal with that and counter with that and, in the public health context."* (CA5)

Interviewer: *Is that something that's a big challenge here in Canada?*

"I wouldn't say, I would say it's a big challenge. I would say that it's probably not as bad here as it is in the United States maybe or in certain European countries. But, so it's a challenge. It is a challenge and it's something that we're all having to deal with in terms of vaccine confidence and people understanding the importance and really the revolutionary role of vaccines in public health because we're a generation or two

removed now, right? The people who are having children now are not the same people who saw their friends in iron lungs or who had children die as, in their school years from measles or scarlet fever or, do you know? So it's a real culture shift so it's a challenge." (CA5)

5.4.7.2 Balance of risk when considering getting the vaccine

Weighing up the perceived risk of pandemic influenza, both contracting the disease and possible outcomes, versus the concerns of the risks of adverse events associated with vaccines, were discussed in interviews. Perceived risks associated with the vaccines included greater concerns of vaccines than antivirals, the risk of side effects were greater with foreign produced products, and the risk of adjuvant vaccine used for pregnant women.

Whether or not there was a risk of side effects associated with the vaccine, one participant questioned what was the worst case scenario of a pandemic influenza: *"...and is it, even with an elevated risk of a particular adverse event, is it better to get the vaccine? And that's a decision that's made with every vaccine but probably much more critical in something like a pandemic where there is clearly a disease that's circulating, so..."* (CA2)

Whilst staff dealt with these vaccine safety concerns, it coincided with the event of a fatality of a previously healthy school boy who died from H1N1 influenza. To generalise, parental fear over vaccine safety was replaced with a surge in

demand, that was greater than the supply, for the vaccine for their children to provide protection against this worrisome disease: *"One of the real, it's really interesting to see the intersection of media and public health because one of the real take off points for our immunisation programme was the death of a teenager in Toronto, a young boy who was a hockey player, I'm not sure, 12, 14, something, but a young hockey player and who was well and then two days later had died of H1N1 influenza and so this was at the very front end when we were starting to roll out our vaccine programme so it really caused a real run on, real pressure on vaccine and, yeah."* (CA5)

Another factor in the safety concern of the vaccine centred on the fact that this was the first influenza vaccine to use an adjuvant: *"...we have had adjuvanted vaccines before that but not for influenza, right? And so there was a lot of concern about the safety of the adjuvant, people understanding why we were using an adjuvant and like if, well, if you don't know why don't you just use the other one? And it's like, well, because we're trying to be globally responsible, dose sparing and make sure that, we're trying not to use up all of the antigens so that other countries, you know. So trying to explain all of that and there's a lot of suspicion around it and, yeah."* (CA5)

When commenting about the safety of public health measures, one Swedish participant made an interesting observation: *"The concern, at least what I see is directly towards vaccination, not to the same extent as using antivirals."* (SW3a)

There was some pandemic vaccine safety concern for the specific population group of pregnant women this was examined in Japan and resulted in pregnant women being offered a vaccine without adjuvant as explained: *"The issue was there in Japan 2009 and we actually provided special measure for this issue, one of worry among pregnant women and also some scientists and physicians is possible side effect of adjuvant yeah. It might adverse the effect of pregnant women and their baby, that's the common worry among pregnant women and some scientists and physicians so we actually produced certain amount of vaccine adjuvant free. In doing adjuvant free we are required to put more antigen in because adjuvant is usually adding and saving technology, by putting adjuvant you can reduce the amount antigen in each vaccination which is a resource saving measure so without adjuvant and also in Japan because of the limited time, considering the limited time we usually use a huge vial, one vial for 18, but for pregnant women we actually produced enough for one shot without adjuvant and we actually amassed all the people concerned about this this issue that okay we provide adjuvant free vaccine single use only for pregnant women. But I think this advertisement and explanation were accepted among pregnant women and physicians, very safe, don't think there is a huge, a big worry about it."* (JA7)

5.4.7.3 Reported side effects

Countries discussed that fever, narcolepsy and anaphylactic shock were raised as side effects associated with the

pandemic influenza vaccines. These side effects were raised before, during and post national vaccination campaigns and evidence was sourced and appraised to determine any apparent risk, association and causation.

A frequent topic of conversation in the interviews by some participants in Sweden covered the subject of narcolepsy reports, particularly in young persons, from 2010 onwards: *"...we didn't hear about it until about the summer of 2010, we didn't hear anything about it during the campaign, we knew about the other side effects, the local side effects in fever, tenderness and the ones we were expecting, but we weren't expecting narcolepsy. So that was the reports in Finland first. [Gets article/report] This is the summary from this county here actually, over the narcolepsy, the paediatricians here, so that's a summary, and they made a study of the different records made the Medical Product Agency."* (SW2)

SW3a: "The only thing that I think of that has been very special is this signal of narcolepsy because we and Finland were the first countries who discovered or at least thought we had a problem. In the beginning it was difficult to, not to persuade, but to have a serious discussion within the European system with the other authorities because I think they were suspicious about this signal because it came originally from one single doctor in the south of Sweden, so it was a very similar situation to this situation with autism, so very many thought now it comes again and it took quite some time and effort from our staff to convince or put enough scientific evidence to the others so they would accept that this might be a problem and that this might be a consequence of the vaccination."

SW3b: "I think it was very much the discussion that well of course if you have read this in the paper that you get narcolepsy then you see that, and then you will report that, just because some other has said, the media. So not true cases, well maybe true cases, but sometimes you get a case but maybe you don't report it. I think..."

SW3a: "But it's a disease that is difficult to diagnose and now we have received several cases of narcolepsy but we still don't know if it's cases that would have been developed, discovered later since there has been so much focus on looking for these cases, maybe we have this now, but within a few years it might decline, but I don't know yet, but it has been a very special situation since the pandemic because there has been several research projects around this issue, we still work with issue almost daily, but it's still a very big part of not the whole agency but some of us work continuously with this issue still."

SW3b: "But I would say that now the most people in the scientific community recognise this is a real affect, that they have a connection to the vaccine."

SW3a: "But we still don't know the cause, mechanism."

SW3b: "But that's a good start because at the beginning there wasn't many people saying this is something, but still the question, is it local, just in Sweden or Finland, now you know that it has certainly has occurred in other places also."

SW3a: "Ireland, France, Norway, UK, there are several reports now that this is a fact or maybe that's too strong but you have seen the same phenomena in other countries so it's no longer a Nordic problem."

Interviewer: Yeah, because when I first started doing a literature review, I saw the research focusing on Sweden and Finland for this and I heard a bit about those two countries, but I hadn't heard beyond those two countries.

SW3a: "There are several reports now, so that is good so we can move it forward, but the only thing is that we are missing cases in Canada, where you should have expected some as well, but we don't know what..."

SW3b: "We haven't seen any cases in Canada, but then used I would say almost exactly the same vaccine, there was some differences but since we don't know what is causing this, so."

Interviewer: Do you think you've got a different or more enhanced surveillance system here and that could be why?

SW3b: "I don't know, I suppose they have a surveillance system."

SW3a: "Yeah, but that could be a reason for us seeing the signal much earlier, than some of the other countries."

SW3b: "Sure, sure."

Interviewer: Canada is one of my countries that I'm going to so, I should...

SW3b: "Right, ask them about narcolepsy, why haven't they seen any, was it a different vaccine..."

Interviewer: They had the same vaccine?

SW3a: "They had the Arepanrix."

SW3b: "It's not actually the same, but it's very similar..."

SW3a: "They're a different manufacturing procedure..."

SW3b: "There are some differences in the manufacturing procedure."

In Japan, there was a demand for the domestic pandemic vaccine to be produced and when the pandemic vaccine from GSK arrived, it had a very low uptake. It was explained that the reason for this was: *"Because one of the side effects of the one from overseas was fever."* (JA4)

Interviewer: That was a concern to the people here?

"Yeah that was part of it. I don't think that the vaccine from overseas was widely available to the general public, so you had to meet current criteria. I believe and that was confirmed, that the vaccine from overseas couldn't be used for the general public, it was not even distributed for use." (JA4)

Interviewer: So was it priority groups like healthcare workers and essential workers?

"I don't even think it was given to medical practitioners. I don't think we used the GSK vaccine, we gave it to a few patients for research purposes. I don't remember why." (JA4)

As also covered by participant JA5: *"Yes from UK GlaxoSmithKline. I have never heard of a patient who has received that vaccine. I know they're imported, that vaccines were imported but I never heard of patients who were immunised with this."*

Interviewer: Okay, do you know why that is? Were they waiting for the domestic one?

"We like Japanese products that's the reason and also we are very conscious of the adverse effect of newly produced or reported vaccines." (JA5)

Interviewer: Okay, so is there a higher trust in the Japanese produced vaccine?

"And also some side effects were reported I think in the news, so not so many patients were immunised through that." (JA5)

5.4.7.4 Legacy of side effects

Concerns were raised by Swedish interviewees that the narcolepsy reports that have surfaced post the 2009 pandemic influenza vaccination campaign may have damaged Sweden's potential future response with engaging with the general public about the importance of vaccination. *"...I don't think that the people in common will be, how should I say, obedient? I don't think they will follow the instructions from the national agencies, the way they did in 2009, they took a large part of responsibility for themselves, but they vaccinated themselves to protect others, so a sort of way of solidarity. I think people will be more afraid of vaccines. It will be more of the individual, we see it nowadays with the general vaccination program, that people are more hesitant, so I... but if you ask me, I think we still did the right thing, we acted on the news that we got, a new strain that is spreading and it could be severe, high mortality in certain age groups, it's very very hard to not to respond to that, it's much easier to look in the mirror, in the retrospect, when you have all the information, it's much easier, but when you are there and you have to make a decision. But it's really hard to say, I don't*

know, I think we still have a political, the politicians still say that we should vaccinate the whole population if it would come again, so their view hasn't changed, but I mean I think the people in common, they are not interested the way they were. But it depends, if you get a severe influenza, it will change overnight." (SW2)

"I think that left a real bad taste, otherwise I think that the information to the public, the effectiveness of the vaccine, I think everybody was kind of content at that time, and they felt safe, that the society took care of them and so on. We did a lot of work to coordinating the information to the public, that was a huge job and we did a lot of it here, yeah." (SW7)

"The main impact is the side effect, of narcolepsy, of course that's a very very tragic, extremely tragic, I think it's a, it will be put in the history books of medicine, like thalidomide, you know like the event in the 60s for example, this is about the same I think. So it's extremely tragic and of course that's been one of the major impacts and of course we are a little bit afraid that the willingness to be vaccinated next time, will decline as a result of that." (SW4)

5.4.8 Vaccine communications and the media

5.4.8.1 Reports of first A(H1N1) mortality event

The first reported deaths due to the 2009-10 influenza A(H1N1) pandemic were major events in the pandemic

response and attracted media and public attention. The study countries of Sweden, Japan and Canadian spoke about the first influenza associated deaths impact: *"then there were occasions when we had the first death in Sweden or people that were very very ill and perhaps some kids died and so on and then there was a big media discussion about that and then about the vaccine of course, who should have it and so on, but I think there were mostly in the media they were like reporting the thing that the agency said."* (SW1)

A few of Canadian participants drew on memories of an early mortality event that became a media headline and created anxiety amongst the general public concerning the danger of pandemic influenza. A previously healthy school boy who had played hockey within the last few days died as a result of contracting pandemic influenza A(H1N1) and caused great shock across Canada and resulted in a public demand for the vaccine: *"Again, with the vaccine issue there was, I don't know when it occurred in the pandemic but there was a death of a, I think a 16 year old boy here in Ontario and that really I think brought things home to people. Across the country there was a very high media attention and that created huge demand right across the country for vaccine and really, I think, brought attention to the pandemic."* (CA2) The memory was also recalled by these participants:

CA3b: *"there was a young hockey player in Ontario."*

CA3a: *"That's right."*

CA3b: "And that one really hit the media, like 12 years old or something like that, died from H1N1, and that was, that was huge."

CA3a: "And then, and then the next day like six hour line ups for people..."

And this participant as well: *"One of the real, it's really interesting to see the intersection of media and public health because one of the real take off points for our immunisation programme was the death of a teenager in Toronto, a young boy who was a hockey player, I'm not sure, 12, 14, something, but a young hockey player and who was well and then two days later had died of H1N1 influenza and so this was at the very front end when we were starting to roll out our vaccine programme so it really caused a real run on, real pressure on vaccine and, yeah."* (CA5)

5.4.8.2 Individuals lambasted in the media for queue-jumping

At the beginning of the vaccination campaign, certain groups, those deemed risk groups during the pandemic influenza, were eligible to receive the vaccine initially. Where individuals or groups, in a sense, queue jumped ahead of these people and had the vaccine before their time, the media and general public were stunned by their actions. The outcome of these instances meant that people stuck more strictly to the immunisation order outlined in the campaign, as illustrated here: *"So one of the other things, we were talking about things that made the media, once the vaccine got rolled out,*

like the first week, one of our national hockey teams ended up getting vaccinated before anybody else, the Calgary Flames.”
(CA3a)

Interviewer: “How did they get that?”

“Yeah, we’re not sure who authorised them to get the product, but that was a huge, like people were not pleased. And so then nobody else, like everybody else respected the, the allocations after that, yeah.” (CA3a)

Although there was a media and public upset about one of the hockey teams getting vaccinated before their schedule, in other countries, famous people and country heads have been filmed or photographed and shown by the media getting the vaccinated in order to boost public confidence and increase immunisation uptake rates. For instance, President Barak Obama was filmed by news channels getting the pandemic influenza vaccine in the early days of the United States vaccination campaign. Perhaps this hockey team may have helped with public confidence in the vaccine and contributed to vaccine uptake rates.

When the priority groups were set by the government, people were expected to strictly follow the schedule order. The importance of keeping to the priority order as set out by government was emphasised in Japan. One instance, where a medic prioritised a family member was exposed in the media as a national scandal: *“That was very strict first of all, very strict, for example one of the doctors at the clinic gave the vaccine, that was prepared for medical staff, to his grandson. At that time one of the doctors gave the vaccine to his grandson during the immunization period for only medical*

staff at the end of October. So this was broadcasted to all of Japan, that was written in Japan. Yeah, his grandson with asthma, in Hyogo is near Osaka, a clinic doctor with the pandemic vaccine. [...] Yes everyone can read it and on television. Very strict, the Japanese custom. It's not a big news I think for you, but in Japan it's a big news." (JA5)

5.4.8.3 Media supporting the effectiveness of the vaccine

Countries spoke about the role of the media in assisting with the pandemic influenza response by releasing information about the efficacy of the vaccine and promoting uptake. For instance, the media covered the effectiveness of the pandemic influenza vaccine in older persons: *"I know there was, there was a lot of press about the efficacy of the vaccine, particularly in older age groups, was it really, was it really effective, but they also said that some people that were older would have had some old immunity, so that it was less of an issue for them, so it wasn't maybe the vaccine that was protecting them, it was the previous exposures because they were that much older, yeah."* (CA1)

5.4.8.4 Media reporting on the safety concerns and adverse effects of the vaccines

The other role of the media was to challenge key pandemic influenza response personnel regarding safety concerns and risk of adverse effects of the newly produced pandemic influenza vaccines. For example, the media discussed a

particular batch of the influenza pandemic vaccine that was associated with a higher than deemed usual amount of adverse events: *"Well, I was, one lot that seemed to be associated with a higher level of adverse events, and so that created a bit of a media issue, but it was one lot of, I don't know how many lots were actually released."* (CA1)

Interviewer: Do you mean by fever and things like that ...

"Yeah, I don't know exactly what the profile was of the adverse events but it was anaphylactic shock, I think there was a higher than expected, and again there was a lot of investigation done both by the company and by Health Canada, and there was never anything determined that could suggest that the lot was associated, that it may have just been an anomaly. But there was a need to track where that lot had gone and to bring back samples for testing, number one, and then to make sure that it, whatever was left at that lot was embargoed and then brought back to the company." (CA1)

Those who had worked on the pandemic influenza response faced challenging questions from the media concerning narcolepsy reports: *"Actually, I've been on a panel on TV one morning, on a morning sofa or something like that, when all these cases of narcolepsy were coming out, and the reporter asked me a question. Would you still recommend this, if you know this, you know the narcolepsy and the vaccine and so on, so I was responsible for the whole government at that time, and I said it's always easy, it's the same answer I gave, it's always easy to be wise afterwards."* (SW7)

Interviewer: When you have all the information.

SW7: "Yes, you always tend to be wiser afterwards, but at that time I thought it was the right decision, my children are vaccinated, so that's the way it is I think, but it's hard, it's really hard, especially when you meet those children I think."

Interviewer: Has there been a huge media focus on individual cases?

SW7: "Yes, yes, yes, it has. But in the same time it hasn't been the same media focus on people dying with the influenza. So that's interesting in a way."

5.4.9 Risk communications regarding vaccines

Communications during the 2009-10 pandemic influenza involved the internet and social media to a far greater extent than previous infectious disease events which would have dominated domains such as TV and newspapers. The speed of communications on the internet and social media was much faster than that of previous communications so pandemic influenza response personnel needed to adapt their method of public health messaging to concurrent popularities. The need to actively manage and have a communications strategy was considered very important: both in releasing new information and addressing circulating stories. The power of one negative story could undermine a colossal amount of national public health work. Communication work was explained as being very resource intensive and challenging during a time of uncertainty. It was difficult for public health officials to speak with confidence about a vaccine that was new to use and where there was no fixed availability date. Consistent

messaging is important but efforts can be derailed in instances where new knowledge requires the need to change public health messages.

"I think it's just public awareness and messaging around the vaccine. I think also what was different about this event than SARS, which is probably a global issue, is the impact of the internet and social media, that during SARS you would have, TV and the newspaper would be your predominant source of information, either daily, weekly or whatever, everything was, the pressure of having in time and there was all kinds, there were videos circulating. There was one on the H1N1 vaccine with somebody walking backwards that went viral about, and it was actually turned out later to be a hoax, but they had somebody with serious neurological effects that were walking and they posted it as look what happened after I took the vaccine and [.....] how one really negative message that may not even be based on anything factual can override positive messaging." (CA1)

An issue that arose in the territories of Canada related to additional resources sourced during the pandemic influenza and became a media headline: *"Yeah, yeah, and then our most negative media for First Nations Inuit Health Branch was the fact that one of the nurses was plan, like supplies were an issue all around, and so she was doing her ordering, and she thought she was being, how's the word? She was, everybody was told like order more things of whatever, so she ordered more body bags for five particular communities than she normally would. And so one of the, the chiefs found out and got upset and then went to the media, and then the media was like oh, Health Canada, this was before the vaccine came*

out, this was in September, they were like oh, so Health Canada is planning, instead of vaccine they're planning to use body bags..." (CA3b)

The vaccine and communication were considered crucial during the pandemic influenza response in Canada: *"Yeah. I think vaccine is really one of, the crucial one, crucial almost and communication. Communication I cannot emphasise the importance of communication, and communication with the public, with the healthcare practitioners, just across the spectrum. Communication was such a challenge and, yeah, huge, I can't even begin, yeah. And so again that's something that we've really identified as a critical element and are trying to work on things like developing clinical guidance, processes for developing clinical guidance during the pandemics or in response to urgent events or things like, yeah, educational materials, developing antiviral guidance, having those things ready to go so that when you need them it's a matter of updating them, tweaking them, changing the H1N1 to an H12N46 or whatever, being, there's something about communication is just such a critical thing and it's so fascinating and I have to tell you that this is probably not a very popular idea. It's the one that I feel I have the least hope for. Human nature is what human nature is, right? And communication is such a challenging thing and I can see for vaccines and for antivirals I see all of these things that we're doing make any difference. Communication it's just so hard to get it right. And it's the one thing that I can guarantee you will be the critical, will be a critical loop link every time."* (CA5)

Providing communications during a time of uncertainty was difficult: *"Also we didn't know when the vaccine would be*

available and or the effectiveness of the vaccine, so that was a difficult communication strategy with the public, it was untested, we didn't have data, true data on its safety and efficacy, or effectiveness early on and that, from a communications strategy is very, very difficult and risk communication strategy to the public, and to physicians right? I mean it's the nurses and physicians that are putting needles to arms and they have to be aware of the risks and we were using a new vaccine, an adjuvanted vaccine which hadn't been used in Canada before, at all, so those were big unknowns. And then when was it going to take off, because we know there's seasonal, what was going to be the seasonal strain and was the seasonal strain going to have any impact? Should we have a seasonal vaccine, should we also have the H1N1 vaccine, and who differentially is going to have, be affected by the virus. So there were significant questions, and then from a system response vantage point, we need leadership from the, you know in Canada it's the Province that funds health, we needed leadership from the Province in terms of what would be funded, what won't be funded, how will we, what communication strategy are we going to have at a provincial level, and will it work hand in glove with the Federal level because you know we have a, I would say a fractured health care system in terms of leadership." (CA6)

The forms of risk communication were similar across countries: press releases, website content, posters, TV adverts, newspaper pieces, social media, etc. "And all the news that we had, that was connected to the pandemic, was published on this website, and it started in April 2009, here is an article about treatment and vaccination for example. And

then it goes up to, so all the news that we had were collected here and for example, I said that we published summaries about adverse events that were reported. Here for example, status for reported adverse events of Pandemrix and then we did that continuously, and then at some point after the vaccination campaign was over, we made a final report and right after that we had this signal of narcolepsy and that work has been going on and is still going on since then. But all these articles are collected here.” (SW3a)

Countries health risk communications were an attempt to be transparent and provide up-to-date information about the current disease activity within and outside each country, provide information concerning the actions individuals could take to prevent illness, build trust between government officials and the public, and to stamp out any surfacing inaccuracies and rumours. Timely risk communications were important and a small number of participants mentioned the endeavour to stay ahead of the presenting events through probability risk communications about pandemic influenza. A participant explained that within Singapore, it was described to the public that the 2009-10 influenza A(H1N1) would arrive into the country before any confirmed cases arrived. Once cases arrived, it was explained ahead of events that some people would experience severe illness and in rare instances some would die: *“...public communication was very important, we had a very insightful Minister at that time [...] he was very calm, he just said that, I would not be surprised by that situation, that situation that we would see cases of this new influenza in Singapore any time soon. So he kind of like pre-empted the headlines by saying that, yeah it’s going to*

happen, it's not an issue at all. [...] within about three weeks the first case of influenza was picked up by laboratory through lab tests you know and confirmed to be the new strain that had just emerged [...] And then he said, I would not be surprised if we get our first case of death any time soon. So he just kind of one step ahead [...] so indeed when somebody died subsequently it wasn't a big issue because he said that's the normal thing with influenza, so it's a lot of communication and managing public you know and I think we also learnt a lot from him." (S17)

5.4.10 Lessons learnt from this pandemic influenza vaccine response and preparations for a future pandemic influenza event

Participants reflected on the 2009-10 influenza A(H1N1) pandemic by discussing the knowledge now known through the response experience. A frequent topic regarding using the pandemic influenza plans in the response was the need for flexibility so that the response could be proportional. It was often explained that plans needed flexibility built in so that the response could be tailored to a mild, moderate or severe pandemic influenza incorporating both low-high virulence and low-high severity. Plans required the ability to both scale up during a pandemic and also scale down a response.

A challenge with the national responses was the differences in disease activity, both internationally and within countries. Canada and New Zealand both had cases at the start of the 2009-10 influenza A(H1N1) pandemic whereas Singapore did

not detect the first case until one month later. Similarly, as the WHO announced the post pandemic influenza phase in August 2010, New Zealand was tackling a large number of A(H1N1) cases. Countries experienced a large variation in disease activity, where a response could be well underway, such as the New Zealand cities, and other areas would have no cases, such as some of New Zealand's small towns and villages.

Both Japan and Singapore's planning had detailed a pandemic response to avian influenza which proved not to be the case in 2009.

5.5 Summary of pandemic influenza vaccine findings

This chapter has presented the vaccine results through the themes that were identified from data analysis. Vaccine sourcing and distribution were significant aspects of the response. Vaccine uptake rates varied between the countries and specific population groups, and demand for the vaccine was high when supply was low. Prioritising the vaccine proved challenging to navigate as it went against countries equitable access beliefs but it proved necessary during the pandemic. The timing of vaccination campaigns varied among the countries with Sweden and Canada commencing campaigns in October 2009 and New Zealand starting in 2010. Concerns about harm caused by vaccines were discussed and the role of communication messages and the media during pandemic response. The interview themes will be included in the following discussion chapter.

6 Vaccines Discussion

This chapter will examine the dominant themes from the vaccine results section. Firstly, the use of influenza vaccines is reviewed, with attention given to supplier choices, differences between the hemispheres in response to influenza pandemics, and the legacy of previous influenza pandemics, in particular, the 1918 Spanish influenza. Secondly, specific population groups such as aboriginal persons and pregnant women are a specific focus, followed by vaccination priorities and influenza vaccine side effect concerns. Thirdly, the A(H1N1) disease activity and vaccine timing is explored alongside the perceived effectiveness of vaccines during the pandemic influenza response.

6.1 Use of vaccines during an influenza pandemic

The 2009-10 influenza A(H1N1) pandemic was the first time in an influenza pandemic scenario that multiple countries had access to a vaccine as a public health measure response. The WHO 2012 report '*Vaccine Deployment Initiative*' outlined the coordination of the global donation of pandemic influenza vaccines to provide equitable access in resource-poor countries. The report explained that the "*deployment effort was the first of its kind and moved unprecedented quantities of a new vaccine around the world.*" (2012: p.2). The 2009-10 influenza A(H1N1) pandemic was the first time that these

quantities of vaccines were produced, and were required by an extraordinary number of countries.

In the other influenza pandemics, it was not always the case that influenza vaccines were available as a public health measure. The 1918-19 A(H1N1) Spanish influenza pandemic was severe; it was estimated to have infected 50% of the global population and resulted in >40 million mortalities. This influenza pandemic began at the end of World War 1 and resulted in more deaths than those caused by the war. It severely affected young adults and specific populations such as those in Alaska, Western Samoa, and aboriginal populations in Australia and New Zealand (Monto and Sellwood, 2013). At the time of the 1918-19 Spanish influenza, vaccines were not invented as a public health measure, and, therefore, measures included border control, quarantine and bed rest, etc.

In 1945, coinciding with the end of World War 2, the United States licenced inactivated influenza vaccines which involved the procedure of producing "*more highly purified vaccines in which reactogenic contaminants had been removed.*" (Keitel, Neuzil and Treanor, 2013: p.313). Hens eggs facilitated the growth of influenza virus and resulted in the large-scale production of seasonal influenza vaccines for the first time (Carrasco and Leroux-Roels, 2013).

Influenza vaccines were used on a small scale during the 1957 A(H2N2) Asian influenza pandemic and the 1968 A(H3N2) Hong Kong influenza pandemic. The United States intended to vaccinate against A(H2N2) in 1957 to prevent morbidity and mortality rates but the vaccine production only provided small quantities of vaccine. When influenza peaked in October 1957,

17 million doses had been manufactured but were too late to make an impact on the pandemic (Henderson et al., 2009). As explained by Henderson et al. (2009: p.272): "*The national spread of the disease was so rapid that within 3 months it had swept throughout the country and had largely disappeared. It was reported that with the end of the fall epidemic, demands for vaccine declined sharply.*" Similarly, vaccines for the 1968 A(H3N2) Hong Kong influenza pandemic appear to have rarely been used; this has been inferred by the lack of literature found on this subject. In the article by Fukumi (1969), there is mention that some outbreaks of influenza infections occurred in August 1968 in the Japanese vaccine laboratories, and further investigation found that cases were confirmed but did not spread easily to close contacts.

Developments in the field of vaccine types have produced a 'whole virus' that is inactivated, as well as 'split virion' which involves procedures of virus disruption and in the case of 'subunit', the partial extraction of antigens. Since 1977, the trivalent inactivated vaccines (TIV) have been utilised in seasonal influenza vaccines which have allowed for the inclusion of three circulating influenza strains (two A and one B virus) and the standardisation of 15µg haemagglutinin protein (HA) antigen per strain. Typically children received half of this HA dose in comparison to adults and more recent research has indicated that the senior population would benefit from a higher HA dose (Keitel, Neuzil and Treanor, 2013; Carrasco and Leroux-Roels, 2013). Subsequently, two distinct influenza B viruses have been identified as circulating as of the 1970s (Hay et al., 2001) which has led to research in the vaccine field for a quadrivalent vaccine to include two A

and two B virus strains in the seasonal influenza vaccine (Keitel, Neuzil and Treanor, 2013). Eggs have largely been utilised to grow influenza viruses in embryonated hens' eggs but during an influenza pandemic, this can potentially create availability problems in vaccine production.

From the 1930s, aluminium was used as an adjuvant in vaccines and continued to be used for many decades. In addition, another adjuvant involved oil-in-water combinations. Over time more vaccines containing adjuvant were included, for example, it was incorporated within the influenza vaccine in the 2000s (Pasquale et al., 2015). Inactivated influenza vaccines are produced in either adjuvanted or non-adjuvanted preparations. The benefits of using adjuvants instead of non-adjuvanted preparations include increased immunogenicity and better vaccine availability as more doses can be produced using less antigen (Pasquale et al., 2015).

Prior to the 2009-10 influenza A(H1N1) pandemic, several countries purchased H5N1 pre-pandemic influenza vaccines in an effort to provide an immediate vaccine in a novel H5N1 influenza scenario. The concern was that in the event of a future pandemic influenza, vaccine production would be too time-consuming and not be available for the first and even possibly the second wave of influenza infection. Before 2009, H5N1 pre-pandemic vaccine stockpiles were considered to have *"the potential to cut the number and severity of cases, but only if two doses are delivered before the onset of a pandemic, which may be logistically difficult to organise."* (Jennings et al., 2008: p.656).

Pre-pandemic influenza vaccines are an example of an anticipatory public health policy approach. Anticipatory measures have been estimated to be cost-effective whereby \$1 spent in advance on preparedness can offset \$4 in emergency relief spending and that prepared communities are more resilient to threats (DeLeo, 2016). Pandemic influenzas are acknowledged threats and, therefore, fit into the category of anticipatory problems, and although they are anticipatory, when risks and hazards such as pandemics do occur they are not detached from the associated uncertainty. Policymakers that participate in anticipatory policymaking ensure that they are able to act in times of uncertainty (DeLeo, 2016). Thus, pre-pandemic influenza vaccines are one example of anticipatory policymaking, and pandemic influenza vaccine agreements with manufacturers is another.

Pre-pandemic influenza vaccines present more risks than typical influenza vaccine purchases to national policy makers. Firstly, will an influenza pandemic occur before the vaccines reach their expiration date? Secondly, will the stockpile of pre-pandemic influenza vaccines match the pandemic virus that emerges? Even in 2008, Jennings et al. pointed out that stockpiles of the H5N1 vaccines were nearing the expiry date and would require government decisions on their use in an interpandemic period or go unused. With the benefit of hindsight, it is now known that the purchase of H5N1 pre-pandemic influenza vaccines was a mismanagement of resources due to the emergence of a novel influenza A(H1N1) virus in 2009: the threat of H5N1 does still remain, however in 2016, the stockpiled pre-pandemic vaccines have either expired or almost reached expiry date. As a result, this short

experience has shown how pre-pandemic influenza vaccines are a double-risk and present complicated decisions for national policy makers to navigate.

The 2009-10 influenza A(H1N1) pandemic was the first time that many countries could access large amounts of vaccine which created issues surrounding public demand for, and expectation of, vaccination within a short time. Prior to 2009, this scarcity issue was commonly recognised, so many countries entered into pandemic influenza vaccine agreements with manufacturers. This both acted as a reserve holding of a number of vaccines per country and informed pharmaceutical companies of potential vaccine requirements. Vaccine manufacturers were experienced with en-masse vaccination through the provision of seasonal influenza vaccines biannually, as well as childhood vaccination programmes. Multiple manufacturers provide these vaccines and this has set a precedent whereby countries may enter into pandemic influenza vaccine procurement agreements with a variety of suppliers.

The 2009-10 influenza A(H1N1) pandemic was the first time that the procurement of pandemic influenza vaccines was tested in real life. A common issue that arose from this measure was the inflexibility of contracts. For instance, in the case of the 2009-10 influenza A(H1N1) pandemic, as 2009 progressed it was found that both the need for, as assessed by key national pandemic influenza response personnel, and the demand from the public for the vaccine waned. In these cases, countries wished to reduce influenza vaccine orders and make amendments to contracts.

One of the legacies for the future born out of the 2009-10 influenza A(H1N1) pandemic will concern the excess vaccines faced by a number of the study countries. The interviewees explained that they had faced criticisms for the unused vaccines; some were questioned if they had over reacted in their response to the pandemic influenza and others were criticised for wasting resources and for the economic cost. The legacy of excess vaccines may influence future policy decisions, where for instance far fewer vaccines are ordered. Alternatively, the ordering of vaccines may be able to move to a more real-time ordering process or countries may be able to order vaccines in batches rather than one contract order so that waste is minimised. A phased order process would allow countries to place vaccine orders in balance with the vaccine demand and uptake rates, which would maintain the appearance to the public of waste avoidance. This would reduce the desire to amend a vaccine order contract later into a pandemic influenza response if countries are faced with unused vaccines.

The experience of excess vaccines may also influence future policy decisions regarding vaccine donations to other countries. Admittedly, the researcher did not draw participants into conversation on country vaccine donations but many countries faced the issue of excess vaccines and as a consequence, the option of vaccine donations became apparent. However, the experience of the 2009-10 influenza A(H1N1) pandemic was an example of vaccine donations arriving too late and in a reactionary response. It is apparent that further work on a formalised real-time donation programme is required where those evaluated as most

vulnerable to severe illness and mortality, and in economic need of support, receive vaccines. The Pandemic Influenza Preparedness (PIP) Framework, which became effective from 2011, has a global role in the sharing of preparedness and response to pandemic influenza and one element of PIP includes the goal of increasing developing countries access to vaccines. In the future, an international approach to a pool of bought vaccines and dissemination may occur in countries that would typically procure vaccines from a pharmaceutical company. In 2013, the European Parliament and the Council of the European Union published their decision concerning the serious cross-border threats to health. This legislative act formally enabled EU Member States to voluntarily form a group that could jointly procure vaccines in a pandemic influenza scenario. This would enable participating countries to have a greater opportunity to obtain the best purchase price, possible order flexibility and equitable access to vaccines by partaking countries.

In this research, it was reported that countries tended to follow two distinct approaches in pandemic influenza vaccine supply: single pharmaceutical company supplier (e.g. Canada, Sweden, New Zealand) or multiple suppliers (e.g. Japan, Singapore). Countries also followed two distinct approaches for the type of pandemic influenza vaccine provided: monovalent (Sweden, Canada, Japan, Singapore) and trivalent seasonal influenza vaccine containing the specific A(H1N1) component (e.g. New Zealand). The decision of how to source the influenza vaccine during 2009, as well as the type of vaccine provided, can be explained by how countries manage

risk at a time of great uncertainty. The supplier approach shall be explained in the next section.

6.1.1 Single or multiple pandemic vaccine suppliers

The study countries single or multiple supplier vaccine arrangements during the 2009-10 influenza A(H1N1) pandemic was an interesting interview topic that highlighted the differing approaches by countries in securing influenza vaccines during a pandemic scenario.

Singapore and Japan both had multiple supplier vaccine agreements which potentially enabled the sourcing of the vaccine as quickly as possible and reduced the risk of reliance on one pharmaceutical company in an emergency public health situation. The importance of securing vaccines to Japan and Singapore located in this region of the world may be reflected by past experience of infectious diseases. Historically, pandemics have been recorded as originating from Asia, and in the twenty-first century South-East Asia experienced outbreaks of A(H5N1) influenza and severe acute respiratory syndrome (SARS) (Monto and Sellwood, 2013), as well as other infectious diseases including Nipah virus, chikungunya and dengue virus (Lee and Pang, 2013). These diseases prior to 2009-10 influenza A(H1N1) pandemic gave the first-hand experience in infectious disease response measures in several countries, including Singapore and Canada, and countries went on to focus on pandemic preparedness. This experience in Singapore and Japan's neighbouring countries, coupled with the anticipated

emergence of a novel pandemic influenza from Asia, provide an understanding of the multiple supplier vaccine arrangements. The reduction of risk and the speed of sourcing vaccines in a pandemic were summarised by a participant in the results section: "*...to not put your eggs all in one basket because supply, demand and supply...*" (SI2).

In comparison, Sweden, Canada and New Zealand opted for a singular pharmaceutical company supplier route for the developed pandemic influenza vaccine. Canada, like Japan, had a supply of vaccines that were made domestically in the country, whereas Sweden and New Zealand had to buy the vaccines into the country from abroad. Canada and Sweden noted that they were amongst the first countries to receive the pandemic vaccine. Therefore, the feeling of being first in line might have contributed to an attitude of reduced risk and the need not to have multiple suppliers. The pandemic influenza vaccine supply to New Zealand was held with a regional manufacturer (Jennings, 2013), however, as explained by interviewees, the size of New Zealand and their presence in comparison to other much larger countries would mean that they would not be the first to gain the vaccine and therefore much emphasis was placed on other public health measures such as antivirals, border management and health communications.

Interestingly, as noted in the Hine (2010) report on the UK's pandemic influenza response, the UK had a multiple supplier vaccine agreements which perhaps indicated the UK's discomfort at the time to 'put all their eggs in one basket' and the pressure to source a speedy and sufficient quantity of vaccines. Since the 2009-10 influenza A(H1N1) pandemic, the

2010 'Standing Senate Social Affairs Science and Technology' report on the Canadian pandemic influenza response, noted that in the future contract in Canada would have "...the added change of having a backup supplier of pandemic vaccine. There is no requirement for the backup supplier to be domestic." (2010: p.31). The new contract established in 2011 required "...that the government must take steps to ensure that the backup supplier will add to Canada's ability to ensure access to a safe and sufficient supply of pandemic vaccine." (2010: p.viii). The report from Sweden concerning their preparations and management of the 2009-10 influenza A(H1N1) pandemic by Socialstyrelsen (2011) made no mention of multiple suppliers in a future pandemic influenza vaccine but that: "Future vaccine contracts should be more flexible, incorporating the possibility of staggered orders, a renegotiation option to meet changed conditions, and a focus on the treatment needed to achieve satisfactory protection rather than on a stipulation of two doses per person." (Socialstyrelsen, 2011: p.40)

6.1.2 Hemisphere vaccine response divide

The timing of the 2009-10 influenza A(H1N1) pandemic disease activity in terms of the epidemiological features such as the arrival, waves and peaks in countries can be further understood with a comparison of the disease activity timings in twentieth-century influenza pandemics.

As noted earlier, the 1918-19 A(H1N1) Spanish influenza pandemic began at the end of World War 1 (Monto and

Sellwood, 2013), with the United States reporting outbreaks in several locations including army camps in March 1918 (Detroit, South Carolina and San Quentin Prison). Then the influenza appeared in France and other parts of Europe and United States areas associated with World War One troop boat landings in April 1918 (Oxford, 2000; Hsieh et al., 2006). The infection was reported in North Africa in May 1918 and then Britain, Russia, China, the Philippines and New Zealand in June 1918 (Potter, 2001). Outbreaks continued to occur during the course of the northern hemisphere summer of 1918. However, the virus became more severe and widespread by autumn of 1918 (Oxford, 2000). Over two years A(H1N1) spread globally in an eastwards direction at first and along shipping trade routes (Potter, 2001). *"Many countries experienced second (1918-19) and third waves (1919-20) of the more virulent form of infection. No figures exist for many parts of the world, but the pandemic is estimated to have infected 50% of the world's population; 25% suffered a clinical infection and the total mortality was 40-50 million"* (Potter, 2001: p.11).

One of the most important lessons learnt from the 1918-19 A(H1N1) Spanish influenza pandemic was that it could cause severe illness and deaths in otherwise healthy persons, with this pandemic ranking as one of the worst epidemics in human history comparable with historical events such as the Black Death (Potter, 2001). It spread quickly to other countries via shipping routes however countries such as Australia managed to delay the arrival of infection for several months through implementing quarantine measures. The influenza characteristics evolved during the course of the pandemic

meaning that the second and third waves of infection were more severe than first. Hospitals, morgues and the workforce, in general, were overwhelmed and war strategies were hampered by the spread of infection and resulting deaths. Therefore, this outbreak showed that an influenza pandemic can pose as much risk, threat and uncertainty within the global population to rival war, natural disasters and other diseases.

The 1957/58 A(H2N2) Asian influenza pandemic originated in Asia and infections were first noted in the study countries of Singapore and Japan in May 1957. The infection spread and took hold in the southern hemisphere during the winter season and reached New Zealand by July. At this time, cases appeared on the west coast of Canada and spread in an eastern direction over land. Sweden reported A(H2N2) influenza from a land route spread westerly from Asia and Europe (Potter, 1998) at the end of June 1957 (Skog et al., 2014).

The 1968 A(H3N2) Hong Kong influenza pandemic first cases occurred in Asia in July 1968 and arrived in Singapore by August (Potter, 1998) and Japan in imported cases in August as well (Fukumi, 1969). Cases did not take hold in Japan until October 1968, with a wave peaking in January to February 1969 (Fukumi, 1969). Cases peaked in Singapore in mid to late August 1968 (Lee et al. 2008). Canada's first wave occurred in the winter of 1968 and peaked in January 1969 (PHAC, 2010).

New Zealand, due to its location in the southern hemisphere and the emergence of the 2009-10 influenza A(H1N1)

pandemic in their autumn (April 2009), managed to avoid many of the pressing vaccine issues as experienced by the northern hemisphere study countries because by the time the first vaccines were available New Zealand went into Spring. In a sense, New Zealand initially was dealt a heavy blow by being the first southern hemisphere country to detect cases on the 25th April 2009 in travellers, and it later experienced a peak of disease activity between June and August 2009 (Jennings, 2013). This timing corresponded to the winter season and it was known that in the 1918-19 pandemic influenza, the first wave arrived in New Zealand's winter and was followed quickly by a very severe second wave in the spring. Due to these early cases at the end of April 2009 and the unavailability of a developed vaccine, New Zealand focused on other public health measures, using their island nation remoteness to their advantage. Located a four-hour flight from south-east Australia and with huge distances from other countries, New Zealand implemented strong airport screening, isolation of suspected cases and antiviral measures. Some interviewees had explained that it was possible that ILI may have become apparent in travellers during the course of flights and so flight crew and airport staffs were vigilant during the first six weeks.

The small supply of monovalent pandemic influenza vaccines in New Zealand became available to healthcare workers in February 2010, although these vaccines had arrived into the country in late 2009. The monovalent vaccines were quickly supplanted by the seasonal trivalent vaccine incorporating A(H1N1). This vaccine event meant that New Zealand almost had the opportunity to sidestep the monovalent pandemic vaccine controversy reported by the northern hemisphere

countries, through rolling out the seasonal influenza vaccine that included A(H1N1). For the next pandemic influenza, if it is compatible with disease emergence and vaccine procurement, problems associated with a one-off mass vaccination programme will be avoided if the novel circulating strain of influenza can be included in the seasonal trivalent vaccine such as the New Zealand experience, as long as the pandemic target groups correspond to seasonal influenza groups. For instance, in the UK the pandemic influenza vaccine strategy prioritised children (Hine, 2010) but at that time, children were not targeted in seasonal influenza vaccination campaigns. However, developments since the 2009-10 influenza A(H1N1) pandemic in the UK have seen the introduction of seasonal influenza vaccination campaigns in childhood from 2013 (Department of Health, 2013) which would normalise influenza vaccination in this population group.

It is likely this hemisphere divide in vaccine response as demonstrated in the 2009-10 influenza A(H1N1) pandemic will perpetuate in future pandemics if disease activity corresponds to peaks in autumn and winter seasons (as typical in temperate countries seasonal influenza patterns) and the months required for vaccine development and production stay the same.

It is interesting to speculate the potential impact of pandemic influenza vaccines in New Zealand, had the vaccines been available within 6 months, such as in Sweden. New Zealand's first wave of 2009-10 influenza A(H1N1) pandemic occurred between April and December 2009, with a peak between June and August, then cases plummeted in early 2010 until the second wave of influenza activity between July and October

2010, with a peak in August 2010 of about two-thirds the amount of the first wave peak. The second wave corresponded to annual seasonal influenza trends in New Zealand (Bandaranayake, 2011).

The vaccination campaign in Sweden commenced in mid-October 2009 using the monovalent A(H1N1) vaccine and had dwindled by February 2010. When considered beside Sweden's first wave of disease activity it can be noted that the timing corresponded loosely with the first wave of disease activity, which peaked in November. Approximately 50% of the population had received one dose of the vaccine by December 2009, with rates far greater in medical risk groups (Örtqvist et al. 2011; Socialstyrelsen, 2011). Sweden did not go on to have another wave.

Countries located in the northern hemisphere typically opted for the monovalent A(H1N1) vaccine thus missing the trivalent influenza vaccine that year but New Zealand, similarly to other southern hemisphere countries had a choice: use the monovalent A(H1N1) vaccine; use the 2010 trivalent influenza vaccine including A(H1N1); use the monovalent A(H1N1) vaccine followed by a trivalent influenza vaccine. New Zealand had a forward purchasing agreement for pandemic vaccines and this provided the seasonal trivalent influenza vaccine including A(H1N1) between April and September 2010. During the pandemic, New Zealand made another agreement whereby 300,000 doses of non-adjuvanted monovalent A(H1N1) vaccine (Celvapan® H1N1) were secured for healthcare workers. This was received at the end of 2009 but not released for use until February 2010 (Bandaranayake, 2011; Jennings, 2013).

If New Zealand had been able to provide the monovalent A(H1N1) vaccine to the wider population, had commenced a vaccination campaign at the start of 2010, where cases reportedly had fallen to zero after the first wave of disease activity, and had been able to share a similar uptake rate achieved in Sweden, then could have a second wave have been avoided? It was reported that between January and October 2010, New Zealand reported 1,768 confirmed cases of A(H1N1) influenza, of which 732 were hospitalised and 15 died (Bandaranayake, 2011). As reported earlier, the timing of New Zealand's second wave did not occur until July 2010; with the benefit of hindsight, this gave several months whereby a monovalent A(H1N1) vaccine was developed and available for purchase. New Zealand, reported an uptake rate of about 24% of the population immunised against A(H1N1) influenza in 2010 (Bandaranayake, 2011), had New Zealand been able to achieve higher rates of immunisation and an earlier monovalent A(H1N1) vaccine campaign, how many of the 2010 influenza cases may have been evaded? Borse et al. (2013) have modelled that a vaccination campaign in the United States during 2009 could have prevented 4.2 million cases if it had commenced 8 weeks earlier. The timing of vaccination campaigns is a significant subject covered in more detail later in this chapter.

The benefit of New Zealand's vaccination approach meant that they could implement a typical seasonal influenza vaccination campaign, that would provide protection to those immunised against the circulating A(H1N1) virus and could be rolled out as per a typical seasonal influenza campaign. The 2010 trivalent influenza vaccine including A(H1N1) rolled out as a

seasonal influenza campaign both would have benefited the healthcare sector in terms of staff working conditions and the use of resources, but it may have helped reduce the perception of risk to the public in a pandemic influenza scenario. Framing the vaccination within the typical public health measure of annual influenza vaccination may have helped avoid the subject of adjuvant in the monovalent A(H1N1) vaccine and sidestep the associated perception of risk and, therefore, increase the acceptance the vaccine.

6.1.3 Legacy of 1918 pandemic influenza

The 1918 pandemic influenza was referenced in both planning documents and interviews and has provided knowledge on the devastating potential impact of pandemic influenza. Although just shy of a century ago the 1918 pandemic influenza weighed heavily on key pandemic influenza response personnel and one learning outcome from that pandemic influenza was that the second wave was characterised as being much more severe than the first. This was referenced by some country participants and supported the need to provide appropriate public health measures should history repeat itself with a severe second wave of disease activity. Even though some participants referenced evidence at the time indicating that the 2009-10 influenza A(H1N1) pandemic first weeks were mild, and that the belief that the second wave would likely be equally mild, the uncertainty provided by prior historical pandemic influenza events and the inability to provide guarantees about future disease activity during

pandemic influenza, meant that countries provided large quantities of pandemic influenza vaccine to their citizens.

What was interesting were the missing references to the 1957 and 1968 influenza pandemics, which although were less severe than the 1918 influenza, would have been lived experiences by some of the interviewees. Instead, knowledge of the 2003 SARS high rates of fatality and quick transmission to many countries and the threat posed by avian influenza virus A(H5N1) as a potential future influenza pandemic were presented.

6.1.4 Aboriginal populations

In past influenza pandemics, and indeed, the pattern occurred again in the 2009-10 influenza A(H1N1) pandemic, aboriginal populations were disproportionately affected by novel influenza in terms of increased severity of influenza illness and increased deaths. Rice (2005) reported that: "*By far the most striking feature of the 1918 influenza pandemic in New Zealand is the massive difference between European and Maori death rates. Maori were seven times more likely than Europeans to die from the flu.*" (2005: p.159). This death rate imbalance is all the more emphasised by the statement of Pool (1973) that: "*The influenza pandemic of 1918-19 was the most important outbreak of disease from any cause in 20th-century New Zealand.*" (1973: p.274). Likewise, reports from the United States (Groom et al., 2009) and Australia of (Massey et al., 2009) found that aboriginal populations were severely affected by the 1918-19 influenza pandemic in

comparison to other population groups and city dwellers. Similarly, the First Nations and Inuit populations in Canada fared badly in the 1918-19 pandemic influenza with reports of the death rate to be over five times higher than the Canadian national average (Humphreys, 2009).

This historical evidence of how aboriginal populations were disproportionately affected in past influenza pandemics may have perhaps contributed to Canada's and New Zealand's sensitivity to this equality issue. New Zealand prioritised the influenza vaccine and provided it to specific groups at no cost; this included Maori and Pacific Island persons living in New Zealand. Canada did not prioritise the pandemic influenza vaccine to First Nation and Inuit populations but indirectly prioritised the majority of these persons by prioritising "*individuals living in rural and remote settings*" (Standing Senate Social Affairs Science and Technology, 2010: p.34). Interviewees in Canada explained that one of the first areas to receive batches of pandemic influenza vaccines were the northern territories in Canada. This was challenging for key pandemic influenza response personnel as the working circumstances involved mobilisation in severe weather conditions, remote locations (at times no running water or alcohol sanitizer allowed on the premise) and lone nurse practitioners working at medical stations.

Overall, pandemic influenza vaccination uptake rates in Canada were reported to be highest amongst the aboriginal populations. However, this vaccination campaign to target this specific group first, in what could be described as positive discrimination to perhaps to avoid a repeat of historical inequality, almost failed at the beginning. Canadian

interviewees explained that a great deal of resources were invested in promoting the safeness of the pandemic vaccine to aboriginal populations and an area of work focused on alleviating vaccine fears: *"Because that was another perception, since aboriginal groups were prioritised to have the first allocation of vaccine, that was at times perceived as oh yeah, sure, you're going to give it to us first before you give it to the white people, because if it hurts us then you won't give it to the white people, so."* (CA3b). By focusing on aboriginal persons in order to avoid a repeat of pandemic influenza history, and by following current released information that First Nation people with A(H1N1) were three times more likely to be hospitalised and admitted to ICU than non-aboriginal persons, it is understandable that key pandemic influenza response personnel would attempt to provide the pandemic influenza vaccine as a priority to aboriginal groups.

On the other hand, the fear from a minority group of having medicine first from the perspective of being 'guinea-pigs' before the wider population, has roots in the history of medicine. One well-known example is the Tuskegee Study, which recruited only black men for trials of syphilis treatment in the United States with devastating ethical standards. The study began in 1932 and continued for 40 years. Not only did the study fail to allow these men to cease participating in the trial nor provide informed consent, but the major controversy was also that once the treatment of penicillin became known and available to treat syphilis the recruited men were not given access to the drug (CDC, 2016). Based on the history of

medicine, the caution shown by ethnic groups for new medicines is understandable.

Ethnicity studies examining aspects of infection rates, hospitalisation and mortality outcomes during the 2009-10 influenza A(H1N1) pandemic have demonstrated useful findings in this field. A study in the UK by Nyland et al. (2015) examined patient medical records, using the ethnicity classifications of white and non-white, and found that although treatment differences were noted (prescription of antibiotics and antiviral drugs), there were no notable differences in terms of admissions, severity of disease at point of admission and clinical outcomes between population groups. However, in contrast, Canadian First Nations and Aboriginal communities did experience a greater burden of disease during the 2009-10 influenza A(H1N1) pandemic: *"A(H1N1) 2009 was associated with a 3- to 8-fold elevated risk of hospitalization and death in Canadian Aboriginal populations (including FN). Similar findings were reported for indigenous populations of the United States, Australia, New Zealand and other parts of Oceania."* (Boggild et al., 2011: p.347). Knowledge of the burden of disease during the 2009-10 influenza A(H1N1) pandemic provides context and understanding for the priority of vaccination by key pandemic influenza response personnel in Canada.

As noted by Nyland et al., (2015) the difference between the UK and Canada is that the minority ethnic population group in the UK is non-indigenous and the result of immigration over more recent decades, whereas the minority ethnic population group of First Nation and Aboriginal communities in Canada are indigenous. Research on ethnic disparities has considered

features such as biological factors and social determinants of health.

New Zealand reported higher healthcare utilisation rates for population groups of Maori and Pacific Islanders. The study in the Wellington region by Verrall et al. (2010) found that *"Pacific Islanders and Maori were 7 to 5 times more likely, respectively, than NZ Europeans to require hospital admission. These findings are consistent with observations from previous influenza epidemics. During the 1918 pandemic, the death rate was 7-fold higher in Maori than in NZ Europeans"* (Verrall et al., 2010: p.101). Ethnic disparities in the United States during the 2009-10 influenza A(H1N1) pandemic were reported by Dee et al., (2011) where it was found that Hispanics and Blacks had increased rate of hospitalisation and Hispanics and Asians/Pacific Islanders had higher rates of child mortality in comparison to White population groups. Dee et al., found that the vaccination uptake rate for Hispanics and Blacks were lower than Whites and that promotion of vaccination against influenza was important, specifically in underrepresented population groups, and would likely contribute to lower burden of disease and ethnic disparities.

6.1.5 Setting vaccination priorities

Seasonal influenza morbidity and mortality is associated with infants, pregnant women, the elderly and persons with co-morbidities (Van-Tam and Sellwood, 2013). Typically, the population groups targeted for vaccination during seasonal influenza comprise populations at risk of severe outcomes and

death: young children, pregnant women, persons aged 65 years and older, persons with chronic conditions (Carrasco and Leroux-Roels, 2013). All five study countries provide seasonal influenza vaccines to population groups by varying degrees.

During pandemic influenza, morbidity and mortality groups may not necessarily correspond to typical seasonal influenza patterns, e.g. elderly persons are a reduced risk group. Therefore, the aims of pandemic influenza vaccination campaign may differ to normal and include *"reducing mortality and morbidity, limiting societal disruption, ensuring maintenance of healthcare systems, ensuring the integrity of critical national infrastructures and limiting economic losses"* (Carrasco and Leroux-Roels, 2013: p. 146). Some countries may have focused on those most at risk of severe outcomes (e.g. pregnant women), those at risk of infection due to work (e.g. healthcare workers), or highly likely influenza carriers and transmitters (e.g. young children). Several priorities are possible during pandemic influenza and all are equally valid. The WHO provided a vaccination priority order during the 2009-10 influenza A(H1N1) pandemic: healthcare workers; pregnant women; persons with specified chronic medical conditions; healthy young adults; etc.

When interviewees explained their country specific prioritisation of the pandemic vaccines, it typically centred on the pandemic influenza risk groups. Interestingly, Singaporean key pandemic influenza response personnel raised the issue of whether the focus should be on identifying those that need the vaccine, not necessarily simply vaccinating all persons in risk groups. This would require knowing who has already seroconverted by the time the pandemic vaccine arrives. In

effect, vaccinating all risk group persons is a waste of doses if they have already been exposed and seroconverted, and therefore, scarce doses would be underutilised in a public health emergency. Thus, prioritisation is about both targeting the right risk groups and targeting those still susceptible (not already infected and recovered) when the vaccine is eventually available for country vaccination programmes.

To add weight to this argument of identifying those who are still susceptible, an interesting article originating from Singapore examined the seroconversion in military persons and this highlighted the incidences of persons who displayed symptoms of influenza and those with asymptomatic infections (Lee et al., 2010). In this article, the aim was to identify whom to target with antivirals and the effectiveness of treatment, but this research highlights the usefulness of identifying who is susceptible to infection and who has seroconverted.

The UK can be used as an example (as one of the so many countries) from the 2009-10 influenza A(H1N1) pandemic in which children aged 3 to 16 years old were identified as most at risk of infection, and prioritised for pandemic influenza vaccination (Hine, 2010). Given that "*data strongly suggest that children act as sentinels for influenza activity within communities and play a major role in propagating transmission in households and communities*" (Van-Tam and Sellwood, 2013: p.4). This highlights the need to examine the appropriateness of targeting pandemic vaccines in this group. Assuming that the pandemic influenza vaccines arrive several months after novel influenza emerges and that children may be the first group to be infected, should not knowledge from a

representative sample be a requirement to determine seroconversion and disease susceptibility in order to best use pandemic vaccines and avoid wasting resources? Canada mentioned the movement away from targeting the vaccination of transmitters (e.g. children) to vaccinating those most likely to require hospital care and those at risk of dying because the vaccine arrived after the wave of disease activity.

6.1.6 Side effects

Pregnant women have long been recommended to avoid drugs in pregnancy, including vaccines, and care of pregnant women has moved away from doctor-led medicalisation of pregnancy care towards a non-illness approach led by midwives where possible. Before 2009, CDC authors reported that pregnant women in the United States should receive a trivalent inactivated influenza vaccine against seasonal influenza. However, the uptake rate was reportedly low, with approximations that pregnant women and healthcare providers were hesitant about the safety of vaccine use during pregnancy. The live influenza vaccine was not approved for pregnant women due to concerns about risks of adverse foetal outcomes (Rasmussen, Jamieson and Bresee, 2008).

The 2009-10 influenza A(H1N1) pandemic was associated with a rapid change of policy in many countries in relation to influenza vaccine use for pregnant women. Pregnant women were recognised as a high-risk group for adverse outcomes from 2009-10 influenza A(H1N1) pandemic infection (WHO, 2009). In the UK, the Joint Committee on Vaccination and

Immunisation (JCVI) recommended for the first time that pregnant women should receive the influenza vaccination and be prioritised. The UK differed from other countries by using a vaccine containing an adjuvant (AS03) for pregnant women. The reason behind this was based on the speed of protection against A(H1N1) and that pregnant women were at increased risk of severe disease outcomes (CMO, 2009).

The 2009-10 influenza A(H1N1) pandemic vaccination policy in the UK was led by doctors wishing to vaccinate pregnant women against A(H1N1) rapidly which went against the grain of the culture of midwives providing care and advice. The UK now offers pregnant women with seasonal influenza vaccination with a reported uptake of 44% in 2014/15 (Department of Health, 2015). Through working with midwives and normalising influenza vaccination in the pregnant women population group, future influenza pandemic vaccination efforts will likely be improved.

Interestingly, Canada and Japan were concerned about the use of adjuvant pandemic influenza vaccines. The explanation for the concern covered the lack of evidence for the safe use of adjuvant vaccines in pregnant women and babies and the possible side effects of the adjuvant on pregnant women and babies. The worry by scientists, physicians and decision makers and the expressed inability to provide assurances to the public about the safety of adjuvant use in this group led both countries to order a specific batch of adjuvant-free pandemic influenza vaccine to provide to pregnant women. Participants from Japan explained that this process was followed even at significant resource cost in the 2009-10 influenza A(H1N1) pandemic. For instance, the adjuvant-free

vaccine required more antigen component in the vaccine. Therefore, the cost was rationalised by one Japanese participant as one vial containing adjuvant would provide 18 doses but one adjuvant free vial would only provide a single dose. As demonstrated, this special measure for pregnant women and babies was resource intensive but not a decision taken lightly by decision makers in these countries. At the time it was considered necessary in Japan and Canada but had the pandemic influenza been more virulent and associated with a larger burden of disease outcomes, it raises the question of whether the use of scarce resources, such as an antigen, is justified.

In contrast to the decision-making in Canada and Japan about securing adjuvant free pandemic influenza vaccine for pregnant women during the 2009-10 influenza A(H1N1) pandemic, the UK specifically chose a vaccine containing adjuvant for UK pregnant women. The UK position in 2009 was to prioritise Pandemrix® (AS03 adjuvant) for pregnant women because early on, pregnant women were at high risk of severe morbidities and mortality. The UK prioritised pregnant women in their pandemic influenza vaccination campaign and received pharmaceutical support on the 1st October 2009: "*The four health ministers heard that the GlaxoSmithKline vaccine had been licensed for those over six months and for pregnant women.*" (Hine, 2010: p.36). Despite the UK efforts to prioritise pregnant women for vaccination and the identification of pregnant women as a high-risk group during the pandemic influenza, the UK did experience a number of deaths in pregnant women as well as those that required intensive hospital care. As highlighted in the opening

of the UK review report concerning the general mild nature of the 2009-10 influenza A(H1N1) pandemic compared to the avian flu as discussed in earlier planning documents: "*Despite this, the relatively few deaths that occurred, including those of otherwise healthy children and pregnant women, were particularly tragic and poignant.*" (Hine, 2010: p.f1). However, it remains unknown whether the deaths of UK pregnant women were due to inadequacies with the vaccine. For instance, were these deaths of pregnant women in those that had refused the vaccine? Or did these women contract influenza before the vaccine was rolled out in late October 2009? These questions were highlighted in research by Dolan et al. (2012) where it was reported that there had been a poor recording of vaccination status in UK pregnant women in the study of 2009-10 influenza A(H1N1) pandemic hospitalisations.

The concerns regarding the use of pandemic vaccines with an adjuvant component in pregnant women and babies were not the only side effect discussed in relation to the pandemic influenza vaccine. After Sweden had completed their vaccination campaign, narcolepsy events reported from the summer of 2010 onwards began to emerge in Sweden and Finland, and this dominated parts of the interviews conducted in Sweden. The research on narcolepsy associated with the use of AS03 adjuvanted pandemic A(H1N1) vaccine appears complicated, conflicting and inconclusive at this point in time. For instance, Partinen et al., (2012) concluded that "*...it likely that Pandemrix vaccination contributed, perhaps together with other environmental factors, to this increase in genetically susceptible children.*" (2012: p.1), and Szakács, Darin and

Hallböök (2013) reported that *"Pandemrix vaccination is a precipitating factor for narcolepsy [...]. The incidence of narcolepsy was 25 times higher after the vaccination compared with the time period before. The children in the postvaccination group had a lower age at onset and a more sudden onset than that generally seen."* (2013: p.1315). However, other research has not found the same conclusions. For instance, Persson et al., (2014) reported that their research *"...could neither confirm any causal association with Pandemrix nor refute entirely a small excess risk. We confirmed an increased risk for a diagnosis of narcolepsy in individuals ≤ 20 years of age and observed a trend towards an increased risk also amongst young adults between 21 and 30 years."* (2014: p.172).

Studies of narcolepsy incorporating other countries have found that *"[a]n increase in narcolepsy diagnoses was not observed in other countries, where vaccination coverage was low in the affected age group, or did not follow influenza A(H1N1)pdm09 vaccination."* (Wijnans et al., 2013: p.1246). Indeed, Sweden had one of the highest vaccination coverage rates. Countries such as Canada also used Pandemrix® but did not report heightened cases of narcolepsy. However, the vaccines used in Canada were manufactured in North America in comparison to the European produced vaccines used in Sweden. This had led to the allegation that this problem was factory-specific even though provided by the same manufacturer, GlaxoSmithKline, who were producing the same product (licenced name of Pandemrix®/Arepanrix®). In truth, there are some minor differences in the manufacturing processes.

Although the research into these narcolepsy events appears challenging and the findings are conflicting, it is no doubt a critical area for key pandemic influenza response personnel and pandemic influenza researchers to examine and understand at this time and apply lessons learnt to future pandemic influenza response.

The side effect concerns discussed in this subsection, as well as communications in general, all relate to health risk communications in an influenza pandemic event. The WHO has released guidance on risk communications, one document of which is the Pandemic Influenza Preparedness (PIP) Risk Communication. The PIP Risk Communication guidance is a key document emphasising that strong risk communication is developed before a pandemic emerges. This includes specially trained risk communication professionals who can work the duration a pandemic response, engaging and listening to local concerns, use of appropriate communication channels, effective and correct public health messaging, trialling risk communication in a pandemic influenza scenario exercise and coordinated communications between relevant agencies, industry and the public. Therefore, countries that experienced challenges during the 2009-10 influenza A(H1N1) pandemic will now need to review the appropriateness of risk communications used and implement any possible improvements in order to strengthen risk communication in the future.

6.1.7 Disease activity timing and vaccine arrival timing; perceived effectiveness

A theme that emerged from the interview data was the desire to implement the pandemic influenza vaccination campaigns quickly and before significant disease activity. However, the disease activity frequently occurred before the arrival of the vaccine. Japan, Canada, New Zealand and Singapore received the pandemic vaccine post-first wave peak of influenza disease activity, leaving just the study country Sweden as an exception.

Sweden's influenza disease activity remained very low during the summer months and the vaccination campaign was implemented alongside the increase in disease activity; campaign staff achieved high uptake rates and no subsequent waves. The vaccination campaign in Sweden was their major public health measure in response to the 2009-10 influenza A(H1N1) pandemic in comparison to the other study countries which utilised other public health measures to varying degrees.

All countries, except Sweden, experienced an influenza activity peak before the arrival of the vaccines. Canada and Sweden received monovalent influenza vaccines from October 2009, Japan imported monovalent vaccines from October 2009, with the domestic supply circulating in early 2010. Singapore had the vaccine from November 2009 and New Zealand had a limited number of monovalent vaccine doses for healthcare workers from February 2010 with the bulk of the vaccination campaign rolled into the trivalent influenza vaccine from April 2010.

The study countries experience in 2009-10 suggests that a well-timed proactive vaccination campaign associated with high uptake rates and before major disease activity may avert subsequent cases and waves of disease activity. The importance of vaccine implementation timing has been demonstrated by Borse et al. (2013).

Borse et al. (2013) modelled the timing of vaccination and the timing of the arrival of 2009-10 influenza A(H1N1) pandemic. The article outlines that the United States vaccination programme from October 2009, calculated with incorporating pandemic influenza data, is estimated to have "*prevented 700,000–1,500,000 clinical cases, 4,000–10,000 hospitalizations, and 200–500 deaths*" (2013: p.439) over six months until April 2010. The authors explained that this prevention of public health burden of disease concerning the 2009-10 influenza A(H1N1) pandemic was due to the timing of the vaccination campaign and also vaccine effectiveness. More importantly, Borse et al. highlighted that if the vaccine had arrived and commenced two weeks earlier, then 2 million cases would have been averted; eight weeks quicker would have prevented 4.2 million cases in the United States.

The northern hemisphere study countries received a supply of influenza vaccines at a similar time of year to the seasonal influenza vaccination campaign. For instance, Canada normally received influenza vaccines from mid-September but in 2009 received vaccines slightly later in October. New Zealand in the southern hemisphere also coincided the vaccination campaign with their autumn which appears more intentional timing than that of the northern hemisphere vaccination campaign timings. However, it was noted that the small batch of

A(H1N1) vaccine did arrive in late 2009 and was released for use in February 2010. Therefore, using the argument presented by Borse et al. (2013), many clinical cases of A(H1N1) infection would have been avoidable if New Zealand had commenced a monovalent vaccination campaign rather than waiting for the seasonal influenza trivalent vaccine campaign in April 2010. The complicated aspects of pandemic influenza response were highlighted by interviewees and the usefulness of incorporating the A(H1N1) vaccine into the seasonal trivalent vaccine may have helped with the public acceptance of immunisation and increased the effectiveness of the vaccines during the pandemic influenza response.

The interviewee language surrounding the disease activity and vaccination timing was polarised. It showed a distinction between the period of waiting for the vaccines to arrive and influenza rapid increases and peaks and the period of plentiful supply of vaccines and the subsidence of disease activity. This concept is illustrated in Figure 28.

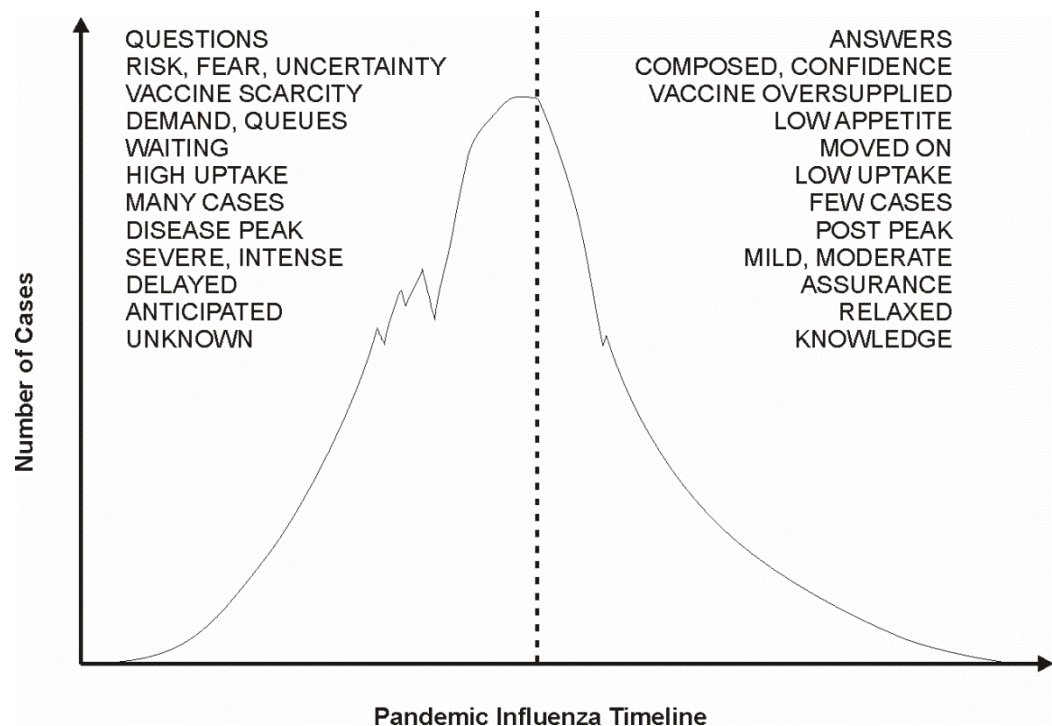


Figure 28: Change in language of participants pre- and post-vaccine arrival

The research covered the key pandemic influenza response personnel opinions on the topic of the effectiveness of the pandemic influenza vaccination. The intention was to review the public health effectiveness of the national vaccination campaigns, for instance, if a country utilised 10 million doses of pandemic influenza vaccines, how many cases, hospitalisations or deaths, may have been averted? What was the impression of the impact on the disease activity? However, upon reflection, this approach is subject to a huge amount of complexity, and the possibility for alternative interpretations by interviewees exists. For instance, from a non-public health and population perspective, key pandemic influenza response personnel with a background such as clinicians, may have first considered the vaccine effectiveness. It was found that on

average the pandemic influenza vaccine provided 90% protection against A(H1N1). Obviously, this distinction was important because, on the one hand, the vaccine may have been highly effective but on the other, the public health vaccine effectiveness may have been very ineffective.

The effectiveness of the pandemic influenza vaccine providing individuals with protection against A(H1N1) was discussed briefly by only a couple of interviewees in Japan: "*In Japan the pandemic vaccine effectiveness was 70%, that was very high*" (JA5). In this instance, the interviewee went on to refer to the study by Yamada et al. (2012) which conducted research in the Hokkaido area of Japan where pregnant women were vaccinated against pandemic influenza A(H1N1) on average two to three months earlier than Japan as a whole. "*More than 60% of pregnant women reported having been vaccinated within 1.5 months after the availability of a vaccine for pandemic (H1N1) 2009, and vaccination effectively reduced infection in this study; if a vaccine had not been available, the expected number of pregnant patients would have been 152 (2.08% of 7328), and if all women were vaccinated, the expected number of pregnant patients would have been 16 (0.224% of 7328). Thus, vaccination reduced the infection rate by 89%.*" (Yamada et al., 2012: p.135)

More commonly referenced by all the study countries was that initially it was believed that two doses would be required for protection but as the pandemic influenza evolved it was found that one dose would suffice. This change during vaccination campaigns caused difficulties for some countries to track how many doses individuals had received and thus the individual level of protection against A(H1N1).

The perceived effectiveness of vaccines during the 2009-10 influenza A(H1N1) pandemic response was grouped into factors including vaccination timing, uptake rates, subsequent disease activity and execution of vaccination campaigns.

With regards to the vaccination campaign timing and the impact of the vaccines on the disease activity, there was often a shared international uncertainty between the interviewees of the impact of the vaccines. Respondents explained how trying to determine what would have naturally occurred in disease activity should no action have been taken is a common public health issue.

There was discordance in the Swedish responses about the impact of the timing of the vaccination campaign on disease activity as there was not an assured answer to give; vaccines may have decreased the duration of the epidemic curve. Similarly, the Canadian responses reflected that the vaccination campaign may have reduced the epidemic curve quicker than what would have played out in due course without public health strategies. Nonetheless, answers were not committed to vaccines as being responsible. The Canadian vaccination campaign was rolled out as the influenza disease was peaking, whereas both the Singaporean and Japanese vaccination campaigns were implemented post-disease wave, so it was felt that the vaccines would not be used to prevent an epidemic. Both Canada and Sweden referenced that no subsequent disease activity waves were experienced after their vaccination campaigns and put forward that vaccines could have played a role or it may have been the result of another factor such as seroconversion.

Responses from some interviewees in Canada and Japan stated that by the time of the vaccination campaigns, some individuals would have been exposed to the disease already and developed immunity. This could have affected the success of vaccination uptake rates if the disease activity was earlier than implemented vaccination campaigns. The New Zealand vaccination campaign timing was an anomaly in the comparison of study countries because the monovalent vaccine was sparsely used from February 2010 and then the trivalent seasonal influenza vaccination campaign incorporating A(H1N1) was rolled out as usual in April.

In Sweden and Canada, interviewees reported high uptake rates of the vaccine and pride in the campaign achievements, whereas the atmosphere was different in the other countries regarding vaccination. In Singapore, there was the belief that the vaccination uptake rate was not high enough for substantial impact upon an epidemic. Both Japan and New Zealand explained there was the sense of wait and demand for vaccines but by the time of the vaccination campaign commenced in each country the 2009-10 influenza A(H1N1) pandemic knowledge base detailed that it was not a severe pandemic as seen in history and there was no vaccine scarcity. It was felt that these factors contributed to lower than anticipated uptake rates.

A few points were raised in terms of the execution of the vaccination campaigns. Interviewees across the countries spoke of the challenges of the prioritisation of the pandemic influenza vaccine in the first weeks of vaccination campaigns; this problem was shared in countries that ordered enough doses for the entire population. For instance, prioritisation was

often not well defined prior 2009 and calculations for specific populations (e.g. number of critical infrastructure personnel) were difficult and time-consuming during the 2009-10 influenza A(H1N1) pandemic. Countries such as Japan have invested resources in defining and calculating priority groups during this interpandemic period as a preparedness measure and after lessons learnt in 2009.

A small handful of participants from Sweden and Singapore questioned the defined priority groups for vaccination in the early weeks, as mentioned in an earlier section. Vaccinating risk groups such as those with chronic respiratory diseases was a measure to avoid severe morbidity and mortality outcomes from the 2009-10 influenza A(H1N1) pandemic infection. However a few interviewees said that was an acceptable measure if that was a country's aim during the pandemic influenza response, but if the ambition was to reduce the transmission of influenza as quickly as possible, then children and young adults should have been prioritised first. Vaccine prioritisation is a valid area of discussion and will no doubt be a future issue in the next pandemic influenza if vaccines are released in limited batches as and when they are produced. This topic will no doubt require significant resources during a pandemic influenza if a consensus is not reached in an interpandemic period and differing views examined. United States researchers Lee et al. (2010) conducted a vaccine prioritisation computer modelling simulation after the 2009-10 influenza A(H1N1) pandemic in order to provide evidence for decision makers for vaccine prioritisation. It was reported that *"defined at-risk populations, rather than just the high transmitters (i.e. children), may result in slightly more*

influenza cases but less overall morbidity and mortality, which corresponds to lower overall costs. [...] While prioritizing children rather than using the ACIP recommendations may reduce the overall attack rate, it also will result in more hospitalizations and cost to third party payers and society.” (Lee et al., 2010: p.4878).

Canada achieved vaccine uptake rates of approximately 90% in specific populations such as First Nations and aboriginal persons. In Sweden, responses about vaccination campaign achievements were frequently replaced by the reports of narcolepsy in children and young people. As one interviewee stated: *“we got 200 young people with narcolepsy, but of course, with that we couldn’t know from the beginning of course, but of course when we evaluating it retrospectively we saved rather few lives, most of those lives were people with diseases, but realistically those saved lives, you could say those who died were mainly people with underlying conditions, so you must also, you shouldn’t just count saved lives, you should also count the saved years, Years Lives Lost and so on. To me, no one has done this calculation, but in my opinion, it’s rather clear that 200 young people, who have a long time to live, with probably chronic, as we know today, they will have this disease for the rest of their lives, in comparison with 50-100 saved lives probably elderly people.”* (SW4)

The point raised by this interviewee is noteworthy in terms of evaluations conducted post-pandemic influenza response. After the 2009-10 influenza A(H1N1) pandemic, the following formal reviews have been published:

- New Zealand: "Report for the Minister of Health from the Pandemic Influenza Mortality and Morbidity Review Group" (Perinatal and Maternal Mortality Review Committee, 2010)
- Canada: "Canada's Response to the 2009 H1N1 Influenza Pandemic" (Standing Senate Social Affairs Science and Technology, 2010)
- Sweden: "A(H1N1) 2009: An evaluation of Sweden's preparations for and management of the pandemic" (Socialstyrelsen, 2011)

Published reviews by Ministry of Health officials in journal article format:

- Japan: "Japan's Actions to Combat Pandemic Influenza (A/H1N1)" (Shobayashi, T. 2011, review by the former Ministry of Health director for the Pandemic Influenza Preparedness and Response Office)
- Singapore: "Influenza A (H1N1-2009) pandemic in Singapore – public health control measures implemented and lessons learnt" (Tay, J., et al. 2010, review by the Ministry of Health Communicable Diseases Division)

These national evaluations have enabled a greater understanding of national pandemic influenza responses in each study country. In particular, the evaluations from Sweden and Canada were very detailed, recording the stages of pandemic influenza, highlighting the successes and challenges. Comparing the country evaluations was difficult because different end dates were applied in reference to the number of cases, hospitalisations and deaths. Also, reporting

significant events is equally important to reporting times of inactivity.

Fortunately, the momentum for pandemic influenza preparedness has continued for many countries beyond the response and evaluations relating to the 2009-10 influenza A(H1N1) pandemic. In recent years there has been the continued international threat of infectious disease outbreaks, such as recent cases of Ebola (from 2014), which has supported the need for national preparedness. Some of the study countries have published new versions of pandemic influenza preparedness plans:

- Singapore: MOH Pandemic Readiness and Response Plan for Influenza and other Acute Respiratory Diseases (2014)
- Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector (some updates, post 2010, have been made to the online subsections to incorporate evidence from the latest pandemic influenza response)
- Sweden: Planering för beredskap mot pandemisk influensa (2015, content in Swedish)
- New Zealand Influenza Pandemic Plan: A Framework for Action 2010 (some updates to the related policies and guidance post 2010)
- Pandemic Influenza Preparedness Action Plan of the Japanese Government was published in 2007 and no post 2010 plans were found in English.

6.2 Evaluation issues and study limitations

The execution of research in several study countries and during a one week stay was a logistical challenge. Understanding the organisational structure was necessary in order to interview the relevant participants in each country. However, the organisational structure of pandemic influenza response varied among the study countries. Country documents and key contacts, in particular, helped with this challenge. By the time this research was conducted, some of the pandemic influenza committees had dissolved, so it involved more effort to contact key participants.

It was unfortunate that New Zealand became the only study country from the southern hemisphere and that none of the three countries from South America could become involved in this research project. Some countries in the southern hemisphere were particularly affected by the 2009-10 influenza A(H1N1) pandemic, thus the inclusion of a sample of these countries was particularly important in the planning phase. Admittedly, these countries may have had associated method challenges, such as interviews with a translator but this was accepted; representation from a sample of countries across the world was more important than the ease of data collection.

The five study countries were similar by study design which meant that the countries were all high income, so the generalisability of the findings will be limited. Although it would have further complicated the research, on reflection it would have been interesting to have a sample that included middle income countries had resources allowed. The inclusion

of the country Mexico would have allowed for greater discussion of the emerging pandemic influenza. Interviewing personnel in Nigeria would have been enlightening as this was the first country in the African continent to publish a pandemic response plan ahead of 2009. Speaking with participants in countries that relied on vaccine donations most likely would have highlighted contrasts between countries because many donated vaccines did not arrive until 2010, which in many cases, was many months after initial cases were detected. Also, the inclusion of countries with high rates of co-morbidity, such as South Africa, would have framed the priority of pandemic influenza against diseases, such as HIV/AIDs, competing for health resources and presenting the potential greater severity of pandemic influenza impact (Nasidi, 2013). Through broadening the scope of the study by the inclusion of a more diverse group of study countries, a greater divergence of themes may have been presented which no doubt would have associated data analysis challenges. Despite these challenges, it would likely have highlighted the global inequality present in the 2009-10 influenza A(H1N1) pandemic.

After conducting the interviews, the challenge of managing and analysing the interview data was apparent. Transcribing accented audio recordings was time-consuming. Planning had reflected the need to transcribe and review the data before undertaking the following country visit. The first two study countries (Sweden and New Zealand) had, on reflection, been scheduled too close together; future country visits allowed for much more time to examine the data. Analysing the research data was a learning curve: using NVivo in the first instance

generated a lot of codes but without much meaning. It drew attention to the frequency of recurrent words in a quantifiable manner rather than the examination of themes. Using the programme NVivo did not simplify the analysis process rather it was another method to be managed and was used in addition to traditional coding methods: all with their own benefits and limitations.

Tong, Sainsbury and Craig (2007) developed a checklist for reporting qualitative research with reference to in-depth interviews and focus groups: 'consolidated criteria for reporting qualitative research' (COREQ). The three main components of the checklist include: research team and reflexivity; study design; analysis and findings. This 32 item checklist has been useful to the researcher for the inclusion of content in the write up phase of this thesis. The use of the COREQ by researchers reporting qualitative interviews and focus groups is an important resource in producing quality qualitative research that is transparent and allows for the possibility that the study can be duplicated in the future.

This thesis began broad and covered four public health measures at interview but ultimately concentrated on pandemic influenza vaccine use. A great deal of information was collected during the interviews but it was daunting and challenging to handle. With the benefit of hindsight, had pandemic vaccines been the focus at an earlier stage, greater depth regarding vaccine use would have been possible.

This research allows for future work to follow either with the inclusion of the study countries or with another sample selection. The usefulness of using a selection of countries from

a worldwide sample is an important feature, particularly with pandemic influenza response. Future research would allow for the exploration of themes such as the vaccine supply difficulties and the associated decisions made since 2010.

The transferability of these study findings to non-influenza pandemics is also a feature developed from this research. The world wide spread of a novel infectious disease other than influenza would present many of the response considerations of an influenza pandemic. As the study countries found during the 2009-10 influenza A(H1N1) pandemic, it is important to define and quantify population groups in order to determine the number of doses of vaccines to secure from a pharmaceutical company. For instance, who are essential workers and how many people fall into this category? This is time consuming and debatable. Therefore, it is important that these conversations are conducted during an interpandemic period and decisions reached where possible. Undertaking these processes will feed into future pandemic preparedness plans. The concept of ordering vaccines in response to a non-influenza pandemic is based on the assumption that the virus is known and a vaccine can be developed within months as is the case for influenza. Beyond this time period other public health measures will undoubtedly become necessary.

The knowledge and experience of study countries implementing a national vaccination programme in reaction to the 2009-10 influenza A(H1N1) pandemic will be transferable to a non-influenza pandemic scenario in the future. Countries will remember the logistical issues of waiting for small batches of vaccines and the necessitation to prioritise the initial vaccines at the point of release into national vaccination

campaigns. Unfortunately a disease other than influenza will not allow for countries to potentially incorporate a vaccine into an annual programme such as the seasonal influenza trivalent vaccine to lessen perceived apprehension of a new vaccine. However, lessons learnt from risk communications will be important to apply within countries. Also, implementing consistent and similar response methods within and between countries may be more important in future pandemic response so that the perception of fairness and safety is upheld in the public and media viewpoint.

6.3 Summary of vaccine discussion

The vaccine discussion has covered the main research themes and made connections with the existing literature. It has included discussion regarding single or multiple vaccine suppliers, hemisphere differences in vaccination campaigns, and the impact of past influenza pandemics on vaccine use. Vaccination use and priority groups of specific populations were covered, as well as side effect concerns and the perceived effectiveness of vaccines. The following chapter gives the conclusions to the research project and includes recommendations.

7 Conclusions

This qualitative research project has examined the use of vaccines during the 2009-10 influenza A(H1N1) pandemic in five study countries. This pandemic, the first of this century, presented the first major opportunity for the use of influenza vaccines en-masse and countries navigated this emergency event with all of the available knowledge at the time and within the context of their specific national circumstances. Variations in pandemic influenza vaccine use materialised throughout the pandemic, and the interview discussion in this area has been enlightening. In this section, a summary of the key research findings will be provided, and an outline of the implications this research raises for future pandemic preparedness policies will be considered.

The vaccine supply generated considerable problems for public health personnel in organising vaccination campaigns and communicating clear messages to the public. The first delivery of vaccine doses arrived later than anticipated in the countries. This led to the re-release of statements both about the number of doses delivered on particular dates and also dates at which priority groups could access the vaccine; this proved problematic and challenging. Interviewees worried that communicating updates would negatively affect the public opinion about national agencies capabilities to manage a pandemic response. It also went against the desire to communicate clear, consistent public health messages. The 2009-10 influenza A(H1N1) pandemic has provided organisations with an experience of vaccine supply during an

emergency event. In the future, vaccine supply would require greater flexibility in order to react efficiently to vaccine delivery changes at short notice. In addition, an improved knowledge base on how to communicate uncertainty to the public would provide response personnel with greater confidence in navigating this complex area.

The other aspect of the vaccine supply that was an interesting theme covered the single or multiple vaccine supplier routes. Both Japan and Singapore had chosen multiple vaccine suppliers, and this reflected the management of recent risk due to SARS and avian influenza experience. Post 2010, Canada has made mention of a non-domestic backup supplier and it will be interesting to see how many other single supplier countries will follow this path. On the other hand, spreading risk through multiple suppliers may reduce the speed of vaccine delivery. Both Canada and Sweden who had single suppliers received their vaccine supplies quickly compared to Japan and Singapore. It is unknown whether countries that ordered the largest number of doses would receive these first. This is something that would need to be considered when assessing the efficacy of vaccine ordering and supply sourcing in the future.

The timing of deliveries and the equity of worldwide country access was brought into focus during the 2009-10 influenza A(H1N1) pandemic. It is questionable whether or not a national pandemic response can be termed successful if an international strategy involving vaccine supply and delivery is not considered. Increased international cooperation may need to be developed in future pandemics in order to overcome

these challenges, particularly in countries that share multiple borders.

It may be possible to take advantage of the hemisphere divide in pandemic influenza response in the future. If the disease activity and vaccine production timing allowed, it may be possible to roll the pandemic virus strain into the seasonal influenza trivalent vaccine for one hemisphere. This may help nations to avoid the public perception of risk from a new vaccine and it would avoid the topic of a monovalent vaccine containing an adjuvant, which posed issues in some countries. Where seasonal influenza vaccination is commonplace, this may form an acceptable option for governments. Many nations have expanded seasonal influenza immunisation to cover more risk groups which will have covered a lot of groundwork for pandemic preparedness and vaccine use. However, this measure is timing dependent, and would require careful assessment of the timescales involved in order to make this approach effective; delaying vaccination during a pandemic event in order to merge with a seasonal vaccination programme may lead to further case development if it delays a response that may have proved critical.

Past pandemic influenza of 1918-19 played an important point of reference to those working on a national response. Whilst the events of 1918-19 have been remembered, the 1957 and 1968 influenza pandemics have had much less of an impact on current influenza awareness. The knowledge gained from the history of 1918-19 has provided a platform on which to build for response uncertainty and a lasting legacy. Some participants discussed how even though the 2009-10 influenza A(H1N1) pandemic was mild in the general population, and

that even though the first wave of disease activity was already underway, decisions were still made to acquire large quantities of vaccines for the total population. This reflected the fact that during the 1918-19 A(H1N1) Spanish influenza, most first waves that occurred in spring 1918 were followed by much more severe disease activity in the autumn. Reportedly, purchasing large quantities of vaccines appeared incongruent to the public when they had been told the disease was mild. This has resulted in the pandemic influenza response personnel suffering criticism of taking an over-cautious approach in an emergency event and wasting country resources.

The waiting times for vaccine delivery during 2009-10 influenza A(H1N1) pandemic and the earlier than anticipated onset of disease activity may lead future nations to invest more heavily in early response measures, for instance, antiviral drugs. This may appear more of a reactionary response to pandemic influenza personnel but perhaps the public would find immediate measures more appropriate as a real-time response can be realised and it requires less of an appreciation of vaccine procurement.

The history of medicine is damaged by instances where population groups have been treated inequitably and harm has been caused. Some countries well-meaning approach of targeting populations, such as First Nations and Inuit persons, who had severe illness disparity in pandemic influenza outcomes, would normally be seen as a logical public health approach. But it could also be seen as a guinea pig approach to new and untested vaccines. Therefore, the historical scars from medical events require attention during an interpandemic

period. Outside of an emergency event, resources can be allocated to work towards equality of health care access and relationships built with respected community leaders. This is not to say that this work is not continually being conducted, but this research has highlighted the importance of this work and the critical foundation it builds for times of pandemic influenza response.

It will be interesting to see how pandemic influenza vaccine priority groups are established in the future. The position in 2009-10 was to provide vaccine priority to the risk groups: those at risk of severe morbidity and mortality outcomes. For instance, pregnant women, persons with chronic respiratory conditions, pre-school children, etc. Some participants discussed the frustration of providing vaccines to the correct people. A dose given to someone who has already seroconverted would be a wasted dose during a time of scarcity. In the future, having quick seroconversion technologies at the point of vaccination would help to allocate scarce resources. It would also reinforce the distinction within the public regarding who does and does not require vaccination. It is not clear how viable this would be in a future pandemic influenza scenario. If vaccine procurement undergoes radical changes in the future and vaccines can be sourced in the early weeks of a pandemic influenza, those considered highly likely to transmit the disease (e.g. children and teenagers) may first be targeted to stem the spread of infection. At the very least, vaccines can be targeted more efficiently if repeat serological surveys are performed.

The 2009-10 influenza A(H1N1) pandemic experience will have an effect on the future of influenza pandemic policies and

it will also influence other areas of medicine. The recognition that pregnant women were at risk of severe outcomes from pandemic influenza led to a sudden focus on the use of vaccines in this population group. The use of a vaccine containing adjuvant (AS03) was catapulted into the frame for a debate with a deadline. Although polarised country decisions were made regarding the use of vaccines containing an adjuvant, pregnant women now have greater opportunities for vaccine use.

The literature emerging concerning narcolepsy reports in Sweden, and its neighbouring countries, appearing after the use of pandemic vaccine continue long after the subsidence of A(H1N1) cases. The discussion of narcolepsy among the interviewees was unique to Sweden; the other country discussions did, however, discuss the variation of public fear of side effects from new vaccines. In order to have high uptake rates, the risk of pandemic influenza needs to be larger than the considered vaccine risks. There is the concern that pandemic vaccine use will be problematic, particularly in Sweden, in a future pandemic influenza. Again, interpandemic resource investment addressing influenza vaccine use and the possibility of combining a vaccine into a trivalent seasonal influenza vaccine during a pandemic influenza scenario may help navigate this complicated area.

Alongside the importance of communication strategies, the role and influence of the media during a pandemic influenza response cannot be ignored. Poignant cases such as the first country death, particularly in instances of otherwise healthy children, quickly became national news. Public health engagement with the media became common; the success or

failure of implementing vaccination campaigns was not just in the hands of pandemic response personnel. The media became an instrument in the response: in the case of Japan, it enforced social conformism to vaccine priority groups; in other countries, politicians were broadcast receiving the vaccine, possibly in order to allay any public fears over new vaccines.

The effectiveness of vaccination campaigns at the point of implementation was in part out of the hands of pandemic influenza response personnel by this point. The timing of disease activity before vaccination was required to encourage the public to have the vaccine, but if the vaccination campaign was too late, then the need for vaccination was no longer desired by the public and the programme ineffective. As explained in the previous chapter, the early timing of vaccination programmes has been shown to avoid cases, hospitalisations and deaths. In the future, if developments in the field of pharmaceutical techniques enable a quicker supply of vaccines, and if the time taken for the safety approval of vaccines can be improved, then vaccination campaigns can be rolled out earlier and become more effective. However, where the speed of vaccine production and the rollout of vaccination campaigns is not improved, the role of pandemic influenza vaccines in a future scenario is questionable. Some countries, such as New Zealand, could not provide pandemic influenza vaccines until 2010. If a more severe pandemic occurs in the future, the vaccine-use time window would be even more critical.

Pandemic vaccines were the cornerstone of the response in Sweden and Canada, in comparison to Singapore, Japan and New Zealand. The focus on vaccines in Sweden and Canada

was associated with a high reported uptake. However, the interview data not included in this thesis highlighted the strong use of other public health measures, such as antiviral drugs, social isolation and border control in the other three countries. Pandemic vaccine use decisions were all taken in light of the investments in various other measures. Similarities across the study countries include that fact that: they all had pandemic influenza plans in place prior to 2009, all had a vaccine agreement secured with one or more pharmaceutical companies, all prioritised the vaccine in the early campaign weeks and all invested considerable resources in providing their citizens with a vaccine during 2009-10 influenza A(H1N1) pandemic.

The similarity in vaccine use across countries demonstrates the significance of the WHO calls for pandemic influenza planning a decade ago; this was first mentioned in the introduction chapter. The work conducted by international organisations laid the groundwork for many countries pandemic influenza vaccine preparations and the 2009 response. The 2009-10 influenza A(H1N1) pandemic was a mild disease for the general population and countries have demonstrated that their health services coped well in response. In the immediate post-pandemic period, countries were in an opportunistic time that was a critical juncture in policy development (Oliver, 2006). This crucial time after a pandemic influenza is an opportunity for reflecting on the successes and weaknesses of vaccine use during the 2009-10 influenza A(H1N1) pandemic. Now we are in an interpandemic phase, where, if clear evaluations of vaccine use have not been made, then a degree of complacency has set in. If

pandemic influenza policy is less of a priority for politicians, then future pandemic influenza vaccine use may be hampered. Regardless of the time since the 2009-10 influenza A(H1N1) pandemic, there is a very real risk of a future pandemic, such as avian influenza.

7.1 Recommendations for policy makers

There are several recommendations that can be made to policy makers in regards to future pandemic influenza policies as a consequence of this research. Preparedness plans need to be flexible and allow proportionality in response to pandemic severity. Plans that are too specific, such as preparedness tailored to a specific strain of influenza (e.g. Avian influenza), may be too restrictive for effective implementation in the future.

Infrastructure within countries needs to be adequate to cope in peak activity periods. This requires a national influenza surveillance system that can detect and report novel influenza in real-time and laboratories that are capable of confirming cases quickly and operating at high capacity for weeks or months at a time.

This interpandemic phase is a time where preparedness activities should be maintained to ensure that responses in the next pandemic influenza event are proactive rather than reactive. Vaccine related issues that are likely to cause contentions during a pandemic influenza response, such as the prioritisation of vaccines in the initial batches, should be discussed, agreed and prepared as much as possible in

advance. Significant resources can be used during a response concerning groups competing for prioritisation and defining population groups within a nation. The interpandemic period is a time of establishing and maintaining networks and collaborations between all agencies likely to have a role in pandemic influenza response. Pandemic influenza scenario exercises have an important role during this time to allow response personnel to test, evaluate and refine preparedness policies.

Future pandemic vaccine policies need to incorporate a greater international and global dimension. Vaccine purchase agreements have demonstrated that vaccines can be secured by high income countries. National actions are contradictory to the nature of the disease of pandemic influenza. In the future, it is hoped that there is a greater collaboration between countries to pool vaccines and allocate these resources to international populations at high risk of severe illness and mortality. If this co-operative vaccine donation scheme cannot be agreed, donated vaccines need to be incorporated into plans and supplied in a timely manner in order to be of use.

The final recommendation returns to the use of the seasonal trivalent influenza vaccine. Countries should either persist with using this vaccine in annual campaigns or for those countries without it, they should incorporate it into national health protection programmes. This will develop familiarity and trust in a vaccine that will be significant in a future pandemic influenza event.

7.2 Personal Reflections

I feel very fortunate to have been granted the opportunity to study the 2009-10 influenza A(H1N1) pandemic at the University Of Nottingham. This experience has challenged me far more than I could have ever anticipated, but by confronting these difficulties I have grown and developed as a researcher.

Not only have I developed my academic skills further during these last four years, I have also acquired additional welcomed extras; self-confidence in lone travel and meetings with senior experts, life lessons in managing a large project and personal growth in becoming more knowledgeable about other cultures. Perhaps the most important acquisition has been to gain an in-depth appreciation of the challenges faced by those working to deal with these global-scale issues, and the effort and determination they must input to analyse, improve and enact upon past experiences to ensure the success of future ones; this is a lesson that I will be carrying with me in my future in public health.

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Appendix A: GSK Ph.D. Funding Proposal

An international study of the interface between public health policy responses to the 2009-10 influenza A/H1N1 pandemic and epidemiological disease pattern.

Background and Context:

During March and early April 2009, the public health authorities in three separate regions of Mexico reported unusual clusters of severe influenza-like illness. On April 21, 2009, CDC reported that two unrelated children in California had recovered from a novel influenza strain A/H1N1, which contained gene segments from swine flu virus. The children had not had contact with pigs. Two days later, CDC reported five more H1N1 cases, three in California and two in Texas. At the same time, the Pan-American Health Organization was notified of several H1N1 cases by Mexican authorities.

On April 24, 2009, Mexico's Health Ministry announced that a new strain of influenza was affecting the country, with just over 1,000 suspected cases. The Mexican government also announced that it was closing schools and cancelling public gatherings such as sporting events and concerts in Mexico City. Subsequently, on April 25 the WHO Director General declared a formal "Public Health Emergency of International Concern" (PHEIC).

By April 27, 2009, WHO announced that containment activities of the outbreak were not feasible and the global pandemic alert level was raised from Phase 3 to Phase 4. Two days later, the WHO Director-General raised the influenza pandemic alert level from Phase 4 to Phase 5 (characterized by human-to-human spread of the virus in at least two countries in one WHO region). The declaration of Phase 5 provided a strong signal that a pandemic was imminent and that the time remaining to finalize the organization, communication, and implementation of the planned mitigation measures was short. By the 30th of April 2009, the CDC reported a total of 1918 suspected cases and H1N1 (including 286 probable and 97 confirmed cases).

On June 11, 2009, after almost 30,000 cases had been confirmed in 74 countries, the World Health Organization (WHO) officially declared that a global pandemic of novel influenza A/H1N1 was underway by raising the global alert level to phase 6. This action was triggered by the emergence and global geographical spread of the new H1N1 virus in at least one other country in a different WHO region.

After the WHO declaration of a pandemic on June 11, the 2009 H1N1 virus continued to spread and the number of countries reporting cases of 2009 H1N1 nearly doubled from mid-June 2009 to early July 2009. As of 31 of July 2009, 168 countries and overseas territories or communities had reported at least one laboratory confirmed cases of pandemic influenza H1N1. All continents were affected by the pandemic.

The pandemic began to taper off in November 2009. As of 21 February 2010, more than 213 countries and overseas territories or communities had reported laboratory confirmed cases of pandemic influenza H1N1 and at least 16226 deaths were also confirmed. As of 25 July 2010, more than 214 countries worldwide and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 and over 18398 related-deaths had been confirmed.

On August 10, 2010, however, following advice from the International Health Regulation Emergency Committee, the WHO Director General declared that the A/H1N1 pandemic was over. Since then, the world has entered the post-pandemic phase. During this period, one of the main activities expected is that evaluations of the pandemic response will be performed within organisations, at local, regional, national and international levels, and by individual Governments in terms of the national response.

Rationale for Study:

Whilst a great many pandemic evaluations are underway at national or sub-national level, relatively few are in progress at international level. WHO has begun an investigation into the global response to the pandemic, under the auspices of its International Health Regulations Committee.¹ However this review will focus predominantly on the global coordinating role

of WHO, the global response in terms of its proportionality to pandemic impact, and the functioning of the International Health Regulations, 2005. Other reviews are also underway or have been recently completed by the European Union (including EU Health Council and Council of Europe),² and the WHO Regional Office for Europe.³

However, these reviews generally concentrate on operational responses and emphasise common underlying themes/areas of difficulty, e.g. communications and coordination. They do not however attempt to analyse the individual public health policy responses made within individual countries, e.g. decisions taken to use or not to use vaccines.

We perceive an opportunity for a study that will compare and contrast different policy approaches to the 2009 pandemic in relation to the epidemiological and public health impact within countries. By making specific international comparisons in areas of known policy discordance, it may be possible to improve future pandemic preparedness and highlight difficulties and problems that arose. By comparing, for example, countries with a high versus low use of pandemic vaccines and the size and duration of post-vaccine influenza activity, lessons might be learned about the potential impact of vaccination on subsequent pandemic waves. This would then feed into the 'risk behaviours' of governments as they balance preparedness for pandemic risk against alternative resource allocations.

An international study of public health policy differences will most likely have important social scientific, public health and policy implications. In relation to the impacts of the research, focusing on this issue from a combined epidemiological and social science perspective may allow further understanding and more successful application of the research findings than would be the case if the research was based within a single discipline. The work would reflect priorities expressed by both Economic and Social Research Council (ESRC) and Medical Research Council (MRC): ESRC for work on the 'social dimensions of preventing and responding to threats from new and existing infectious diseases' and the 'underpinnings of interventions which promote the reduction of infectious diseases'; and MRC for 'research [that] reflects changing health needs such as the global challenge to new forms of 'flu'.

Although the H1N1 strain in the 2009 pandemic has been relatively mild in its effects, it cannot be assumed that the same will be true of future 21st century pandemics and it is important to ensure that appropriate policy conclusions are drawn from the experience in order to inform future response planning. At the same time, there is an opportunity to examine the complex interface between public health policy and the epidemiology of pandemic influenza.

Within Sociology the concept of 'Risk' has developed as a major theoretical strand since Becks 'Risk Society' in 1992.⁴ Beck defined risk as "a systematic way of dealing with the hazards and insecurities induced and introduced by modernization itself".⁴ Becks work highlighted that contemporary societies face risks not faced historically or that risks had changed because of modernisation. Burgess in 2006 argued that Risk has become a framework through which governments conduct their business.⁵ As Tony Blair put it "Risk management... is now central to the business of good government".⁶ Sociologists are not concerned with actuarial risks but rather the processes by which Risk is decided and how it may be amplified or dampened and the way in which they are discussed and managed – both in themselves and in comparison to other perceived risks.^{7,8} A countries culture and political ideology may also impact upon how risk is perceived and the nature of the subsequent response for example decisions to procure and/or deploy antivirals/vaccines and to implement public health measure. Recent studies have also begun to consider the ways in which a sociology of risk can bring new understanding to public health and epidemiology.⁹ This study will utilise the sociology of risk to illuminate public health policy in relation to pandemic flu.

Overall Aims:

1. To examine, compare and contrast differences in public health policy between countries during the 2009-10 influenza A/H1N1 pandemic with reference to specific key areas (see Work Packages below) and in terms of timing (in relation to disease occurrence) as well as implementation and how this was affected by perceptions of risk.

2. To determine any apparent relationship between the timing and extent of public health policy differences in relation to disease activity.
3. To review the implications for public policy in relation to pandemic preparedness and the response to future pandemics of potentially greater severity.
4. To achieve 1-3 through the study of selected participant countries in any region of the world.

Overall approach:

A maximum of ten countries (initial target = 6-8) will be selected on the basis of being discordant from each other in terms of public policy in relation to specific major issues (see Work Packages) and having sufficient epidemiological data to allow for a fairly accurate description of disease activity and intensity at national level. Reserve countries will also be selected to allow for refusal to participate.

A policy and epidemiological picture in each country will be developed based on:

- a) Government information placed in the public domain
- b) Interviews (where granted) with policy makers and public health officials
- c) Publicly available commercial data on the supply/distribution of antiviral drugs and vaccines

*Work Packages:

WP1 a) Literature review on the Sociology of Risk in relation to pandemic preparedness; b) Literature and 'grey literature' review of the policy related response to the 2009/10 pandemic and the epidemiological impact in different countries (purposive review to identify potential countries for further study)

WP2 Based on selected countries, this will examine the overall use or non-use of antiviral drugs (for post-exposure prophylaxis in households, aimed at the slowing of initial spread within countries and for treatment of cases). This will include an examination of the potential impact of policy differences related to 'treat all' or 'treat high-risk only' policies.¹⁰

WP3 Based on selected countries, this will examine the use or non-use of monovalent pandemic influenza vaccines, including timing of deployment and type (inactivated, live, adjuvanted etc.), policy intention (pre-pandemic) versus policy implementation (and reasons for any discordance).¹¹

WP4 Based on selected countries, this will examine public health (non-pharmaceutical) measures such as restrictions on mass gatherings, border closures/restrictions, suspension of urban mass transportation systems to the limited extent that these were practiced during the 2009-10 pandemic.¹²

WP5 An examination of broader societal aspects of the pandemic response in 2009-10. To include: the role of the media; the effectiveness of government health communications; the impact of centralised vs. decentralised health communication; the role of HCPs in providing pandemic response (use of existing health care provision vs. establishing special vaccination centres etc).

**It is not possible to determine the full feasibility of each Work Package in advance. Feasibility may depend upon data availability.*

Support requested:

Funder: GSK

2011/12

PhD student tuition fees (home student): £ 3,570

MRC-set PhD stipend (ex-London): £14,000

Book/Miscellaneous items allowance: £1500

2012/13

PhD student tuition fees (home student): £ 3,675 (est)

MRC-set PhD stipend (ex-London): £14,350 (est)

Book/Miscellaneous items allowance: £1500

2013/14

PhD student tuition fees (home student): £ 3,786 (est)

MRC-set PhD stipend (ex-London): £14,782 (est)

Book/Miscellaneous items allowance: £1500

We anticipate up to 12 international trips of 6-night duration and have set an indicative budget for each trip:

Flight: £1200 (based on BA coach class travel to Buenos Aires or Sydney)

Hotel: £600

Ground transportation: £200

Subsistence: £300

Trip total: £2300

Travel is anticipated in Years 1 and 2 only. Indicative maximum travel expenditure: £13,800 per annum Years 1 and 2.

International travel costs (as agreed with Funder) will be provided for directly by the Funder or cross-charged on the basis of actual costs incurred for economy/coach class air fare and public ground transportation where available/practical.

Publications and Reports arising:

In the interests of global public health, it is important that the findings of this project are placed in the public domain as quickly as possible. The PhD student and supervisors will therefore pursue a policy of ongoing publication as data become available as opposed to after the PhD is completed.

The Funder will receive 6-monthly progress reports from the student, copies of all manuscripts under development and a final bound copy of the completed PhD thesis. In addition the Funder may nominate a senior professional (Dr R.South) to contribute to ongoing study supervision meetings (but not acting as an official academic supervisor).

University Supervisory Staff:

Professor J. Van-Tam, Chair in Health Protection, Epidemiology and Public Health

Professor I. Shaw, Chair in Health Policy, Law and Social Sciences

Proposed Timetable:

PhD study period: February 2011- January 2014

Ongoing Publications from Jan 2012 onwards

References:

1. http://www.who.int/csr/disease/swineflu/frequently_asked_questions/review_committee/en/index.html
2. http://www.ecdc.europa.eu/en/healthtopics/H1N1/pandemic_2009_evaluations/Pages/pandemic_2009_evaluations.aspx

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4. Beck U, (1992) Risk Society: Towards a new modernity. London Sage
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8. Brown B., and Crawford B., (2009) "Post Antibiotic Apocolypse": Discourses of mutation in narratives of MRSA' Sociology of Health and Illness. 31(4) p.508-24
9. Brown B., Nerlich B., Crawford P., Kateyko N., and Carter R., (2009) 'Hygiene and Biosecurity: The Language and Politics of Risk in an Era of Emerging Infectious Disease. Sociology Compass 26. p. 1-13
10. Hessel L. Vaccines. In Eds: Van-Tam J, Sellwood C. Introduction to Pandemic Influenza. 2010, Wallingford: CABI, pp 118-33.
11. Van-Tam J, Gupta RK. Pharmaceutical Interventions. In Eds: Van-Tam J, Sellwood C. Introduction to Pandemic Influenza. 2010, Wallingford: CABI, pp 98-115.
12. Nicoll A, Needham H. National and International Public Health Countermeasures. In Eds: Van-Tam J, Sellwood C. Introduction to Pandemic Influenza. 2010, Wallingford: CABI, pp 136-55.

Appendix B: PICO Search Strategy

Area	MeSH thesaurus headings	Free text
Patient / Population / Problem	pandemic influenza A(H1N1) 2009	(pandemic AND influenza) OR (pandemic AND flu) OR *H1N1* OR *2009* OR *pdm* OR (influenza A) OR (H1N1 influenza)
Intervention	antiviral	tamiflu OR oseltamivir OR relenza OR zanamivir OR inavir OR laninamivir OR peramivir OR rapiacta OR peramiflu OR antiviral* OR (neuraminidase AND inhibitor*) OR prophylaxis
	vaccine	Vaccin* OR (pandemic AND vaccin*)
		border* OR flight* OR travel OR restrict* OR (thermal AND imag*) OR screen*
		(personal AND protective) OR PPE OR hand OR hygiene OR wash* OR gel OR clean* OR mask* OR face OR SFM* OR (respiratory AND hygiene) OR tissue* OR respirator* OR isolat* OR self-isolat* OR home OR quarantine OR distanc*
		school OR school clos* OR educat* OR work* OR closure* OR cancel* OR public gather* OR event* OR reactive OR proactive OR social
	Communicable disease control	
		Phone* OR telephone* OR call OR information* OR press* OR media*
		Contain OR treat OR polic*

		OR phase* OR program* campaign OR respon* OR strateg* OR mitigat*
Comparison	Sweden	Sweden Swedish
	Canada	Canada Canadian*
	Argentina	Argentina Argentine
	Japan	Japan Japanese
	Turkey	Turkey Turkish
	Singapore	Singapore OR Singaporean*
	New Zealand	(New AND Zealand) OR New Zealander*
Outcome	Epidemiology	morbidity* OR mortality* OR healthcare OR pregnan* OR (underlying AND chronic AND medical AND condition*) OR healthy OR hospit* OR (mechanical AND ventilat*) OR ICU OR (intensive AND care) OR confirm* OR (laboratory AND confirm*) OR case* OR effect* OR outbreak* OR disease* OR ill* OR risk OR infant* OR child* OR adolescen* OR pupil* OR student* OR young OR adult* OR old* OR elder* OR people OR person* OR men OR women OR pregnan* OR paediatr* OR pediater* OR geriatr* OR patient* OR public

Search carried out in **MEDLINE (OVID) 1996 onwards.**

Date of search: 23/07/2013.

#	Searches	Results
1	exp Influenza A Virus, H1N1 Subtype/	9214
2	((pandemic and influenza) or (pandemic and flu)).mp. or *H1N1*/ or *2009*/ or *pdm*/ or (influenza and A).mp. or (H1N1 and influenza).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 37734	37734
3	1 or 2	37734
4	exp Antiviral Agents/	181088
5	(tamiflu or oseltamivir or relenza or zanamivir or inavir or laninamivir or peramivir or rapiacta or peramiflu or antiviral* or (neuraminidase and inhibitor*) or prophylaxis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	103290
6	exp Influenza Vaccines/	10989
7	(vaccin* or (pandemic and vaccin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	149838
8	(border* or flight* or travel or restrict* or (thermal and imag*) or	624067

	screen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	
9	((personal and protective) or PPE or hand or hygiene or wash* or gel or clean* or mask* or face or SFM* or (respiratory and hygiene) or tissue* or respirator* or isolat* or self-isolat* or home or quarantine or distanc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	2091098
10	(school or educat* or work* or clos* or cancel* or public gather* or event* or reactive or proactive or social).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1934281
11	exp Communicable Disease Control/	141488
12	(Phone* or telephone* or call or information* or press* or media*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	2079509
13	(contain or treat or polic* or phase* or program* campaign or respon* or strateg* or mitigat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,	2506905

	protocol supplementary concept, rare disease supplementary concept, unique identifier]	
14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	6230723
15	exp Sweden/	31013
16	(sweden or swedish).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	43293
17	15 or 16	43293
18	exp Turkey/	17886
19	(turkey or turkish).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	25702
20	18 or 19	25702
21	exp Canada/	68832
22	(canada or canadian*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	68730
23	21 or 22	88188
24	exp New Zealand/	16801
25	((new and ZEALAND) or (new and zealander*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	30406
26	24 or 25	30406
27	exp Japan/	56436
28	(japan or japanese).mp. [mp=title, abstract, original title, name of	112883

	substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	
29	27 or 28	113364
30	exp Singapore/	5480
31	(singapore or sinaporean*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	7280
32	30 or 31	7280
33	exp Argentina/ 6889	6889
34	(argentina or argentine*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9608
35	33 or 34	9608
36	exp Epidemiology/	11473
37	(morbidity* or mortality* or healthcare or pregnancy* or (underlying and chronic and medical and condition*) or healthy or hospital* or (mechanical and ventilator*) or ICU or (intensive and care) or confirm* or (laboratory and confirm*) or case* or effect* or outbreak* or disease* or ill* or risk or infant* or child* or adolescent* or pupil* or student* or young or adult* or old* or elder* or people or person* or men or women or pregnancy* or paediatric* or pediatric* or geriatric* or patient* or public).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	7453959
38	36 or 37	7455982

39	17 or 20 or 23 or 26 or 29 or 32 or 35	312837
40	3 and 14 and 38 and 39	2217
41	limit 40 to humans	1889

Sweden specific literature:

#	Searches	Results
40	3 and 14 and 17 and 38	129
41	Limit 40 to humans	106

Turkey specific literature:

#	Searches	Results
40	3 and 14 and 20 and 38	259
41	Limit 40 to humans	143

Canada specific literature:

#	Searches	Results
40	3 and 14 and 23 and 38	722
41	Limit 40 to humans	653

New Zealand specific literature:

#	Searches	Results
40	3 and 14 and 26 and 38	155
41	Limit 40 to humans	143

Japan specific literature:

#	Searches	Results
40	3 and 14 and 29 and 38	780
41	Limit 40 to humans	667

Singapore specific literature:

#	Searches	Results
40	3 and 14 and 32 and 38	157
41	Limit 40 to humans	155

Argentina specific literature:

#	Searches	Results
40	3 and 14 and 35 and 38	99
41	Limit 40 to humans	90

Appendix C: Ethics Approval



The University of
Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

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31st March 2016

To Whom It May Concern

**Re: Ethics Application for Leila Pinder, 4181443, University of Nottingham
PhD Thesis**

Ms Pinder submitted her Application for Ethical Approval in March 2013 for her PhD thesis:

'An international study of the interface between public health policy responses to the 2009-10 influenza A/H1N1 pandemic and epidemiological disease patterns'

The ethics application was considered by the School of Sociology and Social Policy Ethics Committee in March 2013. Approval was given for the research to go forward.

Yours faithfully

S. R. L. E.

Dr Simon Roberts
Research Ethics Officer
School of Sociology and Social Policy



Appendix D: Letter to participants

Epidemiology and Public Health

University Of Nottingham

Clinical Sciences Building

City Hospital

Nottingham

NG5 1PB

United Kingdom

17th June 2013

Dear Sir or Madam,

I am writing to you because due to your area of work I would very much welcome your participation in my research project which concerns the 2009-10 pandemic influenza.

By way of introduction, my name is Leila Pinder, a student at the University of Nottingham and I am undertaking a PhD study under the supervision of Professor Jonathan Van-Tam (Health Protection & Influenza) and Professor Ian Shaw (Health Policy & Sociology). Included with this letter is my CV, which shows my education of a Social Sciences undergraduate degree and a Masters in Public Health. It is with this educational background that I approach my PhD project and it is reflective of my discipline interests.

My project is examining the interface between health policies and practices for the management of the 2009-10 pandemic influenza and the epidemiological experiences in various countries. In order to do this research, I will interview key stakeholders to develop an overview of eight countries national public health measures used in the 2009-10 pandemic influenza. The individuals who I would like to speak with may vary by job title somewhat within the study countries, but may

include public health officials, policy makers, national medical officers, epidemiologists etc., and their work role would have concerned their country's national response to the 2009-10 pandemic influenza. I will also report the study countries national epidemiological experience of pandemic influenza, by utilising publically available data. This will enable me to consider the generated interview themes in light of the national epidemiological circumstances. The identity of these individuals will remain confidential.

It is hoped that the international approach in this project will provide further understanding of national health policies and practices decisions, as well as perhaps, risk perceptions and the uncertainties associated with pandemic influenza. Due to the number of countries studied in this student project and the resource limits of one researcher, it is accepted that an overview and not a comprehensive picture will be gathered of each country. However, the multiple study country approach may amalgamate trends across nations and therefore further contribute to an international understanding of a global disease.

My studentship has been financially provided by GlaxoSmithKline. However, GSK have left the direction of the project to my supervisors and me, and as such have no involvement in the data acquisition, analysis or write up of results. My studentship will terminate in 2015 and by this time I intend to publish the study findings. In my thesis, and any journal publications, all interview data will be reported anonymously in order to protect the identity of participating individuals.

If you agree to speak with me, the meeting would involve a one-to-one interview and at your agreement I would like to audio record our conversation. The meeting would take place within a nominated week, as I intend to interview a minimum of six individuals during a one week visit to your country. I anticipate that the interview would take up about 90 minutes of your time, and I hope to hear your thoughts and reflections in order to gather some insight into the management and experience of 2009-10 pandemic influenza within your country. I have a short interview guide, which will help me cover particular interests of the project, but the interviews will be flexible in content and structure. The interview questions will cover areas such as national antiviral use, pandemic vaccine, non-pharmaceutical measures, pandemic risk

assessment, epidemiology of the pandemic, etc. Unfortunately, I am unable to offer financial payment for your time.

When I return to the UK, I will transcribe the interview conversation, as well as the other interviews conducted, and import the generated text into the computer programme Nvivo to assist me with coding the text for the analysis stage of my project. I will do this eight times, as I hope to visit eight countries over the following months.

Should you be prepared to grant me an interview, or if you would like further information about the project before making a final decision, please contact me by email: mcxlp@nottingham.ac.uk I can also make available copies of official letters from the University of Nottingham confirming my PhD studentship and from both tutors confirming supervisory support should you or your organisation wish to inspect these or retain them on file.

Thank-you for reading about my project and I hope to hear from you.

Yours faithfully,

Leila Pinder (Miss)

University Of Nottingham PhD student

Appendix E: Interview Aid Memoire

Below are one or two example questions under each subject covered:

Subject	Example of relevant questions/topics
National overview	Key events during 2009-10 pandemic A(H1N1) influenza Concerns during the pandemic influenza
Risk	Did the risk perception change over the course of the pandemic? Was the response proportionate to the perceived level of risk?
Disease activity	Epidemiological experience in study country (e.g. first cases/deaths timings linked to public health measures implemented at that time)
Antiviral drugs	How were antivirals used during the pandemic influenza (e.g. treatment policy)?
Pandemic influenza vaccines	Vaccines – use, type, amount ordered, timing of vaccination campaigns, uptake rates...
Non pharma measures	What other public health measures were used? How? When? Why?
Wider societal aspects	Health communications. Role of the media Was the existing health service utilised or were special pandemic influenza services provided? (e.g. vaccination centres, fever tents)