RECOMMENDATION FOR INFLUENZA VACCINE COMPOSITION 2009

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A report prepared for the Ministry of Health
as part of the 2008/09 contract
(Service Description: Person-to-Person Infectious Diseases)

by

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October 2008

Client Report
FW08103

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- A(H3N2) an A/Brisbane/10/2007 (H3N2) - like strain
- B a B/Florida/4/2006 - like strain

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1. EPIDEMIOLOGY

It is known that influenza viruses frequently go through antigenic changes, and protection by vaccines is dependent on achieving a good match between vaccine strains and the circulating viruses. Thus, the World Health Organisation (WHO) makes twice-yearly recommendations to guide national/regional authorities on the formulation of influenza vaccines: one recommendation in February for the Northern Hemisphere winter and another in September for the Southern Hemisphere winter. This has been published in 10 October issue of the *Weekly Epidemiological Record, 2008 83(41):366-372* (Appendix 6).

It should be noted that the WHO recommendations are made with respect to reference strains which may or may not be suitable for vaccine production. Thus, even where the WHO recommendation is adopted it is necessary for country/regional authorities to approve the specific vaccine strains to be used and this, in turn, requires the preparation of specific reagents for vaccine standardization.

Since 1969 an Australian Influenza Vaccine Committee (AIVC), with representatives from New Zealand, Australia and South Africa, has met annually in October to approve or update the WHO recommended formulation for influenza vaccines intended for the following winter (March to September of the following year) for these countries. New Zealand uses the influenza vaccine strains recommended by AIVC for the use in the subsequent year.

1.1. Overview of World-wide Influenza Activity, March-September 2008

From February to September 2008, influenza activity was reported in Africa, the Americas, Asia, Europe and Oceania. In general, activity was mild.

In the northern hemisphere, influenza viruses continued to circulate and caused outbreaks in Asia, Europe and North America. Activity in general declined in March in Europe and in April in Asia and North America. A(H1N1) viruses circulated extensively and predominated in many countries. A(H3N2) viruses predominated in the United States of America and circulated less extensively in Asia and Eastern Europe. B viruses co-circulated and outbreaks were reported in some countries.

In the southern hemisphere, influenza activity began in March and increased in April in South America, while in Africa and Oceania, activity started in May and increased in July. Overall, activity declined in August except for in Australia, Brazil and New Zealand. In Africa,

A(H1N1) viruses predominated and caused outbreaks. In South America, A(H1N1) and B viruses co-circulated and were associated with outbreaks. In Oceania, A(H3N2) and B viruses co-circulated, with outbreaks being reported.

From 1 February to 19 September 2008, 36 human cases of influenza A(H5N1) were confirmed in Bangladesh, China, Egypt, Indonesia and Viet Nam. Many of these cases were associated with outbreaks of highly pathogenic avian influenza A(H5N1) in poultry. Since December 2003, a total of 387 human cases have been confirmed from 15 countries. To date, there has been no evidence of sustained human-to-human transmission. The WHO influenza pandemic preparedness level remains unchanged at Phase 3.
(Excerpted from Weekly Epidemiological Record, 2008 83(41):366-372)

The WHO Collaborating Centre for Reference and Research on Influenza in Melbourne, Australia (Melbourne WHOCC) analysed influenza isolates received from 1 January to 29 September 2008. Influenza B was the predominant strain which accounted for 49% (529/1085) of isolates while 11% (120/1085) were influenza A(H1N1) and 40% (436/1085) were influenza A(H3N2) (Figures 2.1 and Table 2.1 in Appendix 2).

1.2. Southern Hemisphere Influenza Activity, March-September 2008

1.2.1. New Zealand

Influenza is not a notifiable disease in New Zealand. A national influenza surveillance system was set up in 1991 as part of the WHO global programme for influenza surveillance. The purpose of influenza surveillance is:

- to describe the incidence and distribution of influenza in the community;
- to detect influenza epidemics within the community in order to assist public health intervention;
- to identify the predominant strains to help plan for effective influenza vaccines for the subsequent year.

There are two forms of influenza surveillance in New Zealand:

1) Sentinel surveillance. This is operated nationally by ESR and locally by surveillance co-ordinators within the public health service in each of 24 health districts. The system operates during the winter "influenza season", usually from May through September each year. Based on the population and geographic distribution, about 90 voluntary sentinel general practitioners throughout the country are recruited into the system, covering roughly 10% of the New Zealand population. This system provides two types of surveillance information, one being disease information and the other being strain information. Every week, each sentinel practice provides consultation data (the number of cases of influenza-like illness) to the WHO National Influenza Centre at ESR. This allows the measurement of the incidence and distribution of influenza. In addition, each sentinel practice provides throat/nasopharyngeal swabs from the first patient seen with an influenza-like illness on Monday, Tuesday and Wednesday of each week. These samples are forwarded to four virology laboratories around the country for viral isolation and identification. Some hospital virology laboratories refer influenza isolates to the WHO National Influenza Centre at ESR for further typing. This provides the national data on predominant strains. The combined information on disease incidence and predominant strain is reported to MoH and WHO weekly, monthly and annually. The weekly report,

Influenza Weekly Update, is distributed in a printed format or accessible on ESR's website (http://www.surv.esr.cri.nz/virology/influenza_weekly_update.php).

2) Laboratory-based surveillance. This system is operated all year around by the four regional virology laboratories at Auckland, Waikato, Christchurch and Wellington and by one public health virology lab, the WHO National Influenza Centre at ESR. This system is conducted by sampling hospital in-patients and outpatients during routine viral diagnosis. The viral isolation data are reported nationally in *Virology Weekly Report*, and distributed in a printed format or on ESR's website (http://www.esr.cri.nz/virology/virology_weekly_report.php)

The data on consultation rates from 1991 to 2000 were reviewed and the thresholds used to describe influenza-like activity were defined (Table 2) *(New Zealand Public Health Report 2000 8(2): 9-13)*.

Sentinel influenza surveillance started in May 2008. The peak of the influenza activity in 2008 is higher than 2007, similar to 2006 (Figure 1). There is a broad high activity period from week 29 (in the middle of July) to week 35 (at the end of August) with two peaks. The first peak occurred in week 29, one week earlier than the peak in 2007. The consultation rate remained below the baseline level from week 18 to week 25 (in the middle of June). Then it increased rapidly and reached the first peak in week 29 (in the middle of July) with the consultation rate for flu-like illness at 93/100,000. The influenza activity continued at a high level for 4 weeks and reached the second peak in week 33 (in the middle of August) with the ILI rate at 95/100,000. Then the influenza activity began to decrease sharply and fell below baseline level in week 37 (in the middle of September). Since then, it has remained below the baseline level. When weekly consultation rates for ILI from 1992-2008 were compared, influenza activity in 2008 is at a low to medium level (Figure 2). In particular, when the data for the last 9 years (2000 to 2008) is compared, influenza activity in 2008 belongs to the low end of the middle range.

Influenza isolates were reported weekly by sentinel and laboratory-based surveillance (Figure 3). There are three interesting features in influenza activity in 2008: 1) The viral isolation for sentinel surveillance peaked in weeks 32 to 36, 3 weeks later than the first peak of the ILI consultation. 2) The viral isolation for laboratory-based surveillance peaked in weeks 29 to 35, in the same range of the broad peak period of the ILI consultation. 3) A greater proportion (49%) of influenza viruses were isolated from sentinel surveillance in 2008 than that of 2007 (36%). A total of 941 influenza viruses were reported by sentinel and laboratory-based surveillance from weeks 1 to 38 in 2008. Sentinel surveillance yielded 462 (49%, 462/941) influenza viruses and laboratory-based surveillance isolated 479 (51%, 479/941) influenza viruses. The increase in the proportion of influenza isolates resulting from sentinel surveillance could reflect more community outbreaks of influenza and/or fewer hospitalisations in 2008 when compared to 2007.

A total of 941 influenza viruses were isolated in 2008 from weeks 1 to 38. Overall, influenza B was the predominant type with 534 viruses (57%, 534/941). There were 407 influenza A viruses in 2008, consisting of 43% (407/941) of total isolates.

Among 407 influenza A viruses, 199 influenza A viruses are yet to be subtyped. 3 influenza A(H1N1) viruses were identified with 2 viruses subtyped as influenza A/Brisbane/59/2007-like strains and they were Tamiflu resistant viruses. In addition, 206 influenza A(H3N2) viruses were identified with 156 viruses subtyped as A/Brisbane/10/2007-like viruses and 50

as A(H3N2) by PCR detection. Influenza A/Brisbane/10/2007-like strain is the predominant strain among all typed/subtyped viruses.

Among 534 influenza B viruses, 67 were typed as B/Malaysia/2506/2004-like strains, 53 as B/Florida/4/2006-like strains and 414 as influenza B viruses yet to be antigenically typed.

Figure 5 shows the temporal distribution of influenza A and B viruses in 2008. Three main strains (A/Brisbane/10/2007-like, B/Florida/4/2006-like and B/Malaysia/2506/2004-like) co-circulated throughout the winter season. In July, A/Brisbane/10/2007-like and B/Florida/4/2006-like strains cocirculated with more A/Brisbane/10/2007-like viruses than B/Florida/4/2006-like viruses. In August and September, more B/Malaysia/2506/2004-like viruses were reported compared to B/Florida/4/2006-like viruses. Overall, more influenza B viruses than A viruses were reported during this period.

Figure 6 shows the percentage of influenza types and subtypes from 2001 to 2008, in particular, for B/Yamagata and B/Victoria lineages. In 2001, all influenza B viruses were B/Yamagata-lineage viruses. In 2002, for the first time, B/Victoria lineage viruses spread to NZ, consisting of 32% (151/478) isolations. In 2003, A(H3N2) predominated the season with only 2 B/Yamagata lineage viruses and 1 B/Victoria lineage virus reported. Again in 2004, A(H3N2) predominated the season with 61 B/Yamagata lineage viruses and 1 B/Victoria lineage virus. In 2005, B/Victoria lineage viruses predominated in NZ, associated with deaths of 3 children. 2006 was predominated with A(H3N2) with only 2 B/Yamagata lineage viruses and 3 B/Victoria lineage viruses. 2007 was again predominated with AH3N2 with 142 B/Yamagata lineage viruses and 2 B/Victoria lineage viruses. In 2008, 67 B/Victoria lineage viruses and 53 B/Yamagata lineage viruses were reported with 414 B as yet to be antigenically typed. It is interesting to see a pattern emerging that B/Victoria lineage virus predominates in every three years whereas B/Yamagata lineage strain circulates at relatively low numbers each year.

Figure 7 shows age group comparison between sentinel and laboratory-based surveillance.
It is interesting to note again that the age group between 0-1 years and 1-4 years and patients over 65 years were represented more in laboratory-based surveillance than in sentinel surveillance. This is consistent with the findings from the past 3-4 years. A greater proportions (35%) of children 0-4 years yielded influenza viruses in non-sentinel surveillance in 2008 than that (18%) of 2007. This may reflect the fact that children 0-4 years are more susceptible to influenza B infections.

The WHO National Influenza Centre (NIC) at ESR established a fluorometric neuraminidase inhibitor assay. Influenza A(H1N1) viruses resistant to the neuraminidase inhibitor oseltamivir has emerged in Europe during the winter of 2007-2008 and spread worldwide. NIC has been closely monitoring influenza viruses resistant to oseltamivir. All influenza viruses collected before the northern hemisphere winter of 2007-2008 were all oseltamivir sensitive viruses. However, this situation has changed and for the first time in New Zealand, oseltamivir resistant influenza A(H1N1) viruses have been detected. A total of three influenza AH1N1 viruses were detected in New Zealand in 2008:

- The first AH1N1 virus, an oseltamivir sensitive virus, was detected by PCR from a nasal swab collected on 14 February 2008 from a 41 year old male traveller returning from Hong Kong. The subsequent sequence analysis showed no mutation at the 275 site of the N1 gene.

- The second AH1N1 virus, an oseltamivir resistant virus, was isolated from a nasopharyngeal swab collected on 1 August 2008 from a 49 year old female who had chest pain. The patient had not had influenza vaccination, not used Tamiflu and also had no travel outside New Zealand prior to her illness.

  Fluorometric neuraminidase inhibition (NI) assay was performed for this virus to assess oseltamivir resistance. The 50% inhibitory concentration (IC_{50}) value showed 690-fold increase (IC_{50} = 573 nM) in resistance to oseltamivir compared with other oseltamivir sensitive AH1N1 viruses.

  The coding sequence of the NA gene was determined from nt 21 to nt 1413 (N1 subtype numbering). A histidine (H) to tyrosine (Y) mutation was observed at residue 275, where this H275Y mutation is already known to confer resistance to oseltamivir. In a BLASTP search of genbank the New Zealand virus showed 99% similarity to other AH1N1 strains that have been reported as oseltamivir resistant during 2007 / 2008, such as A/New Jersey/15/2007(H1N1). Only one additional amino acid change was noted compared with many other strains, that being E268D (GAG -> GAT; G/T nt804; N1 subtype numbering). This is a conservative amino acid change from Aspartic acid to Glutamic acid, where the New Zealand virus has a Glu at residue 268.

- The third influenza AH1N1 virus, an oseltamivir resistant virus, was detected from a nasopharyngeal swab collected on 15 August 2008 from a 15 year old female who had fever and abdominal pain. The patient had no influenza vaccination and had not travelled outside New Zealand prior to her illness

  Fluorometric neuraminidase inhibition (NI) assay was performed for this virus to assess oseltamivir resistance. The 50% inhibitory concentration value showed 932-fold increase (IC_{50} = 773 nM) in resistance to oseltamivir compared with other oseltamivir sensitive AH1N1 viruses

  The coding sequence of the NA gene was determined from nt 22 to nt 919 (N1 subtype numbering). A histidine (H) to tyrosine (Y) mutation was observed at residue 275. In a BLASTP search of genbank the New Zealand virus showed 100% identity to the A/Pennsylvania/02/2008(H1N1) at the amino acid sequence level, where this virus that had been reported as oseltamivir resistant.

Due to vaccine breakthrough and/or failure observed in 2004 (Influenza Annual Report, 2004), the need for surveying influenza vaccine breakthrough/failure was discussed and agreed by health professionals around the country. When GPs take swabs from 3 ILI patients each week, specimen request forms with necessary demographic information are required to be provided. One extra question is included to record whether the patient has been vaccinated against influenza in the same year as the onset of ILI.

A total of 21 vaccine breakthrough cases were recorded from the national influenza database (Table 3) from weeks 1 to 38, comprising 2.2% of total isolates (21/941). The clinical effectiveness of influenza vaccines depends on the immunocompetence of the recipient, previous exposure to influenza and influenza vaccines, and the closeness of the match between the vaccine and circulating influenza strains. Of 21 vaccine breakthrough cases, 10 cases (48%, 10/21) occurred in age groups >50 years. Immunological senescence may explain a higher proportion of vaccine breakthrough cases in the elderly population. In

addition, 11 vaccine breakthrough cases had influenza A(H3N2) viruses and 10 with influenza B viruses.

In addition, 447 ILI cases had information on vaccination history from the ESRLab database for sentinel surveillance specimens. Among them, 47 had influenza vaccination in the same year as the onset of ILI and 361 had none. There were 10 (21%, 10/47) vaccinated patients whose specimens yielded influenza viruses.

1.2.2. Australia

Influenza activity in Australia in 2008 was moderate with some regional variations regarding influenza activities and types/subtypes.

There are seven forms of influenza surveillance system in Australia:

- **National Notifiable Disease Surveillance System (NNDSS).** In Australia, laboratory-confirmed cases of influenza became nationally notifiable from 1 January 2001. All lab-confirmed cases are required to be reported to State and Territory health departments. The NNDSS data indicated that the influenza activity was lower (7602 lab-confirmed cases) in 2008 than that (9915) of 2007. The activity peaked in week 36, three weeks later than in 2007. Young children aged 0-4 years had the highest influenza notification rates compared with other age groups. The Queensland notification was the highest compared with other jurisdictions.

- **Laboratory Surveillance conducted by the Melbourne WHOCC.** A total of 378 influenza isolates from Australia were received for analysis at the Melbourne WHOCC (Appendix 2) from 1 January to 29 September 2008. 262 influenza B viruses (69%, 262/378) were isolated with co-circulation of B/Yamagata (173) and B/Victoria (89) lineage viruses. 23% (87/378) of isolates were A(H3N2) viruses, antigenically related to A/Brisbane/10/2007-like strain. 29 (8%, 29/378) A(H1N1) viruses were isolated and H1 was antigenically similar to A/Brisbane/59/2007-like strain. Regarding oseltamivir-resistant A(H1N1) viruses, the most updated data covering the period from 1 January to 9 October 2008 indicated 45 out of 56 A(H1N1) isolates were oseltamivir-resistant.

- **Australian Sentinel Practice Research Network (ASPREN).** In 2008, 178 general practitioners around Australia reported on ILI through the Australian Sentinel Practice Research Network (ASPREN) and state and territory sentinel GP surveillance programs. New cases of influenza-like-illness (ILI) are reported per 1000 consultation per week all-year-around. This information is forwarded to Commonwealth weekly. Since January 2004, all sentinel GP surveillance schemes use the same case definition of ILI. The sentinel surveillance showed that the consultation rates for influenza-like illness in 2008 were lower than 2007 and peaked at the end of August and beginning of September.

- **The emergency department surveillance in New South Wales**. This surveillance indicated lower influenza activity in 2008 than in 2007. About 29 emergency departments across New South Wales participated in the survey. The peak was recorded at the end of August and beginning of September with the ILI rate at 5/1000 consultations.

- **Absenteeism Survey**. Australia post conducts an absenteeism survey that consists of national employer of more than 30,000 people in all jurisdictions except NT. The absenteeism data is supplied weekly per jurisdiction. The percentage of sick leave for three days or more continuously is reported. These data are not influenza or ILI specific

and absenteeism may be a result of other illnesses. Absenteeism rates in 2008 have been following the similar trends to those seen in 2006.

- **Death Certificate Survey**. The registered death certificates from the births, deaths and marriages office in New South Wales indicated that influenza and pneumonia deaths in 2008 was lower (150 per 1000 deaths) than 2007 (over 200 per 1000 deaths). The highest proportion of deaths occurred in people aged 85 years.

- **Australian Paediatric Surveillance**. A survey of admissions of children aged 15 years and under to Intensive Care Units (ICUs) around Australia following complications due to influenza infection was initiated at the start of July 2008 through the Australian Paediatric Surveillance Unit (APSU). Details of admissions are reported on a weekly basis. Between 1 July 2008 and 10 October 2008, there have been 39 children admitted to ICUs following complications due to influenza infection. Among them, 5 had influenza vaccination.

(Abridged from a report by Dr Leslee Roberts, Department of Health and Ageing, Australia and a report by Dr. Ian Barr, WHO Collaborating Centre for Influenza, Melbourne.)

1.2.3. South Africa

Influenza activity during the South African 2008 winter season was monitored by the Viral Watch sentinel surveillance programme. This program has been expanded in 2008 to include all 9 provinces in South Africa.

The 2008 influenza season started in week 23 and peaked in week 28. Sporadic isolates were made during the first four months of the year, several of which were from patients who had travelled to the northern hemisphere. From early May onward the number of isolates made increased gradually. The number of positive influenza specimens per week increased markedly from week 23, and reached a peak in week 28 when 65 influenza isolates were made. After week 32 (week starting 4 August), there were less than 10 viruses isolated per week.

A total of 435 influenza isolations were made, of which, 371 influenza A viruses and 64 influenza B viruses. Of the influenza A isolates, 306 were further identified as influenza A(H1N1), and 9 as A(H3N2). Among all influenza B viruses, 43 were further identified as B/Yamagata lineage viruses while 11 as B/Victoria lineage viruses.

The most notable outbreak recoded in 2008 occurred in Marydale, a small rural village in the sparsely populated Northern Cape province in July. A total of 154 ILI cases, mainly children, were admitted at the local clinics and hospital. Among 28 collected throat swabs, 22 were positive for influenza A(H1N1).

Sequence analysis was conducted for influenza A(H1N1), A(H3N2) and B:

- Influenza A(H1N1): The HA1 subunit revealed the H1 viruses isolated during the season showed that the majority of the isolates clustered with the clade 2B viruses. The majority shared the common amino acid mutations N183S and A189T compared to the vaccine strain as well as either a G-S or G-N substitution at residue 185. A few had an additional change of E81K or D186V.

All A(H1N1) viruses were oseltamivir resistant. These viruses all had H275Y mutations. Some other genetic drift was also observed in the South African isolates with mutations at residues 23 and 73 in the N1 gene.

- Influenza A(H3N2): Molecular characterization of the HA1 subunit of the H3s revealed that the majority of the viruses sequenced from different provinces in the country were very uniform and showed that several viruses had the K173Q substitution seen in many 2008 viruses from other parts of the world. The remaining South African strains shared common changes at L3F and K173N.

- Influenza B: The phylogenetic tree was constructed from analysis of the HA1 subunit of representative South African 2008 influenza B viruses from both the B/Victoria/2/87 and B/Yamagata/16/88 lineages. The B/Victoria/02/07-lineage influenza B isolates showed two common amino acid differences at K109N and S172P. The South African B/Yamagata-lineage viruses grouped into two clusters with viruses from one cluster sharing common amino acid changes at residues 75 and 108 relative to the B/Florida/4/2006 vaccine strain. The other cluster had three substitutions at positions 150, 165 and 229.

Influenza A viruses were isolated from the respiratory specimens of 6 patients who had received influenza vaccine prior to the onset of the season. Patients were aged between 35 and 73 years.

In summary, the majority of the influenza viruses in South Africa during the 2008 were subtype A(H1N1). 100% of the A(H1N1) viruses tested for antiviral resistance to oseltamivir were highly resistant, unlike the situation in the country in 2007 where all isolates were sensitive to the drug. Antigenic and genetic drift was observed for the influenza A(H1N1) and A(H3N2) viruses compared to the respective 2008 vaccine strains.

(Abridged from a report by Dr Terry Besselaar, National Institute for Communicable Diseases, South Africa.)

2. RECENT STRAIN CHARACTERISATION AND LIKELY VACCINE CANDIDATES

2.1. Influenza A(H1N1)

Influenza A(H1N1) subtype viruses, which re-emerged in 1977, closely resemble strains that circulated until 1956. Because of this, they initially had little impact in the older population. With further antigenic drift in the subtype, there has been evidence of increasing impact in the elderly.

Two antigenically distinct lines of influenza A(H1N1) have circulated in recent years and the current reference strains for these are A/New Caledonia/20/99 and A/Bayern/7/95. An A/New Caledonia/20/99-like strain has been selected as the A(H1) component for vaccine formulations since September 1999, initially because of the increasing incidence of this lineage and the fact that, in humans, vaccines containing viruses of this lineage were found to induce similar antibody responses against both the homologous virus and A/Bayern-like strains whereas the converse was not true. In the past few years, however, viruses with an

A/New Caledonia/20/99 like haemagglutinin antigen have completely replaced A/Bayern/7/95-like strains.

During the 2008 influenza season, 120 A(H1) isolates were received at the Melbourne WHOCC from 9 countries with most coming from Australia, South Africa and Macau.
The virology laboratories in New Zealand use the kit supplied by the Melbourne WHOCC to analyse influenza A(H1N1) strains. The antiserum used for detecting A(H1) was A/New Caledonia/20/99. Three influenza A(H1N1) viruses were detected in New Zealand in 2008 and two of them were antigenically subtyped as A/Brisbane/59/2007-like strains.

Among all A(H1) viruses analysed at the Melbourne WHOCC, most of viruses reacted well with ferret sera to A/Brisbane/59/2007 with only the occasional low reactors. Few viruses were A/Solomon Islands/3/2006-like in their reactivity patterns. Ferret sera raised to the Clade 2C viruses (A/Malaysia/213/2008 or A/Guam/1/2008) did not give broarder coverage compared to A/Brisbane/59/2007 antisera. Clade 2C viruses from South East Asia were also well inhibited with ferret sera toA/Brisbane/59/2007 (Tables 3.1, 3.3, 3.4 & 3.5 in Appendix 3). In addition, sequence analysis of the A(H1) HA-1 region of the haemagglutinin indicated that viruses fell into 2 major clades termed clades 2B and 2C. The majority of viruses from Australia, South Africa and recent viruses fell almost exclusively into the clade 2B while those from some South East Asian countries (eg. Malaysia) and some isolated earlier in 2008 fell into clade 2C. The oseltamivir resistant A(H1N1) viruses fell into the clade 2B viruses, except for one 2007 Cambodian virus (Figure 3.2 in Appendix 3). A total of 119 neuraminidase (N1) genes were sequenced. Genetic groupings for the NA were similar to the HA genes with the same viruses falling into Clade 2B or 2C (Figure 3.3 in Appendix 3). Furthermore, vaccines containing influenza A/Brisbane/59/2007 (H1N1) antigen stimulated postimmunization production of antibodies to HA at titres >= 40 to the influenza A(H1N1) vaccine virus in the sera of 72% of adults and 58% of elderly people. When the sera were tested against recent isolates, the corresponding proportions were similar. Furthermore, the average postimmunisation geometric mean HI titres to the vaccine virus and recent isolates were similar (WER 83(41), and Tables 3.8 and 3.9 in Appendix 3).

In summary, influenza A(H1N1) viruses were associated with outbreaks in southern hemisphere countries. In HI tests, the majority of isolates were antigenically similar to A/Brisbane/59/2007-like strain. Current vaccines containing A/Brisbane/59/2007 antigen stimulated HA antibodies against recent A(H1N1) influenza isolates, which were of similar titre and frequency to those against the vaccine virus. Based on all epidemiological, antigenic, genetic and serological data, the WHO consultation recommended vaccines containing a A/Brisbane/59/2007 (H1N1)–like strain. The AIVC accepts this recommendation.

2.2. Influenza A H3N2

Influenza A(H3N2) has frequently been associated with severe disease and excess mortality in high-risk groups. This subtype has also shown the greatest tendency for antigenic drift as illustrated by the frequency of vaccine formulation changes recommended by the WHO and the Australian Influenza Vaccine Committee (Table 1).

The Melbourne WHOCC has analysed 436 A(H3N2) isolates from 11 countries since January 2007. These viruses made up the majority (40.2%) of all viruses analysed at the Centre. Approximately 20% of A(H3N2) viruses analysed over this period had reduced activity (8

fold or greater) to ferret sera against A/Brisbane/10/2007 (egg derived virus). A(H3N2) viruses were reacted with ferret sera against A/Brisbane/10/2007. HI assays in Tables 4.1, 4.3, 4.4 and 4.5 were performed at the Melbourne WHOCC Centre. In addition, HA gene phylogenetic analysis of 2008 A(H3N2) viruses sequenced showed that most viruses were broadly A/Brisbane/10/2007-like. Within this broad group minor amino acid changes were seen especially at the 173 amino acid position. The majority of Australian, New Zealand, Thailand and Singapore 2008 viruses fell into the 173Q group while smaller numbers had either the 173N or 173E change. Sequence analysis of the N2 NA gene from 36 viruses analysed in 2008 showed that the most recent viruses grouped in a similar manner to their HA patterns with the majority having I215V change in the N2 as well as the K173Q change in their HA gene (Figures 4.2 and 4.3 in Appendix 4). Furthermore, vaccines containing influenza A/Brisbane/10/2007 (H3N2)-like antigens stimulated postimmunization production of antibodies to HA at titres >= 40 to the vaccine virus in the sera of 76% of adults and 80% of elderly people. When sera were tested against recent isolates, the corresponding proportions were somewhat lower: 63% of adult and 61% of elderly people. However, the average postimmunization geometric mean HI titres to the vaccine virus and recent isolates were similar (WER 83(41), and Tables 4.7 and 4.8 in Appendix 4).

In summary, influenza A(H3N2) viruses were associated with widespread outbreaks in many southern hemisphere countries including New Zealand. In HI tests, the majority of isolates were antigenically similar to A/Brisbane/10/2007-like strain. Current vaccines containing the A/Brisbane/10/2007 antigen stimulated HA antibodies against recent influenza A(H3N2) isolates that were similar in titre and frequency than to the vaccine virus. Based on all epidemiological, antigenic, genetic and serological data, the WHO Consultative Group recommended an A/Brisbane/10/2007 (H3N2)-like strain. AIVC accepts this recommendation.

2.3. Influenza B

Two distinct lines of influenza B have co-circulated in many countries during recent years. This dates from the late 1980's when the B/Panama/45/90 variant of influenza B was first observed. This strain and its further variants-Yamagata lineage (most recently representative strain-B/Florida/4/2006) spread worldwide whereas strains of the previous B/Victoria/2/87-like viruses continued to circulate in Asia and subsequently underwent independent evolution as an antigenically distinct lineage (most recent representative strain-B/Malaysia/2504/2004). For reasons not wholly understood, these remained geographically restricted to Asia until 2001. In 2002 the B/Malaysia/2504/2004-like strains were the predominant viruses worldwide.

Both recent B/Victoria-like strains (B/Malaysia/2504/2004 is the current reference strain) and B/Yamagata-like strains (B/Florida/4/2006 is the current reference strain) continued to be isolated worldwide in 2008. Varying proportions of the two lineages were seen in many countries with B/Yamagata lineage strains predominating in New Zealand and Australia in early winter season (June/July) and B/Victoria lineage viruses predominating in late winter season (August/September) in these two countries.

529 influenza B isolates were received in 2008 at the Melbourne WHOCC from 13 countries (49% of total isolates). The majority of isolates (66%) were typed as B/Yamagata-like but reacted poorly with ferret sera raised against egg grown B viruses of this lineage. This is partially due to changes in the egg grown B viruses where there is a loss of an important glycosylation site (N196D) which affects the antigenicity of the virus. Cell grown

B/Florida/4/2006-like (e.g. A/Brisbane/9/2008) react better with some recent cell grown viruses. The remaining 34% of B viruses were of the B/Victoria-like lineage and were moderately well covered by ferret sera against recent B/Victoria-like lineage viruses such as B/Victoria/304/2006 but also suffer from the reduced reactivity seen with ferret sera generated to egg adapted viruses. HI assays in Tables 5.1, 5.4 and 5.5 were performed at the Melbourne Centre. In addition, sequence analysis of the HA1 gene of recent isolates showed that recent isolates fell into one of the 2 major lineages of B viruses (B/Victoria/2/87 or B/Yamagata/16/88). 2008 viruses sequenced from the B/Yamagata line fell into one of 3 groups; either B/Florida/4/2006-like (Group 1) with a change at G230S or B/Brisbane/3/2007-like (Group 2) with a change at P108A or B/Bangladesh/3333/2007-like (Group 3) with a S150I change. The majority of viruses fell into Group 3. The B/Victoria lineage viruses showed little drift from the current reference vaccine virus B/Malaysia/2506/2004 except for recent Australian and New Zealand viruses which formed a distinct subclade with 4 amino acid changes (N75K, V146I, N165K, S172P). All 45 B viruses analysed in 2008 had an NA sequence which can be divided into 2 subgroups that were similar to B/Florida/4/2006 or B/Malaysia/2506/2004. Both subgroups showed continued genetic drift (Figures 5.2, 5.3, 5.4 & 5.5, & Table 5.8 in Appendix 5). Furthermore, vaccines containing influenza B/Florida/4/2006 antigen stimulated postimmunization production of antibodies to HA at titres >= 40 to the vaccine virus in the sera of 73% of adults and 58% of elderly people. When the sera were tested against recent B/Florida/4/2006 isolates (B/Yamagata lineage virus), When the sera were tested against recent B/Florida/4/2006-like isolates (B/Yamagata/16/88 lineage), the corresponding proportions were similar. When sera were tested against recent B/Malaysia/2506/2004-like isolates (B/Victoria/2/87 lineage), the corresponding proportions were lower: 49% of adults and 36% of elderly subjects. The average postimmunization geometric mean HI titres to recent B/Florida/4/2006-like isolates were similar to those against the vaccine virus, but the average postimmunization geometric mean HI titres were somewhat lower to recent B/Malaysia/2506/2004-like isolates than to the vaccine virus (reductions of 47% in adults and 49% in elderly subjects) (WER 83(41), Tables 5.7 to 5.8 in Appendix 5).

In summary, influenza B outbreaks were reported in southern hemisphere countries including New Zealand. The majority of recent isolates was antigenically similar to B/Florida/4/2006 (B/Yamagata/16/88 lineage). B/Yamagata lineage strains predominated in New Zealand and Australia in early winter season (June/July) and B/Victoria lineage viruses predominated in late winter season (August/September) in these two countries. Current vaccines containing B/Florida/4/2006 antigen stimulated HA antibodies that were similar in titre to recently isolated B/Florida/4/2006 – like viruses. Based on all epidemiological, antigenic, genetic and serological data, the WHO consultation recommended a B/Florida/4/2006–like strain. The AIVC accepts this recommendation.

3. SUMMARY

It is recommended that the influenza vaccine formulation for New Zealand in 2009 is:

- A(H1N1) an A/Brisbane/59/2007 (H1N1) - like strain
- A(H3N2) an A/Brisbane/10/2007 (H3N2) - like strain
- B a B/Florida/4/2006 - like strain

3.1. Explanation of "like" Strains Suitable for Inclusion in Vaccine

In the past, some strains of influenza recommended for inclusion in the vaccine formulation have been unsuitable vaccine candidates due to poor growth potential with resulting low yields or poor serological responses in vaccinees. Under the "like" strain concession in the vaccine recommendation, an antigenically similar strain has been substituted which has the qualities lacking in the prototype strain.

The Australian Influenza Vaccine Committee (AIVC) considered information on international surveillance by WHO, recent data from Australia, New Zealand, South Africa and Argentina on epidemiology and strain characterisation, and the recommendations of the WHO annual consultation on the composition of influenza vaccine for the Southern Hemisphere, held in Geneva on 17-19 September.

The Committee agreed to adopt the September WHO recommendations. The influenza vaccine components for year 2009 season should contain the following:

A (H1N1):	an A/Brisbane/59//2007 (H1N1) - like strain,	15 µg HA per dose
A (H3N2):	an A/Brisbane/10/2007 (H3N2) - like strain,	15 µg HA per dose
B:	a B/Florida/4/2006 - like strain,	15 µg HA per dose

The following viruses are suitable vaccine strains:

- A/Brisbane/59/2007 (H1N1) (IVR-148)
- A/Brisbane/10/2007 (H3N2) (IVR-147) or A/Uruguay/716/2007 (NYMC X-175C)
- B/Florida/4/2006 or B/Brisbane/3/2007
- The SRID reference standard reagents for A/Brisbane/59/2007 (H1N1) (IVR-148) strain are available from TGA or NIBSC (UK).
- The SRID reference standard reagents for A/Brisbane/10/2007 (H3N2) (IVR-147) and B/Brisbane/3/2007 are available from TGA.
- The SRID reference standard reagents for A/Uruguay/716/2007 (NYMC X-175C) and B/Florida/4/2006 are available from NIBSC.

4. ACKNOWLEDGEMENTS

The WHO National Influenza Centre, ESR

Virus Laboratories in Auckland, Waikato and Christchurch Hospitals

Participants in the National Influenza Surveillance Programme

WHO Collaborating Centre for Influenza, CSL, Melbourne

National Institute of Communicable Diseases (NICD), Johannesburg, RSA

Australian Influenza Vaccine Committee

Regional Public Health in Wellington

Table 1. Influenza Vaccine Recommendations for New Zealand, 1991-2009

Formulation Recommendations		Vaccine used for	A H3N2	A H1N1	B
NZ & WHO*	2008	2009	A/Brisbane/10/2007	A/Brisbane/59/2007	B/Florida/4/2006
NZ & WHO*	2007	2008	A/Brisbane/10/2007	A/Solomon Islands/3/2006	B/Florida/4/2006
NZ & WHO*	2006	2007	A/Wisconsin/67/2005	A/New Caledonia/20/99	B/Malaysia/2506/2004
NZ & WHO*	2005	2006	A/California/7/2004	A/New Caledonia/20/99	B/Malaysia/2506/2004
NZ & WHO*	2004	2005	A/Wellington/1/2004	A/New Caledonia/20/99	B/Shanghai/361/2002
NZ & WHO*	2003	2004	A/Fujian/411/2002	A/New Caledonia/20/99	B/Hong Kong/330/2001
NZ & WHO*	2002	2003	A/Moscow/10/99	A/New Caledonia/20/99	B/Hong Kong/330/2001
NZ & WHO*	2001	2002	A/Moscow/10/99	A/New Caledonia/20/99	B/Sichuan/379/99
NZ	2000	2001	A/Sydney/5/97	A/New Caledonia/20/99	B/Beijing/184/93
WHO*	2000	2001	A/Moscow/10/99	A/New Caledonia/20/99	B/Beijing/184/93
NZ & WHO*	1999	2000	A/Sydney/5/97	A/Beijing/262/95	B/Beijing/184/93
NZ	1998	1999	A/Sydney/5/97	A/Bayern/7/95	B/Beijing/184/93
WHO**	1997-98		A/Wuhan/359/95	A/Bayern/7/95	B/Beijing/184/93
NZ	1997	1998	A/Wuhan/359/95	A/Texas/36/91	B/Beijing/184/93
WHO**	1996-97		A/Wuhan/359/95	A/Singapore/6/86***	B/Beijing/184/93
NZ	1996	1997	A/Johannesburg/33/94	A/Texas/36/91	B/Beijing/184/93
WHO**	1995-96		A/Johannesburg/33/94	A/Singapore/6/86	B/Beijing/184/93
NZ	1995	1996	A/Guangdong/25/93	A/Texas/36/91	B/Panama/45/90
WHO**	1994-95		A/Shangdong/9/93	A/Singapore/6/86	B/Beijing/184/93
NZ	1994	1995	A/Beijing/32/92	A/Texas/36/91	B/Panama/45/90
WHO**	1993-94		A/Beijing/32/92	A/Singapore/6/86	B/Panama/45/90
NZ	1993	1994	A/Shanghai/24/90	A/Texas/36/91	B/Panama/45/90
WHO**	1992-93		A/Beijing/353/89	A/Singapore/6/86	B/Yamagata/16/88 or B/Panama/45/90
NZ	1992	1993	A/Beijing/353/89	A/Victoria/36/88	B/Yamagata/16/88 or B/Panama/45/90
WHO**	1991-92		A/Beijing/353/89	A/Singapore/6/86	B/Yamagata/16/88 or B/Panama/45/90
NZ	1991	1992	A/Beijing/353/89	A/Victoria/36/88	B/Yamagata/16/88
WHO**	1990-91		A/Guizhou/54/89	A/Singapore/6/86	B/Yamagata/16/88

* WHO recommendations are for the Southern Hemisphere winter
* * WHO recommendations are for the Northern Hemisphere winter
*** USA selected the variant A/Texas/36/91

Table 2. Thresholds Used to Describe Influenza Activity*

Term used		Consultation rate (per 100,000 population)
Baseline		<= 49
Normal seasonal activity	low	50-99
	moderate	100-149
	high	150-249
higher than expected		250-399
severe epidemic		>= 400

*Note: This was published in *New Zealand Public Health Report 2001, 8(1):9-12* "Influenza surveillance and immunisation in New Zealand, 1990-1999"

Figure 1. Weekly Consultation Rates for Influenza-like Illness in New Zealand, 2006, 2007, 2008

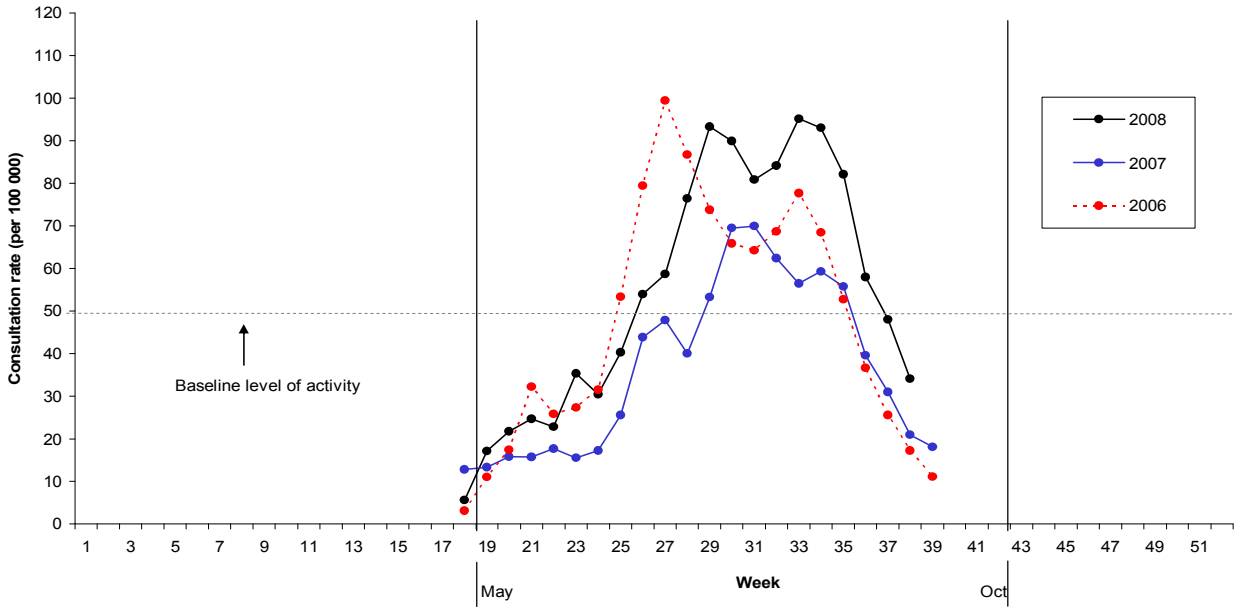


Figure 2. Weekly Consultation Rates for Influenzea-like Illness in New Zealand 1992-2008

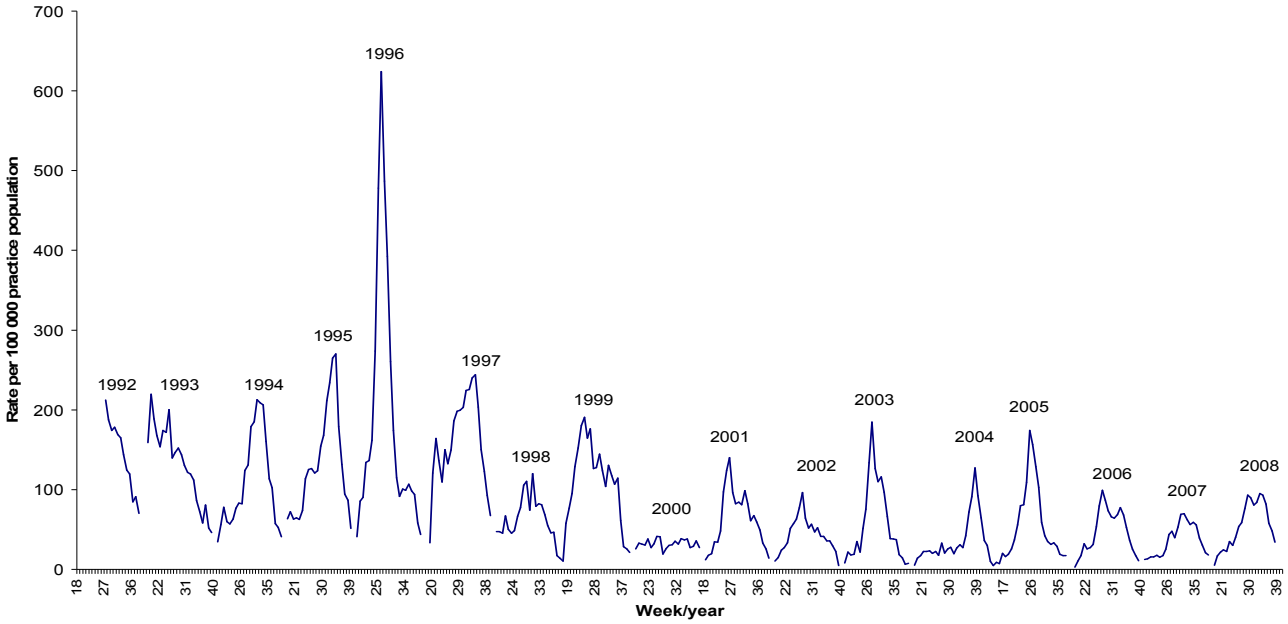


Figure 3. Total Influenza Isolates by Surveillance Type and Week Specimen Taken, 2008

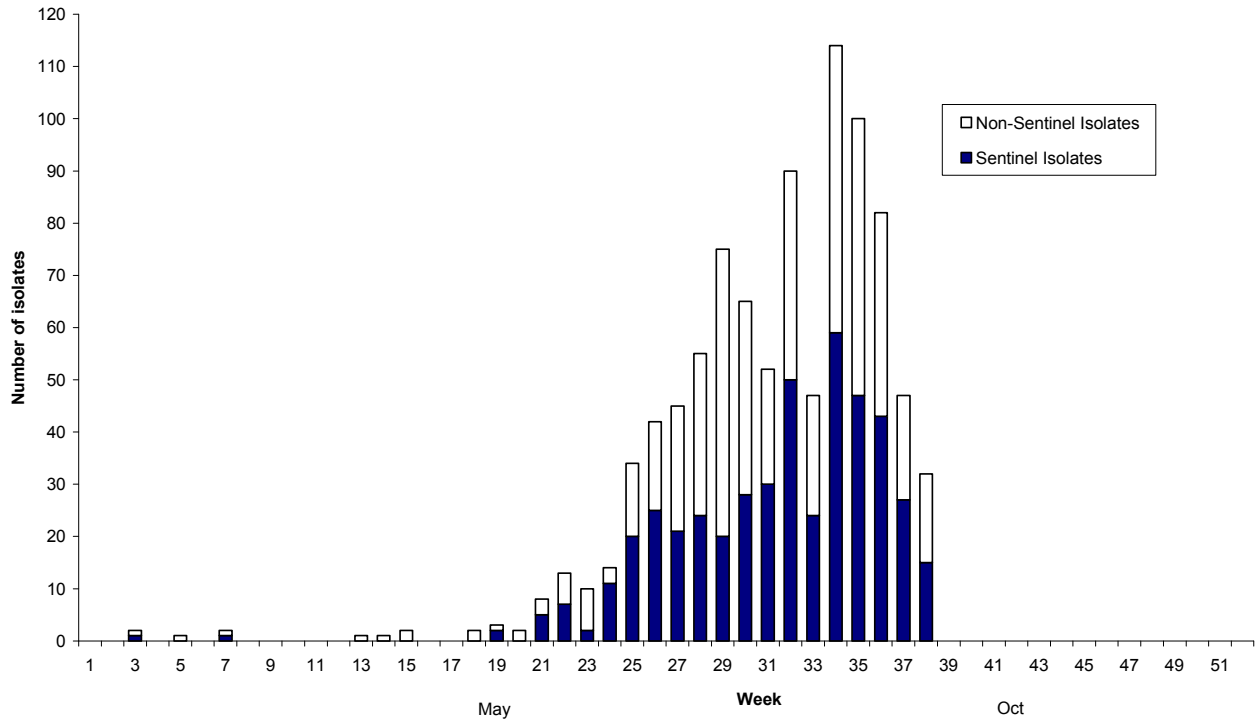


Figure 4. Total Influenza Isolates by Type and Week Specimen Taken, 2008

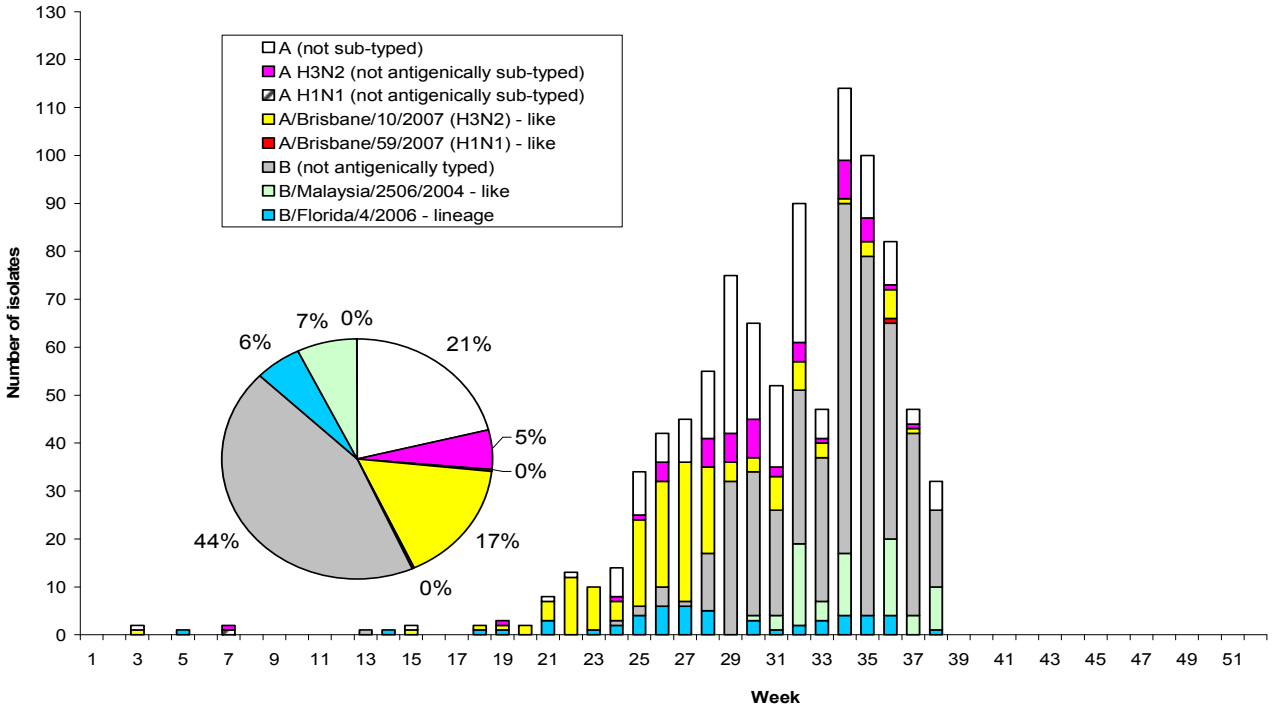


Figure 5. Total Influenza Virus Isolates by Type and Week Specimen Taken, 2008

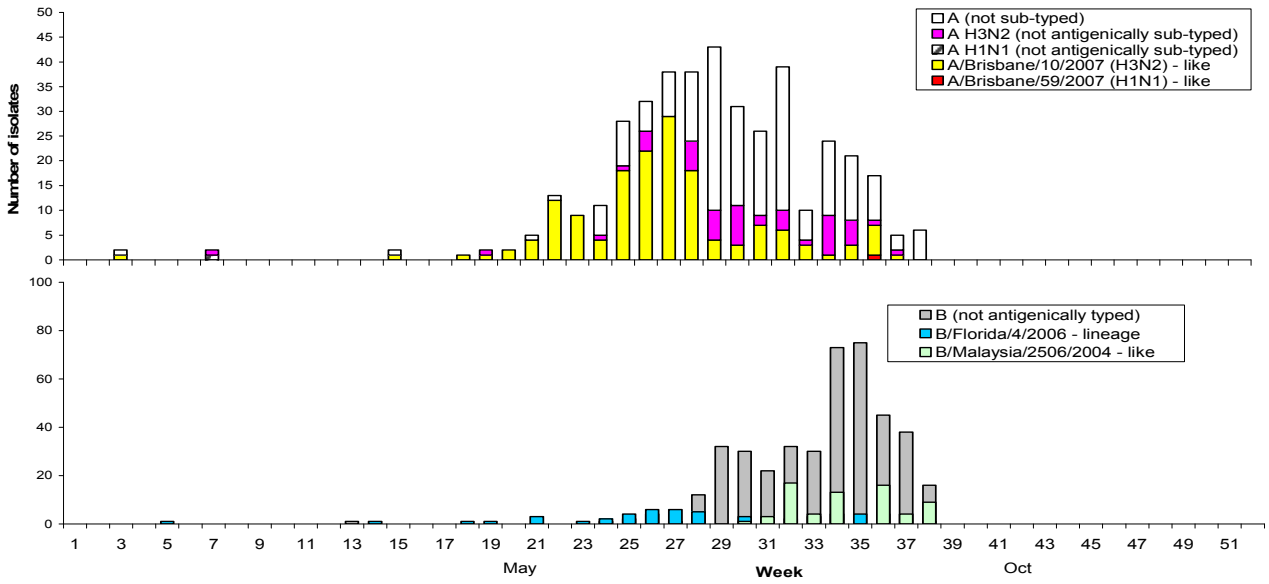
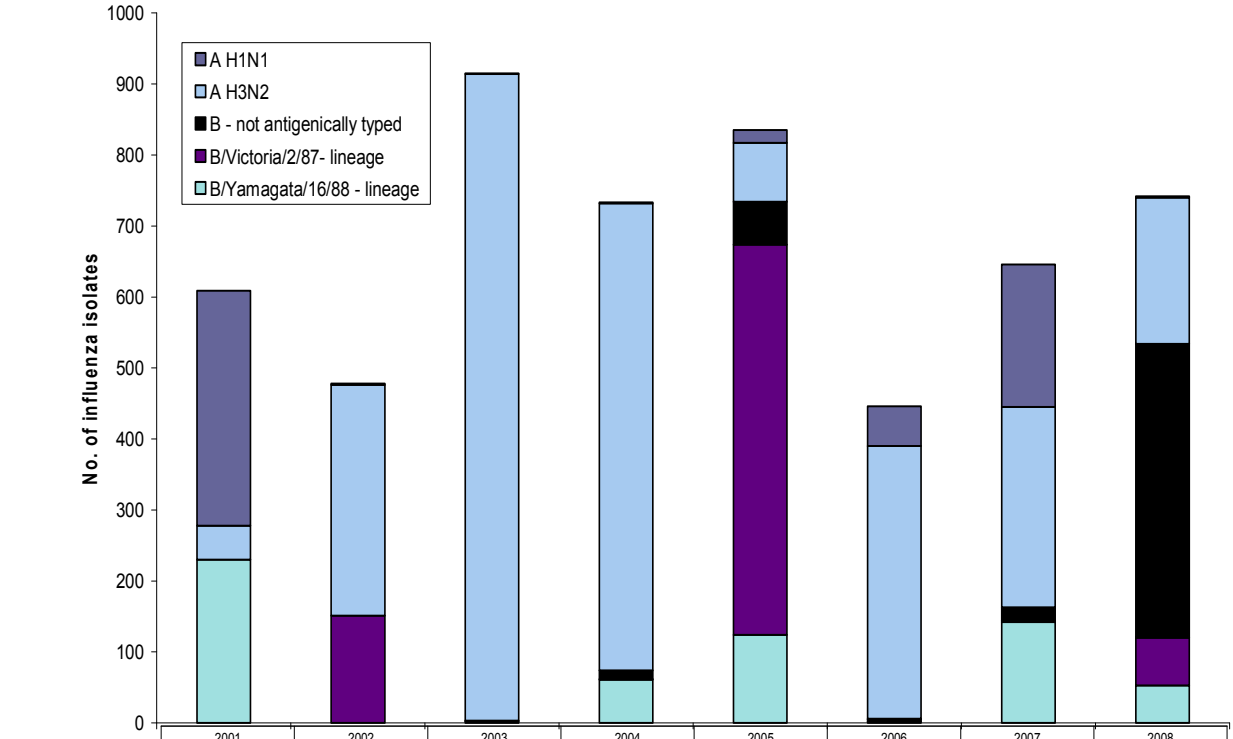


Figure 6. Influenza Isolates by Type, 2001-2008



	2001	2002	2003	2004	2005	2006	2007	2008
A H1N1	54.4%	0.4%	0.1%	0.1%	2.2%	12.6%	31.1%	0.3%
A H3N2	7.9%	68.0%	99.6%	89.8%	9.9%	86.1%	43.7%	27.8%
B - not antigenically typed	0.0%	0.0%	0.0%	1.6%	7.2%	0.2%	2.9%	55.8%
B/Yamagata/16/88 - lineage	37.8%	0.0%	0.2%	8.3%	14.9%	0.4%	22.0%	7.1%
B/Victoria/2/87- lineage	0.0%	31.6%	0.1%	0.1%	65.9%	0.7%	0.3%	9.0%

Figure 7. Comparison of Sentinel and Laboratory-based Surveillance by Age Group, 2008

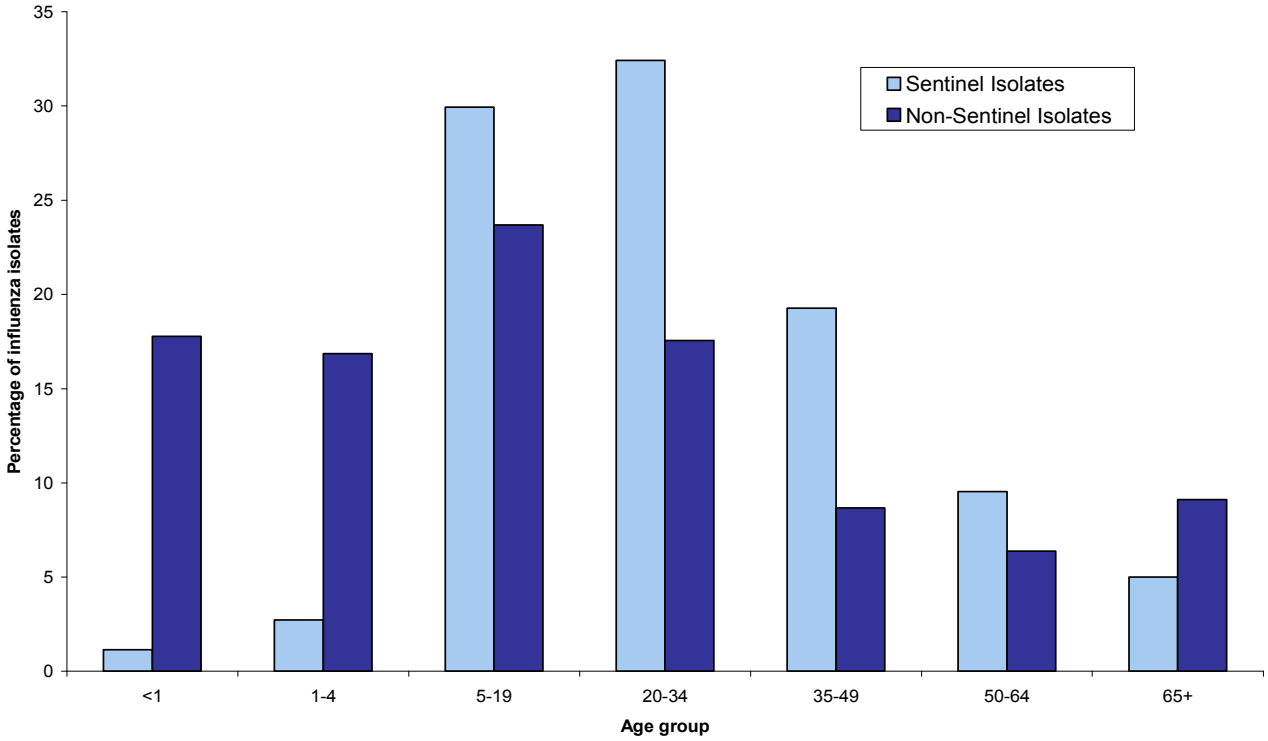


Table 3. Vaccine Breakthrough Cases by Age Groups, 2008

Age Group	A H3N2 (not antigenically sub-typed)	A/Brisbane/10/2007 (H3N2) - like	B (not antigenically typed)	B/Florida/4/2006 - like	B/Malaysia/2506/2004-like	Total
1-4 yrs	0	1	0	0	0	**1**
5-19 yrs	1	0	2	0	0	**3**
20-34 yrs	1	1	1	0	2	**5**
35-49 yrs	0	0	1	0	1	**2**
50-64 yrs	1	0	0	1	0	**2**
65 + yrs	3	3	1	0	1	**8**
Total	**6**	**5**	**5**	**1**	**4**	**21**

APPENDIX 1

The Australia Influenza Vaccine Committee (AIVC) meeting was convened at 1:30 pm on 8 October 2008 in Conference Room 1, TGA, Symonston, Canberra, when overseas participants in the teleconference were connected by Telstra. The New Zealand representative attended the meeting in Canberra.

Composition of the AIVC Committee (2008)

Chairperson: Dr Gary Grohmann, TGAL, TGA
Secretary: Ms Thérèse Marengo, TGAL, TGA

Committee Members:

Dr Gary Grohmann, OLSS, TGA (**Chairperson**)
Prof Anne Kelso, WHO Collaborating Centre for Reference and Research on Influenza
Dr Ian Barr, WHO Collaborating Centre for Reference and Research on Influenza
Prof Ian Gust, Melbourne University
Prof Greg Tannock, RMIT
Dr Mike Catton, VIDRL
Dr Heath Kelly, VIDRL
Dr David Smith, UWA
Dr Ruth Lopert, PMA, TGA
Dr Grahame Dickson, OPM, TGA
Dr Leslee Roberts, OHP, DoHA
Dr Alan Hampson, Interflu Pty Ltd
Dr Sue Huang, CDI, ESR, NZ
*Prof Barry Schoub, National Institute for Communicable Diseases, SA
*Dr Terry Besselaar, National Institute for Communicable Diseases, SA
Dr Tania Dalla Pozza, OLSS, TGA (**Secretary**)

Observers:

Mr David Ryan, CSL Ltd
Mr Peter Schoofs, CSL Ltd
Mr William Cracknell, CSL Ltd
Ms Christine Wadey, CSL Ltd
Ms Alicia Ham, Sanofi Pasteur
Ms Crissa Kyriazis, GlaxoSmithKline Australia Pty Ltd
Mr Tony Wilson-Williams, Solvay Biosciences Pty Ltd
Mr George Weber, Novartis
Dr Maria Fallon, Baxter
Ms Vivienne Christ, A/Director OLSS, TGA
Dr Nick Medveczky, OLSS, TGA
Mr Chris Rolls, OLSS, TGA
Ms Derna Waters, OLSS, TGA
Ms Pearl Bamford, OLSS, TGA

* Participating by telephone

APPENDIX 2

ISOLATES RECEIVED FOR ANALYSIS AT THE AUSTRALIAN WHO COLLABORATING CENTRE

APPENDIX 3

INFLUENZA A (H1N1)

APPENDIX 4

INFLUENZA A (H3N2)

APPENDIX 5

INFLUENZA B

APPENDIX 6

WHO RECOMMENDATION FOR INFLUENZA VACCINES