

Incidence of pandemic (H1N1) 2009 influenza infection in children and pregnant women during the 2009 influenza season in Western Australia — a seroprevalence study

Gary K Dowse, David W Smith, Heath Kelly, Ian Barr, Karen L Laurie, Anthony R Jones, Anthony D Keil and Paul Effler

The first influenza pandemic of the 21st century has raised many questions about the appropriateness of the public health response. Although a relatively mild disease in most people, there have been over 18 000 deaths attributed to the pandemic (H1N1) 2009 influenza virus worldwide since it emerged.¹ During the 2009 Australian winter, the median age of infection, based on laboratory-confirmed cases, was 21 years, with higher median ages for hospitalisation (31 years), intensive care treatment (44 years) and death (53 years).² Overall, mortality from laboratory-confirmed infection and estimates of the case-fatality rate have been lower than anticipated.^{3–5}

Accurate estimates of the population incidence of infection are critical to assessing pathogenicity of the pandemic virus, providing context to indicators of pandemic severity (including rates of hospitalisation, intensive care unit [ICU] admission and death associated with confirmed infection), and estimates of the clinical attack rate and case-fatality rate.^{4,5} Serosurveys measuring antibodies to pandemic (H1N1) 2009 influenza virus capture both people with asymptomatic infection and those who were ill but did not seek medical attention, allowing an estimate of the true proportion of the population infected.

We report the frequency of protective antibody levels determined in two cross-sectional serosurveys using convenience samples of blood specimens collected before and after circulation of pandemic (H1N1) 2009 influenza. We provide estimates of the cumulative incidence of infection (“infection rate”) in children and pregnant women during the 2009 winter season in Western Australia. We targeted these groups because children had the highest notification and hospitalisation rates associated with pandemic influenza and pregnant women were at increased risk of more serious disease.^{6,7} These data improve our understanding of the impact of the pandemic virus, inform understanding of disease activity during 2010 and

ABSTRACT

Objective: To determine antibody levels and estimate incidence of infection with pandemic (H1N1) 2009 influenza in children and pregnant women during the 2009 winter in Western Australia.

Design, setting and participants: Two cross-sectional serosurveys using stored specimens collected for unrelated pathology testing, from before and after (3 August to 30 November 2009) circulation of the pandemic virus, and before commencement of the pandemic vaccination program. Specimens were from three groups: children aged 1–4 years, older children and teenagers aged 5–19 years, and pregnant women aged 21–45 years. The groups were geographically representative of the WA population.

Main outcome measures: Reactivity against pandemic (H1N1) 2009 and seasonal A(H1N1) influenza viruses measured using haemagglutination inhibition (HI) assays.

Results: Antibody titres were determined for 648 individuals in the prepandemic period and 736 in the postpandemic period. In the prepandemic period, HI titres ≥ 40 against the pandemic virus were found in 0 (95% CI, 0.0%–1.6%) children aged 1–4 years, 8.3% (95% CI, 5.3%–12.7%) of older children and teenagers, and 4.5% (95% CI, 2.4%–8.3%) of pregnant women. In postpandemic specimens collected from 1 September 2009 (when influenza activity had declined to near-baseline levels), estimated infection rates (subtracting prepandemic levels) were 25.4% (95% CI for difference, 18.6%–33.4%) in 1–4-year-old children, 39.4% (95% CI, 29.8%–48.5%) in older children and teenagers, and 10.2% (95% CI, 4.1%–17.1%) in pregnant women.

Conclusions: A quarter of preschool children and about 40% of school-aged children and older teenagers had serological evidence of pandemic influenza infection during winter 2009, indicating high levels of mild or asymptomatic infection. The infection rate in pregnant women was much lower. The high infection rates in children help explain the reduced impact of the pandemic virus during the 2010 winter. Augmented by vaccination, there should be sufficiently high levels of immunity in the Australian population to significantly reduce the impact of the virus in future influenza seasons.

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estimates for future years, and guide policy on mitigation strategies, including vaccination.

METHODS

Background

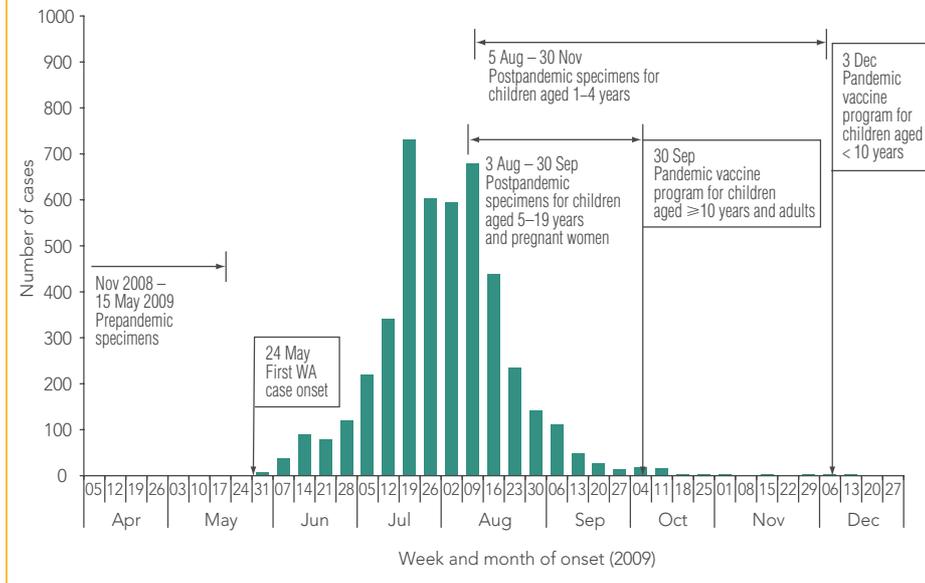
WA is a geographically large state with a population of 2.2 million, of whom 1.6 million (72.6%) live in the capital, Perth. The first person in WA with laboratory-confirmed pandemic (H1N1) 2009 influenza had symptom onset on 24 May 2009, after returning from overseas. Local transmission was established by late June 2009; the epidemic peaked in mid to late July; and activity had declined to near-baseline levels by mid September. This time period was

similar to that expected for seasonal influenza circulation. Between 24 May and 31 December 2009, there were 5016 laboratory-confirmed and typed influenza cases, of which 91.5% were pandemic A(H1N1) 2009, 1.9% were seasonal A(H1N1), 5.6% were A(H3N2) and 1% were influenza B (unpublished data available from authors on request).

Study sample

WA has a single large public health laboratory system — PathWest Laboratory Medicine WA — that provides a high proportion of diagnostic services throughout the state. Specimens were selected from samples received at PathWest for a range of routine diagnostic serological tests. If the patient

1 Laboratory-confirmed cases of pandemic (H1N1) 2009 influenza in Western Australia, and dates of prepandemic and postpandemic specimen collection and commencement of vaccination program



was undergoing testing for respiratory infection, the samples were excluded, as were those with inadequate residual volume.

Eligible specimens were those collected:

- between November 2008 and 15 May 2009, before the entry of the pandemic virus into WA (prepandemic period); and
- between 3 August and 30 November 2009, after the pandemic peak and before the commencement of the pandemic vaccination program for the relevant study group (postpandemic period) (Box 1).

Based on an estimated infection rate of 20% in the target groups, with 5% precision for the 95% confidence interval, we determined an optimal sample size of 246 for the postpandemic period in each of three study groups: preschool children (aged 1–4 years), school-aged children and older teenagers (aged 5–19 years), and pregnant women (aged 21–45 years). An attempt was made to retrieve similar numbers for the prepandemic period. Quotas were calculated so that specimens selected for each study group and period matched as closely as possible the geographical distribution of the WA population, determined by postcode allocation to major administrative regions. Specimens were selected sequentially from the laboratory database until quotas were filled. It was not possible to fill all period quotas, and the final sample comprised 1389 specimens collected from 400 children aged 1–4 years (229 prepandemic; 171 postpandemic),

499 children and older teenagers aged 5–19 years (218 prepandemic; 281 postpandemic), and 490 pregnant women (202 prepandemic; 288 postpandemic).

The selected sera, stored at -20°C until retrieval, were thawed and a 200 μL sample of each was transferred to a tube labelled with the study code. Age, post-code and collection date were linked to the study code. Samples were refrozen, stored at -20°C and transported on dry ice to the World Health Organization Collaborating Centre for Reference and Research on Influenza in Melbourne for testing.

Haemagglutination inhibition assays

Reactivity of sera against pandemic (H1N1) 2009 and seasonal A(H1N1) influenza viruses was measured using haemagglutination inhibition (HI) assays.⁸ Egg-grown A/California/7/2009 virus was purified by sucrose gradient, concentrated and inactivated with β -propiolactone to create an influenza zonal pool preparation (a gift from CSL Ltd, Melbourne). Sera were pre-treated with receptor-destroying enzyme (RDE [II], Denka Seiken, Tokyo, Japan) and tested as described previously.⁹ Titres were expressed as the reciprocal of the highest dilution of serum at which haemagglutination was prevented. HI titres ≥ 40 were regarded as significant, based on accepted criteria for determining immunity and vaccine responses.¹⁰

Statistical analysis

Analyses were performed using SPSS version 17 (SPSS Inc, Chicago, Ill, USA). For calculation purposes, HI titres < 10 were given a value of 5. The Pearson correlation coefficient (r) between \log_{10} -transformed titres against the pandemic (H1N1) 2009 and seasonal A(H1N1) viruses was investigated for each study period. We determined geometric mean titres (GMTs) and used analysis of variance to test differences in GMT. Reverse cumulative distribution curves were plotted comparing prepandemic and postpandemic HI titres. Finally, the proportion of subjects with HI titres ≥ 40 was determined for each group and period, as well as the difference between periods (an estimate of infection rate), and 95% confidence intervals were calculated using methods described by Newcombe.¹¹

For some analyses, the postpandemic samples were subdivided into those collected from 3 to 31 August 2009, and those collected from 1 to 30 September (5–19-years age group and pregnant women) or from 1 September to 30 November 2009 (1–4-years age group). This enabled us to more clearly examine titres in the period when pandemic virus transmission had reached near-baseline levels.

Ethics approval

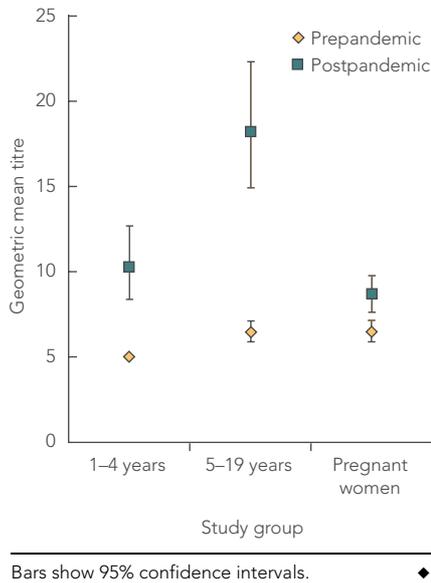
The human research ethics committees of the WA Department of Health, the Child and Adolescent Health Service and the Women and Newborn Health Service approved the study.

RESULTS

Five specimens were excluded because of non-specific haemagglutination (titres ≥ 40) even after red blood cell absorption, leaving 1384 study subjects. The Perth metropolitan area was slightly under-represented, both overall (62.4% of the study population v 77.6% of the state population) and within each study group. However, there was no difference in the regional representation for any study group between the prepandemic and postpandemic periods.

There was a significant increase in the GMT against pandemic (H1N1) 2009 virus in the postpandemic period compared with the prepandemic period for each study group (Box 2). GMT also varied significantly between study groups in the prepandemic period ($F = 15.5$; $P < 0.001$), largely

2 Geometric mean titres by haemagglutination inhibition assay in the pre-pandemic and post-pandemic periods, by study group



reflecting the lower GMT for the 1–4-years age group (5.1 [95% CI, 5.0–5.1]) compared with the similar GMTs for the 5–19-years age group (6.5 [95% CI, 5.9–7.1]) and pregnant women (6.5 [95% CI, 5.9–7.1]). In the postpandemic period, GMT for the 5–19-years age group (18.2 [95% CI, 14.9–22.3]) was significantly higher than that for the 1–4-years age group (10.3 [95% CI, 8.4–12.7]) and pregnant women (8.6 [95% CI, 7.6–9.7]) ($F = 21.2$; $P < 0.001$).

Reverse cumulative distribution curves comparing pre-pandemic and post-pandemic HI titres are shown in Box 3. For both the 1–4-years and 5–19-years age groups, there was a stepwise increase in the cumulative proportion of subjects with HI titres indicating exposure to the pandemic virus in the August and September–November periods compared with the pre-pandemic period. For pregnant women, there was little difference between the curves for August and September.

In the pre-pandemic period, HI titres ≥ 40 against the pandemic virus were found in 0 (95% CI, 0–1.6%) 1–4-year-olds, 8.3% (95% CI, 5.3%–12.7%) of 5–19-year-olds, and 4.5% (95% CI, 2.4%–8.3%) of pregnant women (Box 4). In the postpandemic period, the proportion of subjects with HI titres ≥ 40 increased significantly for each study group for all sample-collection periods.

When the postpandemic period was restricted to specimens collected from 1 September, the estimated infection rate during winter (subtracting pre-pandemic levels) was 25.4% (95% CI for difference, 18.6%–33.4%) in the 1–4-years age group, 39.4% (95% CI, 29.8%–48.5%) in the 5–19-years age group, and 10.2% (95% CI, 4.1%–17.1%) for pregnant women, indicating significantly higher infection rates for both 1–4-year-olds and 5–19-year-olds compared with pregnant women (Box 4). At the end of winter, 47.7% of 5–19-year-olds, 25.4% of 1–4-year-olds, and 14.7% of pregnant women had HI titres ≥ 40 against pandemic (H1N1) 2009.

We compared HI titres against the pandemic and seasonal H1N1 viruses to determine whether cross-reacting seasonal HI antibody was producing positive pandemic HI antibody results in our assay. There was only a weak positive correlation ($r = 0.14$; $P < 0.001$) between \log_{10} -transformed titres against the pandemic and seasonal viruses in the pre-pandemic period, and no correlation in the postpandemic period ($r = 0.07$; $P = 0.08$).

DISCUSSION

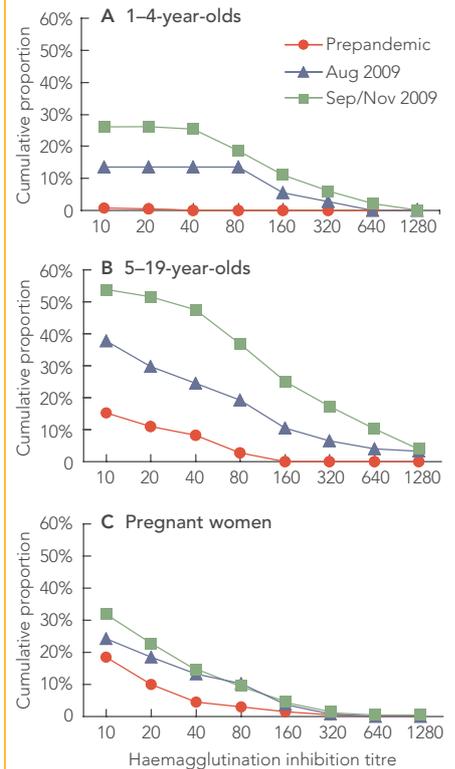
We estimate that pandemic (H1N1) 2009 influenza virus infected around 25.4% of children aged 1–4 years, 39.4% of children and teenagers, and 10.2% of pregnant women during the 2009 influenza season in WA. This is one of the first serological estimates of pandemic (H1N1) 2009 infection rates in a population over a complete influenza season, the first to target pregnant women, and one of the first to study children. The infection rate in children and teenagers was significantly higher than that in pregnant women.

A cohort study testing the same individuals before and after the influenza season, and defining exposure on the basis of a fourfold rise in the HI titre, would be the preferred method to determine pandemic virus infection rates. However, this was not possible given the unexpected emergence of the virus. Instead, we compared two cross-sectional samples, with specimens at each period retrieved opportunistically from residual sera stored after diagnostic testing for non-respiratory indications. There is no reason to believe that this method should confer significant bias to estimates of influenza infection, compared with estimates from a random population sample. Convenience sampling of residual diagnostic sera has been shown to produce similar esti-

mates of immunity to vaccine-preventable diseases in children to those obtained from random population samples.¹² Residual diagnostic sera are also used to evaluate vaccine programs in other countries.¹³

We believe our results are broadly representative of pandemic (H1N1) 2009 virus infection rates in WA. Although the Perth metropolitan area was slightly under-represented in our study sample compared with the state population, there was no difference in the regional representation for any study group, comparing pre-pandemic and post-pandemic periods. Moreover, while the study was not designed to look for regional differences, seroprevalence and HI titres did not vary by region of residence (data not shown). Given the similarity of epidemiological features of the 2009 pandemic

3 Reverse cumulative distribution curves of haemagglutination inhibition titres against pandemic (H1N1) 2009 influenza, by period of specimen collection and study group*



* August specimens were collected from 3 to 31 August 2009 for all three study groups. September–November specimens were collected from 1 to 30 September 2009 for 5–19-year-olds and pregnant women aged 21–45 years, and from 1 September to 30 November 2009 for 1–4-year-olds.

4 Prevalence of haemagglutination inhibition titres ≥ 40 in the pre-pandemic and post-pandemic periods, and estimated infection rates, by study group

Period	Children aged 1–4 years		Children and older teenagers aged 5–19 years		Pregnant women aged 21–45 years	
	No.	Proportion (95% CI)	No.	Proportion (95% CI)	No.	Proportion (95% CI)
Pre-pandemic	0/230	0 (0.0%–1.6%)	18/217	8.3% (5.3%–12.7%)	9/201	4.5% (2.4%–8.3%)
Post-pandemic						
August*	5/37	13.5% (5.9%–28.0%)	37/151	24.5% (18.3%–31.9%)	18/136	13.2% (8.5%–20.0%)
September onwards†	34/134	25.4% (18.8%–33.4%)	61/128	47.7% (39.2%–56.3%)	22/150	14.7% (9.9%–21.2%)
Estimated infection rate‡		25.4% (18.6%–33.4%)		39.4% (29.8%–48.5%)		10.2% (4.1%–17.1%)
Total post-pandemic§	39/171	22.8% (17.2%–29.7%)	98/279	35.1% (29.8%–40.9%)	40/286	14.0% (10.5%–18.5%)
Estimated infection rate¶		22.8% (16.9%–29.7%)		26.8% (19.9%–33.3%)		9.5% (4.3%–14.5%)

* Specimens collected from 3 to 31 Aug 2009 for all three study groups. † Specimens collected from 1 to 30 Sep 2009 for children and older teenagers aged 5–19 years and pregnant women; and from 1 Sep to 30 Nov 2009 for children aged 1–4 years. ‡ Difference in prevalence between September onwards and pre-pandemic periods. § Includes all specimens collected from 3 Aug 2009 onwards. ¶ Difference in prevalence between total post-pandemic (3 Aug 2009 onwards) and pre-pandemic periods. ◆

around Australia,⁶ our findings are likely to be broadly generalisable to Australia as a whole.

There was no evidence to suggest that infection with seasonal A(H1N1) influenza virus or vaccination against seasonal influenza, between May and November 2009, contributed to the increase in antibody titres against the pandemic virus. First, seasonal A(H1N1) influenza infection was very unlikely, as it comprised only 1.9% of isolates during the 2009 season. Second, there was a poor correlation between HI titres against the pandemic A/California/7/2009 virus and those against the A/Brisbane/59/2007 seasonal vaccine strain. Third, antibodies against the pandemic virus were not detected in 1–4-year-olds in the pre-pandemic period, even though WA ran a free two-dose seasonal influenza vaccination program for preschool children in 2008 and 2009, with an estimated coverage of at least 32%. Our data are consistent with the finding of Hancock and colleagues¹⁴ that antibodies produced in response to seasonal influenza vaccines provide little or no cross-protection against the pandemic virus.

In specimens collected from September to November 2009 in WA, estimated infection rates for pandemic influenza were remarkably similar to estimated rates in England following its intense “spring” epidemic wave in 2009. Using a similar study design, Miller and colleagues¹⁵ found an incidence of infection of 21.3% in children aged under 5 years (compared with 25.4% in WA), 42.0% in children aged 5–14 years (39.4% in children aged 5–19 years in WA), and 6.2% in adults aged 25–45

years (10.2% in pregnant women aged 21–45 years in WA). A French study of pregnant women aged 20–39 years, tested around November 2009, found a cumulative seroprevalence of elevated HI titres against pandemic H1N1 virus of 10.6%.¹⁶ These findings, along with recent estimates from other populations using various study designs,^{9,17,18} suggest that the arrival of the pandemic virus in modern urbanised and non-immune populations may have resulted in broadly similar infection rates in both the southern and northern hemispheres.

Annual seasonal influenza infection rates in preschool and school-aged children are generally high, ranging from around 10% to 40% in prospective studies, and children are regarded as the most important source of community-wide influenza transmission.^{19,21} Estimated infection rates for pandemic influenza in children during the 2009 winter in WA were at the upper end of rates observed previously for seasonal influenza.

Based on sentinel surveillance data, clinical attack rates for pandemic influenza were estimated to be about 1% in England (to November 2009)⁵ and 7.5% in New Zealand.⁴ The wide disparity between these estimated clinical attack rates and the serologically determined infection rates from our study and other studies^{9,15,17,18} suggests that the pandemic (H1N1) 2009 virus causes a substantial amount of asymptomatic or very mild infection. This is consistent with data from volunteers infected with seasonal influenza H1N1: a third were completely asymptomatic, while a further third had no fever.²² To properly understand the

pathogenicity of the pandemic (H1N1) 2009 virus, there is a need for prospective studies of the infection and clinical attack rates in the same population, with laboratory confirmation of infection.

Available data indicate that influenza vaccination in children may not only prevent childhood morbidity but also reduce school absenteeism and reduce the impact of influenza infection among adults.^{20,21,23} Disease modelling also suggests that vaccinating schoolchildren may be one of the most effective approaches to reducing the impact of both seasonal²⁴ and pandemic²⁵ influenza in the wider community. Hence, many countries, including Australia, targeted children for vaccination against pandemic influenza (H1N1) 2009.

The high incidence of pandemic virus infection in children during the 2009 southern hemisphere winter indicates that WA achieved at least partial herd immunity during the first wave. Community susceptibility would have been further reduced by vaccination programs in the latter part of 2009 and during 2010, even though uptake was not high.²⁶ These factors explain the reduced impact of the virus in the 2010 winter, and in the absence of significant antigenic drift or increased virus transmission or virulence, should significantly attenuate pandemic (H1N1) 2009 virus activity in future influenza seasons. Even so, for people vulnerable to more severe disease — including pregnant women, in whom our study found relatively low levels of exposure during 2009 — targeted vaccination should continue to be encouraged.

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COMPETING INTERESTS

None identified.

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