Pertussis in Older Adults: Prospective Study of Risk Factors and Morbidity

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Background. There is limited information on the incidence, morbidity and risk factors for pertussis in adults, particularly those aged over 65 years.

Methods. Population-based prospective cohort study of 263,094 adults aged over 45 years (mean 62.8 years) recruited in the Australian state of New South Wales (the 45 and Up Study) between 2006 and 2008, and followed by record-linkage to laboratory-confirmed pertussis notifications, hospitalizations, and death records. The incidence of pertussis notifications and hospitalizations and relative risk (RR) of pertussis according to various participant characteristics was estimated using proportional hazards models.

Results. Over a total follow-up of 217,524 person-years, 205 adults had a pertussis notification and 12 were hospitalized; the incidence rate was 94 (95% confidence interval [CI], 82–108) and 5.5 (95% CI, 3.1–9.7) per 100,000 person-years, respectively. The incidence of a pertussis notification did not differ by age but hospitalization rates progressively increased (2.2, 8.5, and 13.5 per 100,000 person-years in age groups 45–64, 65–74, and 75+ years, respectively; \( P_{\text{trend}} = .01 \)). After adjusting for age, sex, and other factors, adults with a high body mass index (BMI; RR = 1.52; 95% CI, 1.06–2.19 for BMI ≥30 kg/m² vs BMI <25 kg/m²) and with preexisting asthma (RR = 1.64; 95% CI, 1.06–2.55 compared to those without asthma) were more likely to be notified.

Conclusions. Adults older than 65 years are more likely to be hospitalized for pertussis than those aged 45–64 years. Obesity and preexisting asthma were associated with a higher likelihood of pertussis notification. These findings suggest that pertussis vaccination would be particularly important for adults with these characteristics.

INTRODUCTION

Bordetella pertussis is known to cause significant morbidity and mortality in young children worldwide [1]. In regions with long-standing high childhood pertussis vaccine coverage such as the United States and Europe, pertussis is increasingly being diagnosed in adults [2]. In Australia, notification rates for adult pertussis increased earlier than in the United States and Europe [3]. This rise was associated with extensive use of serological testing for pertussis and direct notification of positive tests by laboratories to public health authorities, highlighting the importance of surveillance methods in pertussis recognition and reporting [1, 4]. Like the United States, Australia has had long-standing relatively high coverage for childhood pertussis vaccination, used acellular vaccines exclusively for over 10 years, and has a primary course occurring at 2, 4, and 6 months of age. Unlike the United States, Australia did not introduce a booster at 4–5 years until 1995 [5], and replaced the then fourth dose at 18 months in 2003 with a dose at 12–17 years of age [6]. This decision was based on high rates of pertussis in adolescents and evidence suggesting protection following the 2/4/6-month schedules persisting until 7 years of age [7, 8].

Adult immunization is currently not funded under Australia’s National Immunisation Program, but for some time, vaccination has been recommended for adults planning a pregnancy, new parents, and those working with infants [8]. Recent estimates of adult vaccine coverage are low, with 11% of those over 18 years of age reporting receipt of a pertussis booster as...
an adult or adolescent [9]. Given the increases in pertussis notifications in adults aged over 60 years in Australia [10] and internationally [2], the US Food and Drug Administration’s (FDA’s) recent approval of a combined diphtheria, tetanus, and pertussis vaccine for adults aged 65 years and older [11], and the very limited number of epidemiological studies on pertussis in older adults [4, 12, 13], we investigated pertussis incidence, disease severity, and potential risk factors for incident pertussis in a large prospective study of adults aged 45 years and over.

METHODS

We used data from 263,094 participants joining a prospective cohort study of Australian adults (the 45 and Up Study) who were recruited between January 2006 and December 2008. Detailed information on the recruitment procedures and cohort have been published elsewhere [14]. Briefly, adults aged 45 years and older and a resident of the Australian state of New South Wales (NSW) were randomly selected from the Australian Medicare database, which has a nearly complete coverage of the entire resident Australian population, and invited to take part. An estimated 18% of those invited were recruited. The cohort includes approximately 10% of all NSW adults aged ≥45 years and 11% of all those aged ≥65 years [15]. All participants completed a questionnaire at study entry on their health and lifestyle. Compared to participants in a NSW population-based health survey, study participants had higher household incomes, fewer reported comorbidities, better self-reported health, and lower smoking rates [16].

Participants were followed for incident pertussis diagnoses, hospitalizations, and deaths by record linkage of the cohort to respectively the NSW Notifiable Conditions Information Management System (NCIMS) [17], the NSW Admitted Patient Data Collection (APDC), and the NSW Registry of Births, Deaths and Marriages (RBDM). In Australia, pertussis is a “notifiable” disease; reporting of both confirmed and probable cases by health practitioners and laboratories is mandatory [17]. Pertussis cases are confirmed based primarily on either laboratory detection of B. pertussis (using polymerase chain reaction [PCR] or culture) or a combination of suggestive laboratory evidence (single-point whole-cell immunoglobin A [IgA] serology or B. pertussis antigen immunofluorescence) with clinical evidence (see “Appendix 1” for more details). During this study, in NSW, pertussis testing was government subsidized, and the standard and most commonly used approach to diagnosis in symptomatic adults was single-point whole-cell IgA serology [18, 19]. The NCIMS database contains a record of all pertussis diagnoses in NSW, including the estimated onset date, whether the case was laboratory confirmed, and the type of specimen used for confirmation. The NSW APDC includes a record of every hospitalization in NSW and includes the admission and discharge dates, the main diagnosis responsible for the admission, and up to 49 additional diagnoses. Diagnoses are coded according to the International Classification of Diseases version 10 (ICD-10) [20]. Data available from the NSW RBDM included a record of all deaths in NSW and the date of death but not cause of death. We had data for study participants from all 3 databases up to 31 December 2008. The record linkage was conducted by the NSW Centre for Health Record Linkage, and audits demonstrate false positive and false negative rates of respectively <0.5% and <0.1% [21].

We defined participants as having a pertussis diagnosis if they had a linked NCIMS record of a pertussis notification. We defined participants as having a hospitalization related to pertussis if they had a linked APDC record where the main or an additional diagnosis was coded with an ICD-10 code prefixed with A37 (whooping cough) [20] or if they had a NCIMS record of a pertussis notification and a hospital admission record within a period of 1 week prior to and up to 6 weeks following the date of pertussis diagnosis where the hospital discharge diagnosis was coded as a disease of the respiratory system (ICD-10 J-codes) or as cough (ICD-10 R05). All participants provided written informed consent to be included in the study and this study was approved by the NSW Population and Health Services Research Ethics Committee and the University of New South Wales Human Research Ethics Committee.

Statistical Analyses

Study participants recruited after the last date of follow-up (ie, 31 December 2008) were excluded. To estimate pertussis incidence, follow-up was calculated from the date of study entry to the first diagnosis of pertussis, death, or 31 December 2008, whichever came first. Incident pertussis-related hospitalizations were estimated using the first admission date for a pertussis-related hospitalization. Pertussis incidence was also calculated according to various sociodemographic factors and health characteristics and behaviors, including: age (45–64, 65–74 and 75 + years); sex; annual household income (5 categories, from <$20,000 to $70,000+ and unknown); education (3 categories: those not completing a higher school certificate, those with a higher school certificate, trade certificate or diploma, and those with a university degree); speaking a language other than English at home; living in residential care; social visits, defined as the number of times a week spent with family or friends not living in the household (<3, 3+); body mass index (BMI; <25, 25–29.9, 30+ kg/m²); smoking (never, current, past); alcohol intake (none, ≤1, >1 unit/day); vigorous physical activity (<once/week, once or more a week); physical limitation (in categories of none, moderate, or severe...
limitation based on the Medical Outcomes Study–Physical Functioning Score [22, 23]); use of medications/supplements, including prescribed and over-the-counter formulations, attending organized screening programs (mammography, prostate-specific antigen testing, or bowel cancer screening); and history of asthma or cardiac disease [4].

We then examined the relative risk of pertussis according to various sociodemographic and health characteristics that had either been reported to be associated with adult pertussis in previous studies [4] or were associated with the incidence of pertussis in the cohort: age, sex, household income, BMI, smoking, vigorous physical activity, medication or supplement use, and history of asthma. Proportional hazards models were used and analyses were adjusted firstly for age, sex, household income, and then for all other factors in the model. We also examined the relative risks with additional adjustment for education, other language spoken at home, and alcohol use. All analyses were conducted using STATA 12 software.

Finally, we compared findings from the cohort to routinely collected pertussis notification and hospitalization data for the whole state of NSW for the period 2006–2008 using similar databases as those that the study participants had been linked to [17]. Hospital separations were extracted if they had an ICD-10 code of A37 in the principal or any additional diagnoses fields. Rates of notifications and hospitalizations for the whole of NSW in equivalent age bands to the cohort were calculated using Australian census projections [15] with 95% confidence interval (CI) calculated using a Poisson distribution. Data from each year extracted was weighted to reflect the proportion of the 45 and Up Study participants in the study for each year (ie, 2006 = 10%, 2007 = 16%, and 2008 = 74%).

### RESULTS

The 263 094 adults included in the analyses yielded a total of 217 524 years of follow-up; an average of 0.83 years per person. The mean age of study participants at recruitment was 62.8 years (SD 11.2) and 46.4% were men. There were 205 adults with a linked pertussis diagnosis during follow-up. All diagnoses were laboratory confirmed; 80% (n = 164) were based on serology [24], 17% (n = 35) on PCR detection of B. pertussis, and 3% (n = 6) were unknown. Of the 205 adults with pertussis, 12 were also hospitalized with pertussis or a respiratory condition. Five of these hospitalizations had an ICD-10 primary diagnosis code on the hospitalization record of A37. The other 7 were hospitalized for nonspecific diagnoses, ranging from “unspecified disease of upper respiratory tract,” “unspecified lower respiratory tract infection,” “other chronic obstructive pulmonary disease,” “pneumonia,” and “cough.” All except 2 of the hospitalizations occurred within 1 week of the pertussis diagnosis date. Of those hospitalized, the median length of stay was 5.5 days (interquartile range [IQR] 5, 9.5), and 2 participants died within 3 weeks of the date their pertussis was diagnosed.

Pertussis incidence in the cohort was 94 per 100 000 (95% CI, 82–108). This did not differ by age group (P = .9) but did by sex, with women more likely to be diagnosed than men (P = .03); see Table 1. Counting only hospitalizations coded as whooping cough (ICD-10 A37), about 2% of those diagnosed with pertussis also had a hospitalization (incidence rate 2.3 per 100 000; 95% CI, 9.5–5.5) but when all hospitalizations defined as pertussis-related were considered, this rose to over 5% (incidence rate 5.5; 95% CI, 3.1–9.7 per 100 000).

**Table 1. Incidence of Pertussis Diagnoses and Pertussis-Related Hospitalizations in Adults According to Age and Sex in the 45 and Up Study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pertussis Diagnosis</th>
<th>Pertussis-Coded Hospitalizations (Only A37)</th>
<th>Pertussis-Related Hospitalizations (A37 and Other Respiratory)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Incidence (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Age at recruitment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–64 years</td>
<td>127</td>
<td>95 (80–113)</td>
<td>.7 (.1–5.3)</td>
</tr>
<tr>
<td>65–74 years</td>
<td>44</td>
<td>94 (70–126)</td>
<td>4.3 (1.1–17.0)</td>
</tr>
<tr>
<td>75+ years</td>
<td>34</td>
<td>92 (65–128)</td>
<td>5.4 (1.3–21.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>81</td>
<td>78 (63–97)</td>
<td>2.9 (9–8.9)</td>
</tr>
<tr>
<td>Women</td>
<td>124</td>
<td>109 (91–130)</td>
<td>1.8 (4.7–0)</td>
</tr>
<tr>
<td>Total</td>
<td>205</td>
<td>94 (82–108)</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*Per 100 000 person-years.
Hospitalizations were found to increase with increasing age ($P_{\text{trend}} = .01$) but they did not differ by sex ($P = .4$); see Table 1.

Figure 1 shows pertussis incidence by sociodemographic and health-related characteristics. Besides sex, incidence was greater among those with higher BMI (respectively 82, 87, and 133 per 100 000 person-years in those <25, 25 to <30, and 30+ kg/m$^2$; $P = .02$), among those taking medications or supplements compared to those who were not (101 vs 58 per 100 000 person-years; $P = .01$), and among those with a diagnosis of asthma compared to those without (161 vs 89 per 100 000 person-years; $P = .01$). Incidence did not differ significantly by any of the other 12 factors examined.

After adjustments, high BMI, taking medications or supplements, and a history of preexisting asthma remained significant predictors of incident pertussis (see Table 2). Those with a BMI of 30 kg/m$^2$ or more were 50% more likely than people with a BMI <25 kg/m$^2$ to have pertussis diagnosed, while for those taking medications or supplements, and those with asthma, the risk was about 60% greater than those without asthma or those not taking medications. These estimates did not alter significantly when additional adjustments were made for education, other languages spoken, and alcohol use.

Comparing the cohort findings to the routinely collected pertussis notification and hospitalization data for all NSW residents, the notification rates for the whole state were substantially lower than those estimated in the cohort (particularly in the older population), but hospitalization rates, based on a diagnosis code of ICD-10 A37, were more congruent (Table 3).

### DISCUSSION

This is the first prospective population-based cohort study we are aware of to examine the incidence of pertussis and potential risk factors specifically in middle-aged and older adults. We found an incidence of pertussis of 94 per 100 000, with about 5% of those with incident disease also hospitalized for pertussis or a respiratory illness. While the incidence of diagnosed infections did not differ by age, hospitalization rates did, with substantially higher rates in older adults—11.5% (9/78) of those over 65 years with notified pertussis were hospitalised, compared with 2.4% (3/127) of those aged 45–64 years (Table 1). After adjusting for various factors, we also found that adults with a higher BMI, those taking medications or supplements, and those having a history of asthma had a 50%–60% greater risk of incident pertussis.

Given the limited information on pertussis incidence in older adults, we extracted information on this age group from 2006 to 2008 from routinely collected data in NSW (Table 3), the state where the cohort study was conducted. Compared to the 45 and Up Study participants, these data suggested a lower absolute incidence of pertussis diagnoses, but for hospitalizations, based only on those coded with ICD-10 A37, rates were more comparable. Diagnosing pertussis in adults can be difficult because of nonspecific symptoms [25] and it is known that routine surveillance data, such as was used for case ascertainment in this study, will underestimate true population incidence [2, 26, 27]. We used linked pertussis notifications in the cohort study and would therefore expect our incidence estimates to be similar to that for the whole of NSW from routinely collected surveillance data; however, the 45 and Up cohort may be more health conscious (as their smoking and private health insurance status suggests [16]) and therefore more likely to seek medical attention for persistent coughs. This may explain the higher age-specific rates of pertussis diagnoses in the study population. The similarity in age-specific hospitalization rates between the cohort and whole of state data based on a diagnosis with ICD-10 code A37 alone is reassuring, as hospitalizations are less likely to be influenced by health-seeking behavior. Taken together, the difference in diagnosis rates but similarity in hospitalization rates suggests that the incidence estimates from the cohort are valid and may better reflect real pertussis incidence through greater ascertainment in a more health-conscious population.

Previous case series have suggested that female sex, asthma, and smoking may be associated with increased severity of pertussis symptoms [4, 28]. We found that obesity, asthma, and use of medications/supplements, but not smoking, were associated with incident pertussis infection after adjusting for age, sex, and other factors. It is difficult to differentiate whether the associations with pertussis infection were observed because adults with these characteristics are predisposed to more severe disease or if they are simply more likely to present for medical attention and therefore be diagnosed. While we did not have enough events in this study, in the future, with increased follow-up of the cohort, the use of pertussis-related hospitalizations to assess factors associated with severe disease may be more informative in identifying important risk factors. While we know of no studies that have previously identified obesity as being associated with pertussis infection, obesity appears to predispose adults to other respiratory infections, such as community-acquired pneumonia and influenza [29, 30]. It is therefore plausible that it also increases the risk of an individual contracting or presenting with clinical manifestations of other respiratory pathogens such as pertussis.

The strengths of this study include the large study population, particularly the substantial numbers of adults aged over 65 years, prospective independent ascertainment of pertussis diagnoses in relation to patient risk factors and characteristics, and the use of laboratory-confirmed pertussis diagnoses. Study limitations include the use of passive notification data,
Figure 1. Incidence of pertussis per 100,000 person-years according to various characteristics. *See methods for how categories were defined. Abbreviation: BMI, body mass index.
which will underestimate true population rates compared with active surveillance [26, 31], and variations in the sensitivity of the laboratory tests used for pertussis notifications in Australia. Single-point whole-cell IgA assays are not ideal [32], but such tests have been shown to have high specificity in Australian evaluations when performed in the presence of characteristic symptoms [3, 24]. Also, while PCR testing is more sensitive than culture [33], tests done in Australia do not typically involve multiple primers and therefore there is a possibility of cross-reactivity with other Bordetella types [34]. Regardless, as the majority of diagnoses in this cohort were based on serology, we do not think our estimates are affected by differences in ascertainment through greater use of PCR diagnoses in particular populations.

Regarding loss to follow-up, a small but unknown proportion of participants may have migrated out of the state after recruitment; however, given the relatively short follow-up period, this is unlikely to be great. Similarly, notifications and hospitalizations occurring for participants in neighboring states would not be captured, but for hospitalizations, these are estimated to make up fewer than 2% of admissions in NSW residents. There was insufficient information on contact with young children or other individuals with pertussis in the baseline questionnaire to allow us to examine the possible role of this factor. We also did not have information on immunization settings and not provided at the population level. Given the age range of study participants and that our follow-up ceased at the end of 2008, we would expect that the number of adults recently immunized for pertussis would be extremely low [9]. Therefore, prior to 2009, free adult vaccination was mostly limited to healthcare workers in pediatric and maternity settings and not provided at the population level. Given the age range of study participants and that our follow-up ceased at the end of 2008, we would expect that the number of adults recently immunized for pertussis would be extremely low [9].

Finally, while the study cohort may be healthier than the general NSW population, this is unlikely to bias risk estimates made within the study population [16].

In order to reduce morbidity from pertussis, we need to improve our knowledge of its epidemiology. Although routinely collected data have limitations, our study provides unique prospective information on incident pertussis in older adults. We found that when we accounted for all temporally related respiratory hospitalizations, the hospitalization rate among middle-aged to older adults with pertussis infection was over 5% and that hospitalizations increased with increasing age. This suggests that the burden to health systems from adult pertussis in aging populations may be substantial. The availability of combined diphtheria-tetanus-pertussis vaccine for adults aged over 65 years provides an opportunity to prevent morbidity from pertussis in older adults, and our results,
which identify factors predisposing to pertussis infection, could be considered when targeting pertussis immunization to adult populations.

Notes

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Potential conflicts of interest. P. M. has had the costs of travel paid by the World Health Organization and by Fondation Merieux to attend expert meetings convened by them related to pertussis. P. M. and H. Q. sit on the Australian Government expert advisory committee for immunization, which includes pertussis immunization. E. B. chairs the Australian Government Advisory Committee on the Safety of Medicines, which provides advice on the safety of vaccines. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References