Seroepidemiologic Effects of Influenza A(H1N1)pdm09 in Australia, New Zealand, and Singapore

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To estimate population attack rates of influenza A(H1N1)pdm09 in the Southern Hemisphere during June–August 2009, we conducted several serologic studies. We pooled individual-level data from studies using hemagglutination inhibition assays performed in Australia, New Zealand, and Singapore. We determined seropositive proportions (titer ≥40) for each study region by age-group and sex in pre- and postpandemic phases, as defined by jurisdictional notification data. After exclusions, the pooled database consisted of, 4,414 prepandemic assays and 7,715 postpandemic assays. In the prepandemic phase, seropositive proportions ranged from 3.5% in Singapore to 11.9% in New Zealand. In the postpandemic phase, seropositive proportions ranged from 17.5% in Singapore to 30.8% in New Zealand, with highest proportions seen in school-aged children. Pregnancy and residential care were associated with lower postpandemic seropositivity, whereas Aboriginal and Torres Strait Islander Australians and Pacific Peoples of New Zealand had greater postpandemic seropositivity.

Australia, New Zealand (NZ), and Singapore all experience regular influenza seasons that coincide with winter in the Southern Hemisphere. After pandemic influenza A(H1N1) 2009 (A[H1N1]pdm09) emerged during spring in North America (1), influenza notifications and other markers of influenza activity peaked in Australia, NZ, and Singapore during July 2009 (2–4). The 3 countries continued to experience the circulation of an influenza strain closely related to the original virus until at least the following winter (5).

Most influenza surveillance systems are passive, laboratory-based systems that capture only symptomatic patients who seek medical advice and are then appropriately tested and case notifications sent. Therefore, these systems are likely to underestimate the true attack rate. Measurement of antibodies against A(H1N1)pdm09 can be used to assess the extent of population exposure to the virus (6). The emergence of a novel influenza virus provided a unique opportunity to study the behavior of influenza viruses to better understand their differential effects across various population groups.

Standardization of epidemiologic and serologic techniques across our region enabled more direct comparison of the effects of pandemic influenza on the different popula-

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A list of the group’s members can be found at the end of this article.
tions studied. Three of the countries in our region performed such studies, with publications originating from Australia (7–15), NZ (16), and Singapore (17). We pooled individual-level serologic data from studies that used the hemagglutination inhibition (HI) assay to describe the effects of the 2009 winter influenza pandemic in the Southern Hemisphere.

Methods

Identification of Studies

A working group for pandemic influenza serologic studies was formed with assistance from the Australian Seasonal Influenza Surveillance Strategy Working Group. The aims of this group included standardization of methods to facilitate analysis of pandemic serosurveillance research undertaken across Australia. The group convened its first teleconference on September 29, 2009, and continued to meet regularly as the studies were performed. Through this group and its contacts, 11 teams of researchers were identified who had performed serologic studies. After expressions of interest from researchers in Singapore (which lies just north of the equator but has a mid-year peak in influenza notifications) and NZ, 2 additional groups were identified.

Additionally, we searched Embase and PubMed for the period January 2009 to April 2011 using a combination of database-specific controlled vocabulary and general free text terms, including the following: “influenza A virus,” “H1N1 subtype,” “seroepidemiology studies,” “influenza,” “seroepidemiology,” “serosurvey,” and geographic terms for regions of the Southern Hemisphere. No further studies were identified by using these search strategies.

Inclusion Criteria

Studies were eligible for inclusion if they assessed serologic immunity against A(H1N1)pdm09 by HI assay across a population group in the Southern Hemisphere or Singapore. Studies were eligible if collected before vaccination programs against the virus commenced or if strategies were in place to allow for vaccine effect. Investigators from contributing studies provided HI assay titers, collection date, age, and geographic location at the individual level. The Figure shows the study profile.

Pandemic Phases

We defined the study region as NZ, Singapore, or Australian state or territory. Because the definition of pandemic phases varied between included studies, we defined pandemic phases using generally more stringent criteria than those used in contributing studies. Prepandemic specimens were defined as those collected before the first notified case in the corresponding region. Postpandemic phases were defined using notification data from NZ and the Australian Government Department of Health and Ageing by week and region. For these countries, we defined postpandemic specimens as those collected at least 2 weeks after the date on which 90% of 2009 laboratory notifications had occurred for the region. In Singapore, continuing pandemic activity was noted through late 2009. Because the adult studies from Singapore were repeated collections from prospective cohorts, the latest collection was used for estimates of postpandemic immunity, generally from October 2009. The postpandemic collection from children in Singapore was from September 1, 2009, to June 2, 2010, and all of these specimens were included as postpandemic. Specimens that did not meet criteria for prepandemic or postpandemic were defined as intrapandemic and excluded from further analysis.

Statistical Analysis

Most studies were performed as cross-sectional or analysis of continuous prospective collections of available specimens collected for other purposes. Studies that used a purposive sampling technique were analyzed in the same way as
those that used convenience collections. In the case of cohort collections and clinical trials, pre- and postpandemic assays from the same person were delinked and analyzed independently for consistency with other study techniques. For clinical trials, preintervention data from the intervention group and all data from the control group were included, whereas postintervention data from the treatment group were excluded. One study (M) used a postpandemic, cross-sectional design with retrospective assessment of prepandemic titers for those specimens found to be seropositive. For this study, only the postpandemic collection was included.

All studies used 2-fold serial dilutions from an initial dilution of 1:10 to determine titers. A titer of ≥40 was used to define seropositivity because all included studies used this cutoff value. Two studies (L, O) reported the geometric mean of 3 assays for each specimen, and for these studies, geometric mean titers of ≥40 were used to define seropositivity. Seropositive proportions are expressed as the proportion of reciprocal titers ≥40, with 95% CIs. Seropositive proportions are only reported for groups represented by ≥20 specimens. For comparability, age-standardized assessments of the proportion seropositive were calculated, weighted by 5-year age brackets to a reference population (Australian population on June 1, 2009) (18). Attack rates are calculated (for populations for which pre- and postpandemic seropositive proportions were available) as the difference in proportions of the immune population between pre- and postpandemic groups, age-standardized to the same reference population.

Using data from the 11 community-based studies, we performed multivariate logistic regression for the outcome of seropositivity in pre- and postpandemic phases. Exposure variables included in the model consisted of sex, age group, and study region because no other variables were consistently available across datasets.

To quantify the effect of study methods and the presence of potential risk factors on seropositivity, we compared pairs of studies performed in similar populations, using multivariate logistic regression, on the outcome of seropositivity. Data from the reference study were included along with data from a study of persons with the most similar characteristics. Exposure variables consisted of age, sex, and the binary variable of comparison group versus reference group. Analyses were restricted to specimens taken from patients during the same pandemic phase with comparable demographic characteristics (age, region, and population). Data management and statistical analysis were carried out with Stata 11.0 (StataCorp LP, College Station, TX, USA).

Results

Datasets were received from 11 groups of investigators, consisting of data from 10 published and 3 unpublished studies. Data were received from NZ, Singapore, and New South Wales (NSW), the Northern Territory (NT), Queensland, Tasmania, Victoria, and Western Australia in Australia. Datasets are listed by study design and population, with pandemic phases referring to investigators’ definitions, which resulted in 19 datasets for analysis. Study designs consisted of 4 prospective cohorts (E–H), 3 randomized controlled trials (I, O, R), 2 prepandemic cross-sectional studies (A, D), 1 retrospective cohort study (M), and 6 unpaired pre- and postpandemic cross-sectional studies (I, J, K, N, P, S). Eleven datasets were community based, whereas 8 were from groups with potential risk factors.

Laboratory techniques common to all studies included HI assay, per inclusion criteria, and use of egg-grown, β-propiolactone–inactivated A/California/07/2009 reference virus as the antigen source. All studies provided titers and patient’s age in years for each assay, and all Australian studies provided geographic data to at least state/territory level. Table 1 illustrates study characteristics that differed between included studies, with studies differing by design, enrollment criteria, specimen type, and specific HI method (a longer version can be found online; wwwnc.cdc.gov/EID/article/19/1/11-1643-T1.htm). All studies but 2 (I, K) provided data on patient’s sex for all assays. All studies attempted to avoid contamination of specimens from vaccination effect, but approaches used to achieve this differed.

Received data consisted of 18,279 individual specimens, of which 18,131 assays (from 14,036 persons) were eligible for analysis, whereas 148 did not meet inclusion criteria. Samples were reclassified as prepandemic (4,414), intrapandemic (6,002), or postpandemic (7,715), according to the criteria described, with intrapandemic assays excluded from further analysis (Figure). The timing of the pandemic phases and the sample taking is summarized in the online Technical Appendix (wwwnc.cdc.gov/EID/pdfs/11-1643-Techapp.pdf). Of the assays eligible for analysis in the pre- or postpandemic groups, 125 prepandemic specimens and 2,065 postpandemic specimens were from risk groups, while the remainder were from community-based datasets.

Tables 2 and 3 show seropositive proportions in the pre- and postpandemic periods. Overall, the age-standardized prepandemic seropositive proportion was 9.4%, with regional estimates of 10.6% in Australia, 11.9% in NZ, and 3.5% in Singapore. Higher levels of immunity were seen with increasing age, with only 1 of 5 studies (A) of children finding evidence of preexisting immunity in age group 0–4 years, whereas markedly higher seropositive proportions were seen in those ≥75 years of age.

In the postpandemic period, the age-standardized seropositive proportion was 24.3%, giving an attack rate of 14.9% (Table 3). Attack rates by country were 13.1% for Australia, 19.0% for NZ, and 14.0% for Singapore. For all regions in which children 5–14 years of age were assessed,
Table 1. Characteristics of selected collections included in database to estimate population attack rates of influenza A (H1N1) 2009 in the Southern Hemisphere, winter 2009.

<table>
<thead>
<tr>
<th>Code (reference)</th>
<th>Study design</th>
<th>No. assays by redefined phase</th>
<th>Population</th>
<th>Age range, y</th>
<th>Enrollment</th>
<th>Region</th>
<th>Monovalent pandemic vaccine effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (16)</td>
<td>Pre cross-section</td>
<td>524 pre</td>
<td>Outpatients</td>
<td>1–99</td>
<td>Opportunistic from stored specimens</td>
<td>NZ</td>
<td>Not applicable</td>
</tr>
<tr>
<td>B (16)</td>
<td>Post cross-section</td>
<td>1147 post</td>
<td>Primary care patients</td>
<td>1–89</td>
<td>Active recruitment of registered GP patients</td>
<td>NZ</td>
<td>Collection prior to vaccination program</td>
</tr>
<tr>
<td>C (16)</td>
<td>Post cross-section</td>
<td>532 post</td>
<td>HCWs‡</td>
<td>21–109</td>
<td>Active recruitment of hospital and clinic staff. Outbreak investigations of non-H1N1 viruses</td>
<td>NZ</td>
<td>Collection prior to vaccination program</td>
</tr>
<tr>
<td>D (7)</td>
<td>Pre cross-section</td>
<td>152 pre</td>
<td>Residents of aged-care facilities‡</td>
<td>59–100</td>
<td></td>
<td>NSW</td>
<td>Not applicable</td>
</tr>
<tr>
<td>E (17)</td>
<td>Prospective cohort (pre and post collections)</td>
<td>788 pre 671 intra 689 post 1 pre 1,138 intra 391 post</td>
<td>Community residents</td>
<td>21–74</td>
<td>Sub-cohort of existing cohort collection</td>
<td>Singapore</td>
<td>Collection prior to vaccination program</td>
</tr>
<tr>
<td>F (17)</td>
<td>Prospective cohort (pre and post collections)</td>
<td>300 intra 250 post</td>
<td>Staff and residents of long-term care facilities‡</td>
<td>19–109</td>
<td>Active recruitment by invitation</td>
<td>Singapore</td>
<td>Collection prior to vaccination program</td>
</tr>
<tr>
<td>G (17)</td>
<td>Prospective cohort (pre and post collections)</td>
<td>1915 intra 637 post</td>
<td>Military personnel‡</td>
<td>18–62</td>
<td>Active recruitment by invitation</td>
<td>Singapore</td>
<td>Collection prior to vaccination program</td>
</tr>
<tr>
<td>H (17)</td>
<td>Prospective cohort (pre and post collections)</td>
<td>447 pre 221 intra 229 post 201 pre 170 intra 116 post 474 pre</td>
<td>Community residents</td>
<td>0–19</td>
<td>Opportunistic from pathology laboratory</td>
<td>WA</td>
<td>Collection prior to vaccination program</td>
</tr>
<tr>
<td>I (8)</td>
<td>Pre and post cross-sections</td>
<td>750 intra 497 post</td>
<td>Pregnant women‡</td>
<td>21–45</td>
<td>Opportunistic from pathology laboratory</td>
<td>WA</td>
<td>Collection prior to vaccination program</td>
</tr>
<tr>
<td>J (8)</td>
<td>Pre and post cross-sections</td>
<td>166 intra</td>
<td>Outpatients</td>
<td>0–100</td>
<td>Opportunistic from pathology laboratories</td>
<td>NSW</td>
<td>Collection prior to vaccination program</td>
</tr>
<tr>
<td>K (9)</td>
<td>Pre and post-cross-sections</td>
<td>166 intra</td>
<td>Healthy adults</td>
<td></td>
<td>Active recruitment of volunteers</td>
<td>Adelaide</td>
<td>Collection prior to vaccination program</td>
</tr>
<tr>
<td>L (10)</td>
<td>RCT of pandemic vaccine (pre-vaccine collection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*An expanded version of this table showing all collections in the database is available online (www.cdc.gov/EID/Content/19/11-1643-T1.html). NZ, New Zealand; H1N1, healthcare workers; NSW, New South Wales; WA, Western Australia; RCT, randomized controlled trial.  
†Age range for specimens included in pre- or postpandemic phases.  
‡Defined as risk groups for analysis.

This age group had the highest levels of postpandemic seropositivity, except for NSW, in which those 15–34 years of age showed the greatest seropositivity. Among risk groups, unweighted seropositive proportions were 28.4% in HIV-positive persons in NSW, 21.5% in hemodialysis patients in NSW, 26.7% in NZ health care workers, 9.5% in Singaporean health care workers, 33.9% in Singaporean military personnel, 6.8% in staff and residents of Singaporean residential care facilities, 14.7% in pregnant women in WA, 29.5% in indigenous residents of the NT, 34.3% in Maori in NZ, and 43.7% in Pacific Peoples in NZ.

Logistic regression performed in assays from postpandemic, community-based collections showed that the age groups 5–14 years and 15–34 years, as well as residence in NZ, were associated with increased seropositivity. Negative effects were seen for older age groups and those with residence in Singapore (Table 4).

In 2 instances, the same demographic group was assessed by 2 studies using different methods, allowing for assessment of the effect of study design. The 2 cross-sectional studies performed in adults in NSW in the postpandemic phase (performed in different laboratories) were
Table 2. Prepandemic seropositive proportions by country, region, and risk group of influenza A (H1N1) 2009 in the Southern Hemisphere, winter 2009

<table>
<thead>
<tr>
<th>Code</th>
<th>Pop.</th>
<th>Age groups, y</th>
<th>Sex</th>
<th>Overall</th>
<th>Raw</th>
<th>Age-stand.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, E, I, N, P, R, S</td>
<td>Overall</td>
<td>1.4</td>
<td>2.7</td>
<td>12.0</td>
<td>4.8</td>
<td>11.5</td>
</tr>
<tr>
<td>I, N, P, R</td>
<td>AU</td>
<td>0</td>
<td>1.6</td>
<td>12.2</td>
<td>7.9</td>
<td>12.3</td>
</tr>
<tr>
<td>A</td>
<td>NZ</td>
<td>7.0</td>
<td>14.9</td>
<td>8.4</td>
<td>5.3</td>
<td>20.1</td>
</tr>
<tr>
<td>E &amp; S</td>
<td>Sing</td>
<td>0</td>
<td>1.6</td>
<td>12.7</td>
<td>20.1</td>
<td>1.4</td>
</tr>
<tr>
<td>K</td>
<td>NSW</td>
<td>0</td>
<td>0</td>
<td>5.1</td>
<td>14.2</td>
<td>4.4</td>
</tr>
<tr>
<td>P</td>
<td>NT</td>
<td>0</td>
<td>0</td>
<td>4.4</td>
<td>8.7</td>
<td>8.2</td>
</tr>
<tr>
<td>N</td>
<td>QLD</td>
<td>0</td>
<td>0</td>
<td>12.3</td>
<td>11.3</td>
<td>14.4</td>
</tr>
<tr>
<td>I, R</td>
<td>WA</td>
<td>0</td>
<td>0</td>
<td>15.7</td>
<td>0</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Risk group collection

D NSW 26.0 50.5 55.8 23.7 46.0

Pop., population; age-stand., age-standardized; AU, Australia; NZ, New Zealand; Sing, Singapore; NSW, New South Wales; QLD, Queensland; NT, Northern Territory; WA, Western Australia; res., resident; Blank cells indicate no data, CI's are included in online version.

Discussion

We obtained estimates of the full epidemiologic effects of A(H1N1)pdm09 in the 2009 Southern Hemisphere winter by pooling data from several serologic studies performed across our region. We believe that population-based serologic studies give a more direct measure of community exposure to the virus than notification-based data, which are inherently limited by the proportion of cases of infection that are captured by the notification system. The individual-level data enabled us to apply consistent statistical methods across studies. This enabled estimates of seropositivity to be made across more directly comparable groups, as well as assessments of the effects of specific risk factors on seropositivity.

Our community-based, age-standardized estimates of prepandemic seropositive proportions ranged from 3.5% to 11.9%, with Singapore demonstrating a lower level of prepandemic immunity than Australia and NZ. The increased levels of prepandemic immunity in those ≥75 years of age are likely to be partially due to cross-reacting antibody responses to influenza A/South Carolina/1/1918 and related viruses that were circulating in the early 20th century (20). However, the steady increase in seropositivity with age across age groups suggests more recent circulation of influenza viruses with the potential to elicit cross-reacting antibody responses (21).

The finding of peak prepandemic seropositivity in the 5- to 14-year age group is consistent with greater social mixing of school-aged children, lower prepandemic immunity, and results from other population-wide studies (22,23). Despite the low level of prepandemic cross-reactive antibodies to the virus, Singapore remained the region with the lowest proportion of population-standardized seropositivity in the prepandemic phase (17.5%), whereas estimates from Australia and NZ ranged from 22.1% to 32.8%. The implication of lower prepandemic seropositivity in more tropical regions is consistent with estimates from India and Hong
Table 3. Postpandemic seropositive proportions by country, region, and risk group of influenza A (H1N1) 2009 in the Southern Hemisphere, winter 2009, with age-characterized AR

<table>
<thead>
<tr>
<th>Code</th>
<th>Pop.</th>
<th>Age groups, y</th>
<th>Sex</th>
<th>Overall Age stand.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0-4</td>
<td>5-14</td>
<td>15-34</td>
</tr>
<tr>
<td>A, B, E, I, K, N, O, P, R, S</td>
<td>Overall</td>
<td>27.6</td>
<td>34.3</td>
<td>30.5</td>
</tr>
<tr>
<td>I, K, N, O, P, R</td>
<td>AU</td>
<td>24.0</td>
<td>32.2</td>
<td>29.8</td>
</tr>
<tr>
<td>B</td>
<td>NZ</td>
<td>37.2</td>
<td>46.3</td>
<td>38.1</td>
</tr>
<tr>
<td>E, S</td>
<td>Sing.</td>
<td>24.5</td>
<td>29.6</td>
<td>17.2</td>
</tr>
<tr>
<td>K, N</td>
<td>NSW</td>
<td>17.3</td>
<td>18.4</td>
<td>37.8</td>
</tr>
<tr>
<td>P</td>
<td>NT</td>
<td>16.7</td>
<td>37.2</td>
<td>22.0</td>
</tr>
<tr>
<td>N</td>
<td>QLD</td>
<td>29.6</td>
<td>9.3</td>
<td>14.8</td>
</tr>
<tr>
<td>N</td>
<td>Tas</td>
<td>35.9</td>
<td>28.9</td>
<td>26.7</td>
</tr>
<tr>
<td>N, O</td>
<td>Vic</td>
<td>36.1</td>
<td>30.8</td>
<td>12.5</td>
</tr>
<tr>
<td>I, N, R</td>
<td>WA</td>
<td>24.0</td>
<td>39.5</td>
<td>31.6</td>
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</table>

Risk group collections

<table>
<thead>
<tr>
<th>Code</th>
<th>Pop.</th>
<th>Age groups, y</th>
<th>Sex</th>
<th>Overall Age stand.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0-4</td>
<td>5-14</td>
<td>15-34</td>
</tr>
<tr>
<td>M</td>
<td>NSW, HIV+</td>
<td>29.5</td>
<td>30.4</td>
<td>21.7</td>
</tr>
<tr>
<td>Q</td>
<td>NSW, hemo.</td>
<td>31.3</td>
<td>23.7</td>
<td>27.6</td>
</tr>
<tr>
<td>C</td>
<td>NZ, HCWs</td>
<td>11.0</td>
<td>6.8</td>
<td>11.1</td>
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<tr>
<td>G</td>
<td>Sing. res. care</td>
<td>4.3</td>
<td>2.7</td>
<td>6.8</td>
</tr>
<tr>
<td>H</td>
<td>Sing. military</td>
<td>35.7</td>
<td>3.4</td>
<td>34.5</td>
</tr>
<tr>
<td>J</td>
<td>WA, preg. women</td>
<td>13.3</td>
<td>19.2</td>
<td>14.7</td>
</tr>
<tr>
<td>P</td>
<td>NT, indig.</td>
<td>37.5</td>
<td>28.4</td>
<td>28.1</td>
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<tr>
<td>B</td>
<td>NZ, Maori</td>
<td>42.3</td>
<td>26.2</td>
<td>20.6</td>
</tr>
<tr>
<td>B</td>
<td>NZ, Pacific People</td>
<td>56.0</td>
<td>55.6</td>
<td>53.1</td>
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</table>

Overall attack rates, community-based studies

<table>
<thead>
<tr>
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<th>Age groups, y</th>
<th>Sex</th>
<th>Overall Age stand.</th>
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<td></td>
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<td>0-4</td>
<td>5-14</td>
<td>15-34</td>
</tr>
<tr>
<td>A, B, E, I, K, N, O, P, R, S</td>
<td>Overall</td>
<td>26.2</td>
<td>31.6</td>
<td>18.5</td>
</tr>
</tbody>
</table>

Overall geometric mean titers, community-based studies

Kong (23,24), as well as with the nonsignificant trend toward greater seropositivity in the more northerly Australian regions (NT and Queensland) on logistic regression. Although overall attack rates were similar for Australia and Singapore, this finding highlights the geographic heterogeneity of influenza spread and suggests that latitude may be a critical predictor of susceptibility to influenza, which might be explained by increased efficiency of transmission of influenza in cold temperatures (25) or population levels of vitamin D stores (26). The negative overall attack rate in those ≥75 years of age may have been an anomaly, because this age group had the smallest number of specimens and the prepandemic specimens were predominantly from NSW, while the postpandemic specimens were a combination of specimens from NSW, NZ, and NT. Other age groups had more similar compositions between pre- and postpandemic phases and so are likely to be more directly comparable. Alternative explanations include waning immunity in elderly persons in the months after seasonal influenza vaccination or limitations of study K, which observed the greatest decrease in titer in this age group.

Although several coexisting conditions have been found to be associated with severity of infection with A(H1N1)pdm09, most laboratory-confirmed cases across the Southern Hemisphere have occurred in persons without known risk factors (27). We found no increase in risk for postpandemic seropositivity among hemodialysis patients and a group of persons with generally well-controlled HIV infection. These
results are consistent with the observation that HIV-infected patients admitted to a hospital for influenza have similar clinical outcomes as do non-HIV patients (28). Pregnant women represented ≈7%–9% of patients with laboratory-confirmed cases, severe infections, and admissions to intensive care units in the Southern Hemisphere (27). Although it has been postulated that this occurred because of the patients’ younger ages and close contact with children, our results suggest that pregnancy is associated with a lower likelihood of infection, possibly because pregnant women actively avoid infection. Therefore, pregnant women appear more susceptible to severe illness with A(H1N1)pdm09 infection, which may relate to lower levels of immunoglobulin G (29). By contrast, our results suggest that the 6- to 7-fold higher rates of hospitalization seen in indigenous persons in our region are likely to be partially attributable to a higher attack rate in Australia (30). We did not find evidence for a higher attack rate among health care workers or military personnel, with levels of seropositivity comparable to those of the general community. A study in a Finnish garrison found that 22.3% of personnel had titers of ≥40, a level lower than the 33.9% observed in Singaporean military personnel postpandemic, even though this study was performed in response to a recent outbreak (31). Levels of seropositivity in those living in residential care appeared lower than in community-living persons of comparable age, both in a prepandemic comparison in NSW and in a postpandemic comparison in Singapore.

The unavoidable limitation to our comparisons is that they included data from multiple studies that used differing methods. Studies differed by epidemiologic approach, specimen type, and laboratory methods, and the jurisdictions studied exhibited different public health responses.

We excluded from analysis data we considered to have been obtained with methods that were unlikely to give a population-wide estimate of serologic immunity, for example, 1 retrospective prepandemic collection from persons with postpandemic seropositivity (M) and the post-intervention assessments from clinical trials (L, O, R, S). Several studies used convenience collections of specimens taken for clinical indications before routine discarding. These studies enabled population-based estimates but were subject to selection bias, given that conditions predisposing to influenza might increase the chance of being tested. By contrast, the use of blood donor specimens may select for a healthier sample. Cohort studies (E–H) were analyzed in the same manner as for cross-sectional surveys, although samples included in these datasets were determined by selection biases related to original enrollment in the cohort as well as to enrollees dropping out. Previous evidence indicates that this is a valid approach to estimating population-wide immunity (32). Moreover, our analysis found no effect from differing study methods when comparing 2 pairs of studies performed in the same populations. Therefore, while the differences seen between the risk groups could have been caused by differences in study method, we found no evidence of this from the data available.

Whether the epidemiologic differences are due to differences in transmission in differing populations or because of the effectiveness of public health responses is difficult to gauge. In Australia, most jurisdictions moved from the Delay to the Contain phase on May 22 and from the Contain to the Protect phase on June 22. Only Victoria, which contributed 234 specimens to this pooled analysis, differed in the timing of its response phases (33). Although there were
### Table 5. Multivariate logistic regression models comparing specific collections on outcome of seropositivity, with exposures of region, age group, and sex, in community-based studies of influenza A (H1N1) 2009 in the Southern Hemisphere, winter 2009*

<table>
<thead>
<tr>
<th>Comp. group/study compared with ref.</th>
<th>Male sex ORs 95% CI for exposure variables</th>
<th>Characteristics of model</th>
<th>Restrictions to inclusion</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>K</strong> N 493 Residence in NSW; post; age 16–77 y</td>
<td>0.98 (0.65–1.49); 0.74 (0.66–0.84); 1.37 (0.89–2.09);</td>
<td>Stored pathology specimens survey vs. survey of blood donors (NSW)</td>
<td>K</td>
<td>0.93 p = 0.93; 0.93 p = 0.001; 0.93 p = 0.15</td>
</tr>
<tr>
<td><strong>R</strong> N 204 Residence in WA; post</td>
<td>1.05 (0.56–1.98); 1.06 (0.86–1.31); 1.48 (0.79–2.79);</td>
<td>Patients voluntarily enrolled in RCT vs. blood donors (WA)</td>
<td>R</td>
<td>0.88 p = 0.88; 0.88 p = 0.56; 0.88 p = 0.22</td>
</tr>
<tr>
<td><strong>D</strong> K 278 Pre; age ≥58 y</td>
<td>0.51 (0.31–0.79); 2.79 (2.01–3.86); 0.34 (0.15–0.79);</td>
<td>Persons in res., care vs. community control group (NSW)</td>
<td>D</td>
<td>0.003 p = 0.003; 0.003 p = 0.001; 0.003 p = 0.01</td>
</tr>
<tr>
<td><strong>M</strong> K 278 Post; age 19–77 y</td>
<td>0.80 (0.62–0.90); 1.26 (0.74–2.16);</td>
<td>Persons with HIV infection vs. community control group (NSW)</td>
<td>M</td>
<td>0.74 p = 0.74; 0.74 p = 0.74; 0.74 p = 0.74</td>
</tr>
<tr>
<td><strong>Q</strong> K 192 Post; age 43–88 y</td>
<td>0.90 (0.42–1.95); 0.91 (0.68–1.21); 1.65 (0.75–3.63);</td>
<td>Hemo. patients vs. community control group (NSW)</td>
<td>Q</td>
<td>0.23 p = 0.23; 0.23 p = 0.003; 0.23 p = 0.48</td>
</tr>
<tr>
<td><strong>J</strong> N, R 316 Res. in WA; post; age 21–45 y</td>
<td>0.92 (0.70–1.22); 0.95 (0.88–1.03); 1.09 (0.83–1.42);</td>
<td>Preg. women vs. community control group (WA)</td>
<td>J</td>
<td>0.56 p = 0.56; 0.56 p = 0.26; 0.56 p = 0.54</td>
</tr>
<tr>
<td><strong>C</strong> B 1316 Post; age ≥21</td>
<td>1.12 (0.74–1.71); 0.78 (0.66–0.93); 0.85 (0.41–1.01);</td>
<td>HCWs vs. community control group (NZ)</td>
<td>C</td>
<td>0.59 p = 0.59; 0.59 p = 0.006; 0.59 p = 0.06</td>
</tr>
<tr>
<td><strong>F</strong> E 1080 Post</td>
<td>1.19 (0.75–1.88); 0.71 (0.58–0.85); 0.97 (0.58–1.60);</td>
<td>HCWs vs. community control group (Singapore)</td>
<td>F</td>
<td>0.45 p = 0.45; 0.45 p = 0.001; 0.45 p = 0.89</td>
</tr>
<tr>
<td><strong>H</strong> E 996 Post; age 21–62 y</td>
<td>1.38 (0.89–2.16); 1.38 (0.68–0.96); 1.44 (0.22–0.90);</td>
<td>Military personnel vs. community control group (Singapore)</td>
<td>H</td>
<td>0.15 p = 0.15; 0.15 p = 0.02; 0.15 p = 0.03</td>
</tr>
<tr>
<td><strong>G</strong> E 858 Post</td>
<td>0.95 (0.73–1.22); 0.88 (0.82–0.94); 0.96 (2.08–3.42);</td>
<td>Res. care group vs. community control group (Singapore)</td>
<td>G</td>
<td>0.68 p = 0.68; 0.68 p = 0.001; 0.68 p = 0.001</td>
</tr>
<tr>
<td><strong>P</strong> P 1689 Post</td>
<td>1.05 (0.74–1.22); 1.17 (0.82–0.94); 1.26 (2.08–3.42);</td>
<td>Aboriginal and Torres Strait Islanders vs. nonindig. people (NZ)</td>
<td>P</td>
<td>0.68 p = 0.68; 0.68 p = 0.001; 0.68 p = 0.001</td>
</tr>
<tr>
<td><strong>B</strong> B 1147 Post</td>
<td>0.95 (0.73–1.22); 0.86 (0.82–0.91); 1.17 (0.83–1.64);</td>
<td>Maori vs. nonindig. people (NZ)</td>
<td>B</td>
<td>0.66 p = 0.66; 0.66 p = 0.001; 0.66 p = 0.38</td>
</tr>
<tr>
<td><strong>B</strong> B 966 Post</td>
<td>1.04 (0.76–1.37); 1.17 (0.82–0.92); 1.99 (1.41–2.82);</td>
<td>Pacific Peoples vs. nonindig. people (NZ)</td>
<td>B</td>
<td>0.80 p = 0.80; 0.80 p = 0.001; 0.80 p = 0.001</td>
</tr>
</tbody>
</table>

*ORs, odds ratios; comp., comparison; ref., referent; NSW, New South Wales; post, postpandemic phase; WA, Western Australia; RCT, randomized controlled trial; pre, prepandemic phase; res., residence/residential; hemo., hemodialysis; preg., pregnant; HCWs, health care workers; NZ, New Zealand; NT, Northern Territory; nonindig., nonindigenous.

†Age is considered as a continuous variable with OR for each decade of increasing age.

Notable differences between public health management of the response to the outbreak in NZ and Singapore, the timing of the transition to containment was broadly similar, with NZ focusing primarily on containment from April 25 to June 21 (34), while Singapore began its transition during the Mitigation phase on June 29 (35).

Protocols for the HI assay may differ between laboratories in terms of specimen source and preparation (serum or plasma, erythrocyte adsorption), reagents (erythrocyte species, antigen preparation), procedure (incubation conditions), and controls. Furthermore, use of fresh erythrocytes for HI assays means inherent within-laboratory variability must be managed. To minimize variability between laboratory method and erythrocyte batches, control panels of serum samples were shared and results were standardized. A common source of virus antigen was also shared. Such comparative experiments were performed early in the pandemic between 3 of the 4 laboratories described in this analysis, with minimal variation seen. These 3 laboratories used a common source of A(H1N1)pdm09 antigen for at least 15 of the 19 datasets included. International standards were also available in 2009 for standardization of serologic assays around the world. Notably, the source of erythrocytes to detect influenza virus may vary, depending on the binding specificity of the hemagglutinin protein for each virus. A(H1N1)pdm09 virus recognized human, turkey, and guinea pig erythrocytes. This
enabled laboratories to use cells that were available and that they were experienced in handling.

Although all studies used a titer of $\geq 40$ as the cutoff for seropositivity, this is an oversimplification of the complex immune response to influenza infection, which includes both cellular and humoral components (36). Although a titer of 40 was achieved in 80%–90% of persons with PCR-confirmed infection with A(H1N1)pdm09 (37), in unpaired analysis, no single cutoff reliably determines past infection and subsequent immunity. Serologic studies that incorporated interviewing participants about symptoms of influenza-like illness suggest that as many as half of those with serum titers of $\geq 40$ in the postpandemic phase do not have a history of a compatible illness (16,31). This finding partly reflects the fact that a proportion of those patients who were seropositive in the postpandemic phase were already seropositive in the prepandemic phase, but also suggests that some persons who seroconverted did not experience or report symptoms. Despite this, pre- and postpandemic cross-sectional serologic surveys are the most convenient and inclusive method for assessing population-wide serologic immunity.

Our results provide a broad picture of the effects of A(H1N1)pdm09 in the Southern Hemisphere during the winter of 2009. The absence of clear differences between estimates with different study methods suggests that pooling of data is likely to be useful in estimating the effects of the virus across population groups. We found greater levels of prepandemic seropositivity as patient’s age increased, particularly in those $\geq 75$ years of age. By contrast, in the postpandemic period, school-aged children showed the greatest levels of immunity. Health care workers, military personnel, persons with HIV infection, and hemodialysis patients had levels of postpandemic seropositivity similar to those of the general community. Pregnancy and residential care appeared protective from infection, suggesting more severe disease in those infected. Despite recording the lowest prepandemic levels of immunity, Singapore retained comparatively lower levels of seropositivity after the pandemic.

The following are members of the Australia, New Zealand and Singapore Pandemic Serosurveillance Study Group: Li Wei Ang, Michael Baker, Ian Barr, Don Bandaranayake, Richard Beasley, Ange Bissel, Robert Booy, Mark Chen, SQF Chew, Michelle Cretikos, Gary K Dowse, George Doukas, Dominic Dwyer, Lucinda Franklin, Gwendolyn Gilbert, Kristina Grant, Michael Greenberg, Virginia Hope, Sue Huang, Linda Hueston, Jen Kok, Gulam Khandaker, Ann Koehler, Karen Laurie, Peter Marmey, Rhonda Owen, Stewart Reid, Sally Roberts, Brian O'Toole, Vernon Lee, Graham Mackereth, Jane Rautach, Kristy Richards, Jodie McVerden, Christine Selvey, Robert Shaw, David Smith, James Trauer, Scott Walter, Tim Wood.

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