The Pediatric Infectious Disease Journal Publish Ahead of Print

DOI: 10.1097/INF.0000000000001441

Increasing Incidence of Life-Threatening Pertussis: A Retrospective Cohort Study in New Zealand

Emma Macdonald-Laurs[1], MBChB, Anusha Ganeshalingham[2], MB BS, Jonathan Lillie[2], MB BS, Brent McSharry[2], MB BS, Elizabeth R. Segedin[2], FRACP, Emma Best[3,6], FRACP, Avinesh Pillai[4], MSc, Anthony Harnden[5], FRCPCH, Catherine A. Gilchrist[6], PhD, and Cameron C. Grant[1,6], FRACP

Affiliations: [1]General Paediatrics, Starship Children's Hospital, Auckland District Health Board, Auckland, New Zealand; [2]Paediatric Intensive Care Unit, Starship Children's Hospital, Auckland District Health Board, Auckland, New Zealand; [3]Infectious Diseases, Starship Children's Hospital, Auckland District Health Board, Auckland, New Zealand; [4]Department of Statistics, University of Auckland, Auckland, New Zealand; [5]Nuffield Department of Primary Care Health Sciences, University of Oxford, United Kingdom; [6]Department of Paediatrics: Child & Youth Health, University of Auckland, Auckland, New Zealand.

Address correspondence to: Dr. Cameron Grant, Department of Paediatrics: Child and Youth Health, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Wellesley Street, Auckland 1142, New Zealand, E-mail cc.grant@auckland.ac.nz, Phone +64 9 923 6192.

Abbreviated title: Increasing Incidence of Life-Threatening Pertussis

Running head title: Incidence of Life-Threatening Pertussis

Conflict of Interest: Dr. Grant reports to and is a member of the Immunisation Subcommittee of PHARMAC's Pharmacology and Therapeutics Advisory Committee, which

provides advice to the New Zealand government on vaccines to be included in the national immunization schedule. Dr. Best is a member of the Anti-infectives Subcommittee of PHARMAC's Pharmacology and Therapeutics Advisory Committee, which provides advice on funding restrictions, safety, and implementation of new anti-infectives to the New Zealand government. The other authors have no conflicts of interest to disclose. Dr. Best reports grants from Glaxo-Smith-Kline, outside the submitted work. The remaining authors have no financial relationships relevant to this article to disclose.

Financial support: We received no financial support for this study.

Abstract

Background

Pertussis immunization programs aim to prevent severe infant disease. We investigated temporal trends in infant pertussis deaths and pediatric intensive care unit (PICU) admissions and associations of changes in disease detection and vaccines used with death and PICU admission rates.

Methods

Using national data from New Zealand (NZ) we described infant pertussis deaths and PICU admissions from 1991-2013, over which time national immunization coverage at age 2 years increased from <80% to 92%. In NZ, pertussis became a notifiable disease with polymerase chain reaction (PCR) diagnosis available in 1997 and acellular replaced whole-cell vaccine in 2000.

We used Poisson regression to model temporal trends and compared rates in time intervals using rate ratios (RR) with 95% confidence intervals (CI).

Results

There were 10 pertussis deaths and 159 infant PICU admissions with pertussis from 1991-2013. The annual number of infant pertussis PICU admissions increased from 1991 to 2013 (P=0.02) but the number of pertussis deaths did not (P=0.09).

The risk of PICU admission during infancy with pertussis was increased in the notification/PCR vs. the non-notification/PCR era (RR=1.12, 95%CI 1.02-1.19) and when acellular replaced whole-cell vaccine (RR=1.19, 95%CI 1.06-1.31). Median pediatric index of mortality scores during 2001-2013 were lower than during 1991-1999 (P<0.001).

Conclusions

Infant PICU pertussis admission rates have increased in NZ despite improvements in immunization coverage. Higher rates have occurred since pertussis notification/PCR became available and since acellular replaced whole-cell vaccine. The severity of disease in infants admitted to PICU with pertussis has decreased in recent years.

Key Words: Diphtheria-Tetanus-acellular Pertussis Vaccines; Infant; Intensive care; Whooping cough; Mortality.

Introduction

Pertussis remains a severe and sometimes fatal disease to which very young are exquisitely vulnerable. The prevention of fatal and severe disease in young infants remains the primary aim of pertussis immunization strategies.[1]

During the past decade, reported pertussis incidence has increased in several countries including Australia, Portugal, the United Kingdom (UK) and the United States (US).[2-6] It is uncertain whether these increases are due to more disease or an improved capacity to detect disease. In Australia, for example, since 2008 pertussis incidence has increased but pertussis hospitalization rates have remained unchanged and reported deaths from pertussis have decreased. This suggests that most of the increase in pertussis incidence was due to increased detection of less severe disease made possible by polymerase chain reaction (PCR) assays for *Bordetella pertussis*, which became available in Australia in 2000.[3]

In the 1980s and 1990s, driven by the desire for a less reactogenic vaccine,[7] many industrialized countries replaced whole-cell pertussis vaccine with acellular pertussis vaccine.[8] Although acellular vaccines are less reactogenic, they provide less protection against pertussis than the whole-cell vaccines they replaced.[9-12]

Infants experience the most severe pertussis disease, with approximately 60% requiring hospital admission.[13] One-in-ten infants hospitalized with pertussis require admission to the intensive care unit,[14] one-in-six of whom die or are left with brain or lung damage.[15] Significant numbers of infant deaths have characterized recent pertussis epidemics in Australia, England, and the US.[2, 5, 16] Therefore, focusing attention on the epidemiology of fatal or life-threatening pertussis, as defined by the need for intensive care, in young infants provides one of the most relevant information sources for informing decision-making about pertussis prevention strategies.

Relative to other developed countries NZ has a large pertussis disease burden. Infant pertussis hospitalization rates in NZ (2000-2009 average annual rate: 196/100,000)[17] are more than three times higher than in the US (2008: 39/100,000; 2009: 58/100,000).[18] Using data from the New Zealand national disease notification system and New Zealand's only Pediatric Intensive Care Unit (PICU), we aimed to describe changes in pertussis deaths and PICU admissions over the past two decades and to determine associations of rates of such severe disease with changes in pertussis identification and in vaccine policy over this period.

Methods

Study design and setting

We described a national case series of infant pertussis deaths and a retrospective cohort of all infants in New Zealand (NZ) admitted with pertussis to the Starship Children's Hospital PICU from 1991-2013. Since opening in 1991, Starship Children's Hospital PICU has provided NZ pediatric intensive care services to all of NZ. We defined a pertussis PICU admission case as an infant (aged <12 months upon PICU admission); with an International Classification of Diseases discharge diagnosis code for pertussis; and where pertussis was the principal reason for PICU admission. The Northern A Health and Disability Ethics Committee and the Auckland District Health Board Research Review Committee granted ethical approval.

Immunization schedule and coverage in New Zealand

New Zealand has an annual birth cohort of approximately 60,000 which remained stable over the study interval (1991: 61,055, 2013: 58,717).[19] New Zealand has a 3-dose infant primary pertussis vaccine series. A two-year booster was introduced in 1996 and a four-year booster in 2002. In 2006 the two-year booster was discontinued and an adolescent (11-years-old)

booster dose introduced.[20] In the NZ immunization schedule, acellular replaced whole-cell pertussis vaccine in August 2000 (Figure 1).[20]

Immunization surveys from the 1990s and 2000s showed low immunization coverage in NZ (< 80% fully immunized at age two years).[21, 22] In 2007 improving immunization coverage became a national health target and more precise measurement was enabled by the introduction of a National Immunization Register in 2005.[22, 23] Since 2011, immunization coverage at age 2 years has been between 90 and 95%.[24]

Pertussis surveillance, diagnosis and disease burden in New Zealand

Pertussis became a notifiable disease in NZ in 1997. Since then the annual total population pertussis notification rates per 100,000 have been between 4 and 133 (Figure 2), with infant rates between 44 and 781. The proportion of notified cases with laboratory confirmation has ranged from 0.24 (2007) to 0.71 (2002).[25] Since 1997, pertussis PCR gradually became available in NZ for the diagnosis of *B. pertussis* infection.

Data collection and measurements

We utilized national data sets to identify infant pertussis fatalities and two complimentary datasets to identify infant pertussis PICU admissions. Infant pertussis fatalities nationally were determined from NZ Ministry of Health analytical services (1991-2011) and from the annual national public health surveillance pertussis reports for 2012 and 2013.[26]

We have previously described the hospital course and outcomes for all pertussis admissions to the Starship PICU from 1991 until 2003.[15] We extended this series to include infants with a PICU admission date on or before 31st December 2013. Two databases were audited: (i) the Auckland District Health Board (ADHB) database, which is used to report, to the Ministry of Health, all admissions to Starship Children's Hospital since the hospital opened in 1991 and includes measures of the intensity of care received (i.e. PICU admission); and (ii) the Starship

PICU database, which records all admissions to PICU since the PICU opened in 1991 and is used for reporting to the Australian and NZ Intensive Care Society. Information collected on our pertussis cases included demographic and immunization data, presenting clinical characteristics, clinical course in the PICU, and outcomes.

Area-level socio-economic deprivation was measured using the NZ Index of Deprivation (NZDep06), grouped as quintiles. NZDep06 combines nine socioeconomic characteristics from 2006 census data collected at aggregations of approximately 100 people and assigned to individual observations based on geo-coded address data.[27]

Data analysis

We described the number of pertussis infant deaths, the number of infant pertussis PICU admissions and the infant pertussis hospitalization rates in NZ from 1991 to 2013 and NZ pertussis notification rates for all ages from 1997 to 2013. We determined whether the number of infant pertussis deaths, the number of infant pertussis PICU admissions, and the rates of infant pertussis hospitalizations and pertussis notifications for all ages changed over this time interval.

Poisson regression was used to determine if there were changes in the number of events per year, based upon the assumption that both pertussis deaths and PICU admissions are rare events. Poisson model fit was assessed using the goodness of fit chi-square test, and over-dispersion using the deviance statistic divided by the model degrees of freedom. The model was an adequate fit to the data. We used linear regression to determine whether infant pertussis hospitalization rates and pertussis notification rates for all ages changed over time.

Comparisons were made of the infant pertussis mortality rate and infant pertussis PICU admission rate by time intervals defined by changes in (i) pertussis disease identification capability, (ii) in national immunization coverage estimates, (iii) the number of pertussis

vaccine booster doses in the immunization schedule and, (iv) the type of pertussis vaccine used (Table 1).

The denominator used for these rate comparisons was the annual national birth cohort obtained from Statistics NZ.[28] Comparisons of rates during time intervals were described using rate ratios (RR) and 95% confidence intervals (CI). Data collected during the year in which the changes occurred was excluded from these comparisons. For example, the comparison of periods of less versus greater pertussis disease identification capacity excluded the pertussis infant deaths and PICU admissions that occurred in 1997, the year in which pertussis became a notifiable disease and PCR became available.

For the infants admitted to PICU with pertussis, we compared their demographics and immunization status, and illness presentation and management between the same time intervals defined by changes in pertussis surveillance and in vaccine coverage, schedule, and type. We included in these comparisons each infant's Pediatric Index of Mortality (PIM) score. The PIM score utilizes measures of the presenting illness, clinical and metabolic instability, and intensity of care required to estimate the risk of death on admission to PICU.[29]

For these comparisons, we used the chi-square or Fisher's exact tests for categorical variables and the Wilcoxon rank sum test for continuous variables. As 33 variables were compared between each pair of time intervals, a Bonferroni adjustment for multiple comparisons was made and the level of significance set at a *P*-value of <0.0015. Data were analyzed using SAS version 9.3 (SAS Inc. Cary, NC, USA) and Statsdirect version 2.7.9 (Altrincham, Cheshire, UK).

Results

National infant pertussis mortality and pediatric intensive care unit pertussis admissions

There were 10 infant pertussis deaths during the study period (Figure 2). Median age at hospital presentation of those who died was 30 days. Only one of these infants (age 53 days) was old enough to, and had received, the first (6-week) pertussis vaccine dose.

One-hundred-and-sixty-six children were admitted to PICU with pertussis from 1991 to 2013, 164 listed in the ADHB database and 160 in the PICU database. Of these 166, 159 (96%) were <12 months old at the time of PICU admission.

From 1991 to 2013, the number of infants admitted to PICU with pertussis each year ranged from zero and twenty-two, and the annual infant pertussis hospital admission rate ranged from 54 to 724 per 100,000 (Figure 2), with year-to-year variation in keeping with the established 2-5 year cycle of epidemic pertussis in NZ.[30]

In Poisson regression models, from 1991 to 2013 the annual number of infants admitted to PICU with pertussis increased (P=0.02), but neither the number of infants dying each year from pertussis (P=0.09) nor the number of infants admitted to hospital with pertussis (P=0.12) changed (Figure 2).

The average annual infant mortality rate from pertussis did not differ in comparisons between time intervals defined by changes in pertussis surveillance or in vaccine coverage, schedule, or type (Table 1). The average annual infant pertussis PICU admission rate was higher when pertussis was a notifiable disease and PCR confirmation was available (1998-2013), compared with when pertussis was not a notifiable disease and PCR was unavailable (1991-1996) (RR=1.12, 95% CI 1.02-1.19). Compared with when the pertussis immunization schedule had zero boosters, the average annual infant pertussis admission rate was higher

when the immunization schedule included one (RR=1.38, 95% CI 1.14-1.58) but not two (RR=1.11, 95% CI 0.98-1.22) booster doses. When the national immunization schedule used acellular pertussis vaccine the average annual pertussis PICU admission rate was also higher, compared with when the whole-cell vaccine was used (RR=1.19, 95% CI 1.06-1.31).

Demographics, immunization status and household cough contacts of infants with pertussis admitted to the pediatric intensive care unit (PICU) (Table 2)

We observed no differences in infant demographics, number of pertussis vaccine doses received, or exposure to household contacts with cough when comparing time intervals defined by pertussis identification capacity (notification/PCR unavailable versus available) and pertussis vaccine received (whole-cell versus acellular). Infants living in more deprived households appeared at increased risk of admission to PICU with pertussis, with 76 (50%) of the 151 infants, for whom household deprivation was defined, living in the most deprived quintile of NZ households. A coughing contact was present in the households of 87 (70%) of the 125 infants for whom household coughing contacts status was defined.

Clinical characteristics of illness on hospital presentation of infants with pertussis admitted to the pediatric intensive care unit (Table 3)

The clinical characteristics of pertussis illness on hospital presentation did not differ in comparisons between time intervals defined by pertussis identification capacity. Compared to when whole-cell vaccine was in use, when acellular vaccine was in use a smaller proportion of infants with pertussis had apnea as a hospital presenting symptom (57% vs. 88%, $P<0.001$).

Length of pediatric intensive care unit (PICU) stay and ventilatory support provided to infants with pertussis admitted to the PICU (Table 4)

The PIM score varied between the time intervals compared, being significantly lower in the acellular compared with the whole-cell vaccine era ($P<0.001$) with the comparison between time intervals defined by pertussis identification capacity approaching statistical significance ($P=0.006$). No differences were evident in the duration of PICU stay or in ventilator support requirements in comparisons of time intervals defined by pertussis identification capacity. The comparison of the median duration of PICU stay during the period when acellular (8 days) versus whole-cell (4 days) vaccine was used approached statistical significance ($P=0.002$).

The proportion of infants who, during their PICU admission, had pneumonia, seizures, shock, or pulmonary hypertension did not differ in comparisons of pertussis identification capacity or of pertussis vaccine type.

Discussion

Our study reports data from 23 years (1991-2013) of pertussis experience in the NZ PICU setting and is the only case series to date that covers a period of sufficient length to investigate temporal trends in infant pertussis requiring intensive care. Over this period, during which national immunization coverage improved substantially, we observed an increase in the annual number of infants admitted to PICU with pertussis but not in the number of pertussis deaths or the national infant pertussis hospitalization rate. The risk of PICU admission with pertussis varied during overlapping time intervals defined by the availability of pertussis notification/PCR and by the type of vaccine, whole-cell or acellular, used in the national immunization schedule. Based upon the PIM score, infants admitted to PICU in recent years had a lower risk of death.

Our PICU has contributed data to the Australian and NZ Pediatric Intensive Care Registry since establishment of the registry in 1997 and benchmarking against the entire registry occurs annually. A steering committee scrutinizes the efficiency (length of stay) and effectiveness (mortality) of the PICU each year. Since 1997, our PICU has been within the 95% confidence intervals for acceptable efficiency and effectiveness.[29]

To minimize the risk of missed cases, we used two complimentary databases. We have previously shown that underreporting of the number of infants hospitalized with pertussis in NZ is modest (16-19%).[14] Underreporting of pertussis cases occurs less frequently in younger patients with more severe disease.[31, 32] Recent data shows that the underestimation of infant pertussis deaths in England is small (approximately 2%).[16]

Our study has some significant limitations. Due to the short time-interval between the introduction of pertussis notification/PCR (1998) and the acellular vaccine replacing whole-cell vaccine (2000), we were unable to assess the independence of the relationship between these factors and the risk of PICU admission with pertussis. Lower PIM scores emerged with the advent of pertussis notification/PCR (1998) and were evident following the adoption of acellular vaccine (2001). This implies that there has either been increased identification of less severe cases of pertussis or changes in PICU admission criteria during recent years. The annual PICU admissions for several conditions of comparable prevalence to pertussis, for example cerebral bleed, encephalitis, and Guillain–Barré syndrome, remained unchanged over the study interval (data available from corresponding author). Therefore, it seems more likely that this change in PIM score reflects the increased capacity that PCR has provided for diagnosing pertussis, despite the atypical presentations characteristic of the young infant age group.[15]

A smaller proportion of infants had apnea when the acellular pertussis vaccine was included in the NZ national immunization schedule. A recent US study found that apnea was less prevalent in patients infected with *B. pertussis* deficient in the adhesion molecule, pertactin (PRN^-).[33] PRN^- *B. pertussis* strains appear to have a selective advantage in individuals immunized with the acellular pertussis vaccine and PRN^- strains have recently emerged in regions where the acellular pertussis vaccine is in use, including Australia, Israel, Europe, and North America.[33-36] Although we do not have data on the prevalence of PRN^- *B. pertussis* in NZ, the reduction in apnea observed during the acellular vaccine era may be a result of infection with PRN^- *B. pertussis*.

Our data cannot establish causality for the associations observed between pertussis control strategies and infant pertussis PICU admission rates. Over the period of our study, overlapping changes occurred in our capacity to identify pertussis cases, immunization coverage, and the number of doses and types of pertussis vaccine in the immunization schedule, each of which had the potential to influence infant pertussis PICU admission rates. For example, PCR increases the capacity for laboratory confirmation of *B. pertussis* infection by approximately 20% among infants admitted to a PICU or a pediatric ward with a respiratory illness consistent with pertussis.[37] Timeliness of the primary immunization series reduces the risk of hospital admission with pertussis during infancy.[38] Discontinuation of the year two booster dose of pertussis vaccine since 2006 could have resulted in more rapid waning on immunity in preschool aged children,[39] age groups known to be important transmitters of *B. pertussis* and other respiratory pathogens to young infants.[40] The more rapid waning in immunity that occurs in school-aged children and adolescents who receive an immunization series that only includes acellular vaccine, compared with series that contain at least one dose of whole-cell, could also result in these age groups having become a more important source of *B. pertussis* transmission to young infants in NZ in recent years.[9]

The characteristics of the children, the illnesses and their management of this case series are comparable to that reported from a National Institute for Health and Human Development (NICHD) Critical Pertussis study in their prospective cohort study of infants admitted to 25 PICUs in the US from 2008 to 2011.[41, 42] For example, the infants enrolled in our study and the NICHD study were comparable with respect to median age at PICU admission (46 versus 49 days), duration of cough pre-PICU admission (6 vs. 8 days), percentage requiring mandatory ventilation (43% vs. 43% (NICHD)), and percentage dying in PICU (5% vs. 9%).[41] Characteristics of the infants with pertussis who died in this case series are consistent with other contemporary studies that have described that fatal pertussis occurs almost exclusively in those too young to be immunized.[43, 44]

Alongside this US multicenter study,[41] the recent establishment of other multicenter networks of hospitals that provide intensive care for infants with pertussis in Australia[29] and Europe[45] will allow for better understanding globally of temporal trends of severe infant pertussis disease burden and the impact on this of changes in disease prevention strategies and in the response of *B. pertussis* to these disease control strategies, such as the emergence of PRN^- *B. pertussis* in association with exposure to acellular pertussis vaccine.[33, 46]

Of concern, the increase we observed in the annual number of infants admitted to PICU with pertussis occurred over a period when immunization coverage in NZ increased from <80% in 1991 to 92% in 2013.[47 48] Immunization coverage since the late 2000s is the highest that NZ has ever achieved. However, immunization timeliness remains suboptimal. In the 12 months to December 2013, although 93% of infants in NZ had received the complete three-dose primary immunization series (due at 6 weeks, 3 months and 5 months) by age 12 months, only 77% had completed the series by age six months.[48] In our study, the majority (73%) of the infants admitted to PICU with pertussis were unimmunized. Although virtually all of the infants admitted to PICU with pertussis were too young to have received their complete

immunization series, 50% were aged 6 weeks or older when hospitalized and hence old enough for at least one dose of pertussis vaccine, which provides protection against hospital admission with pertussis.[39]

Our study reports national rather than regional data, allowing consideration of infant pertussis requiring intensive care in the context of national pertussis notification and hospitalization data, and changes to national immunization schedules and coverage. During the study period vaccine coverage increased in NZ, potentially due to adoption of the acellular pertussis vaccine. While the annual number of pertussis PICU admissions increased following the change to acellular vaccine, the severity of their disease decreased. Therefore, the increase in number of PICU pertussis admissions is more likely due to increased disease identification than to an effect attributable to the acellular vaccine.

As the prevention of fatal and severe pertussis disease in young infants remains the primary aim of pertussis immunization strategies,[1] the increase in number of PICU admissions implies that the switch to aP has not as yet had the desired effect on pertussis control in New Zealand.

The data reported here indicate the need to consider additional refinements of pertussis control in NZ, in addition to improving the timeliness and completeness of delivery of the current child and adolescent immunization schedule. The demonstration that a dose of acellular pertussis vaccine given during pregnancy reduces the risk of pertussis in infants <3-months-old makes the achievement of high coverage with this vaccine dose a clear priority.[49]

Fifty-five percent of the infants in our series lived in the most deprived 20% of NZ households, which includes approximately 31% of NZ families with children.[27] In NZ, immunization timeliness is poorer for children living in more socioeconomically deprived households.[24] However, infants living in poorer households require the timeliest immunization, as they have a higher risk of pertussis requiring hospitalization.[50] In order to

gain the full population benefits of immunization, we must give greater priority to achieving timely immunization in this at-risk group. Improving immunization delivery to population subgroups with a greater burden of vaccine preventable disease is an achievable goal, as has been demonstrated with sustained improvements in immunization coverage in American Indian and Alaska Native children.[51]

Acknowledgements

We wish to acknowledge the assistance of Lauren Moss, Data Analyst, Business Intelligence, Auckland District Health Board. The Department of Paediatrics at the University of Auckland funds Dr. Gilchrist's medical writer position. Cameron Grant had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. There was no external funding for this study.

References

1. McIntyre P, Wood N. Pertussis in early infancy: disease burden and preventive strategies. *Curr Opin Infect Dis*. 2009;22:215-223.

2. Government of Western Australia. Ongoing pertussis epidemic in Western Australia. . *DiseaseWatch*. 2012;16.

3. WHO SAGE pertussis working group. WHO SAGE pertussis working group. Background paper. SAGE April 2014. 2014. Available at: http://www.who.int/immunization/sage/meetings/2014/april/1_Pertussis_background_FINAL4_web.pdf?ua=. Accessed 22nd September, 2015.

4. Amirthalingam G. Strategies to control pertussis in infants. *Arch Dis Child*. 2013;98:552-555.

5. Roehr B. Whooping cough outbreak hits several US states. *BMJ*. 2010;341:c4627.

6. Cherry JD. Epidemic Pertussis in 2012 — The Resurgence of a Vaccine-Preventable Disease. *New Engl J Med*. 2012;367:785-787.

7. Cherry JD, Olin P. The science and fiction of pertussis vaccines. *Pediatrics*. 1999;104:1381-1383.

8. Cherry JD. Comparative efficacy of acellular pertussis vaccines: an analysis of recent trials [see comments]. *Pediatr Infect Dis J*. 1997;16:S90-96.

9. Witt MA, Arias L, Katz PH, Truong ET, Witt DJ. Reduced risk of pertussis among persons ever vaccinated with whole cell pertussis vaccine compared to recipients of acellular pertussis vaccines in a large US cohort. *Clin Infect Dis*. 2013;56:1248-1254.

10. Tartof SY, Lewis M, Kenyon C, et al. Waning Immunity to Pertussis Following 5 Doses of DTaP. *Pediatrics*. 2013;131:e1047-1052.

11. Klein NP, Bartlett J, Fireman B, Rowhani-Rahbar A, Baxter R. Comparative effectiveness of acellular versus whole-cell pertussis vaccines in teenagers. *Pediatrics*. 2013;131:e1716-1722.

12. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. *New Engl J Med*. 2012;367:1012-1019.

13. Cortese MM, Baughman AL, Zhang R, Srivastava PU, Wallace GS. Pertussis hospitalizations among infants in the United States, 1993 to 2004. *Pediatrics*. 2008;121:484-492.

14. Somerville RL, Grant CC, Grimwood K, et al. Infants hospitalised with pertussis: estimating the true disease burden. *J Paediatr Child Health*. 2007;43:617-622.

15. Surridge J, Segedin ER, Grant CC. Pertussis requiring intensive care. *Arch Dis Child*. 2007;92:970-975.

16. van Hoek AJ, Campbell H, Amirthalingam G, Andrews N, Miller E. The number of deaths among infants under one year of age in England with pertussis: results of a capture/recapture analysis for the period 2001 to 2011. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin*. 2013;18.

17. Grant CC. Recent indication of progress in pertussis hospitalisation rates in NZ. *Aust N Z J Public Health*. 2012;36:398.

18. Auger KA, Patrick SW, Davis MM. Infant hospitalizations for pertussis before and after Tdap recommendations for adolescents. *Pediatrics*. 2013;132:e1149-1155.

19. Statistics New Zealand. Cohort life tables 2014. Available at: http://www.stats.govt.nz/browse_for_stats/health/life_expectancy/cohort-life-tables.aspx.

20. Ministry of Health. *Immunisation Handbook 2014*. Wellington: Ministry of Health; 2014.

21. Lennon D, Jarman J, Jones N, et al. Immunisation coverage in North Health. Comparative results from North Health's 1996 immunisation coverage survey. Auckland: Northern Regional Health Authority; 1997:1-31.

22. Ministry of Health. The National Childhood Immunisation Coverage Survey 2005. Wellington: Ministry of Health; 2007.

23. Ministry of Health. Health Targets: Moving towards healthier futures 2007. Available at: http://www.moh.govt.nz/healthtargets. Accessed 14th December 2012, 2012.

24. Ministry of Health. National and DHB immunisation data. 2013. Available at: http://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/immunisation-coverage/national-and-dhb-immunisation-data.

25. Institute of Environmental Science & Research Limited. Public Health Surveillance Annual Surveillance Summary 2014. Available at: https://surv.esr.cri.nz/surveillance/annual_surveillance.php.

26. ESR, Ministry of Health. Public Health Surveillance pertussis report 2014. Available at: https://surv.esr.cri.nz/surveillance/PertussisRpt.php. Accessed 20th November, 2014.

27. Salmond C, Crampton P, Atkinson J. NZDep2006 Index of Deprivation. Wellington: Department of Public Health, University of Otago; 2007.

28. Statistics New Zealand. Births 2014. Available at: http://www.stats.govt.nz/browse_for_stats/population/births.aspx.

29. Straney L, Clements A, Parslow RC, et al. Paediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care. *Pediatr Crit Care Med*. 2013;14:673-681.

30. Somerville RL, Grant CC, Scragg RK, Thomas MG. Hospitalisations due to pertussis in New Zealand in the pre-immunisation and mass immunisation eras. *J Paediatr Child Health*. 2007;43:147-153.

31. Fine PE, Clarkson JA. Seasonal influences on pertussis. *Int J Epidemiol*. 1986;15:237-247.

32. Sutter RW, Cochi SL. Pertussis hospitalizations and mortality in the United States, 1985-1988. Evaluation of the completeness of national reporting. *JAMA*. 1992;267:386-391.

33. Martin SW, Pawloski L, Williams M, et al. Pertactin-Negative *Bordetella pertussis* Strains: Evidence for a Possible Selective Advantage. *Clin Infect Dis*. 2015;60:223-227.

34. Bamberger E, Abu Raya B, Cohen L, et al. Pertussis Resurgence Associated with Pertactin-Deficient and Genetically Divergent *Bordetella Pertussis* Isolates in Israel. *Pediatr Infect Dis J*. 2015;34:898-900.

35. Zeddeman A, van Gent M, Heuvelman CJ, et al. Investigations into the emergence of pertactin-deficient *Bordetella pertussis* isolates in six European countries, 1996 to 2012. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin*. 2014;19.

36. Tsang RS, Shuel M, Jamieson FB, et al. Pertactin-negative *Bordetella pertussis* strains in Canada: characterization of a dozen isolates based on a survey of 224 samples collected in different parts of the country over the last 20 years. *Int J Infect Dis*. 2014;28:65-69.

37. Fry NK, Duncan J, Wagner K, et al. Role of PCR in the diagnosis of pertussis infection in infants: 5 years' experience of provision of a same-day real-time PCR service in England and Wales from 2002 to 2007. *J Med Microbiol*. 2009;58:1023-1029.

38. Grant CC, Roberts M, Scragg R, et al. Delayed immunisation and risk of pertussis in infants: unmatched case-control study. *Br Med J*. 2003;326:852-853.

39. Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of protection after first dose of acellular pertussis vaccine in infants. *Pediatrics*. 2014;133:e513-519.

40. Jardine A, Conaty SJ, Lowbridge C, Staff M, Vally H. Who gives pertussis to infants? Source of infection for laboratory confirmed cases less than 12 months of age during an

epidemic, Sydney, 2009. *Communicable diseases intelligence quarterly report*. 2010;34:116-121.

41. Berger JT, Carcillo JA, Shanley TP, et al. Critical pertussis illness in children: a multicenter prospective cohort study. *Pediatr Crit Care Med*. 2013;14:356-365.

42. Burr JS, Jenkins TL, Harrison R, et al. The Collaborative Pediatric Critical Care Research Network Critical Pertussis Study: collaborative research in pediatric critical care medicine. *Pediatr Crit Care Med*. 2011;12:387-392.

43. Mikelova LK, Halperin SA, Scheifele D, et al. Predictors of death in infants hospitalized with pertussis: a case-control study of 16 pertussis deaths in Canada. *J Pediatr*. 2003;143:576-581.

44. Winter K, Zipprich J, Harriman K, et al. Risk Factors Associated With Infant Deaths From Pertussis: A Case-Control Study. *Clin Infect Dis*. 2015;61:1099-1106.

45. Heininger U, Weibel D, Richard JL. Prospective nationwide surveillance of hospitalizations due to pertussis in children, 2006-2010. *Pediatr Infect Dis J*. 2014;33:147-151.

46. Hegerle N, Dore G, Guiso N. Pertactin deficient *Bordetella pertussis* present a better fitness in mice immunized with an acellular pertussis vaccine. *Vaccine*. 2014;32:6597-6600.

47. Anonymous. Immunisation coverage in New Zealand. *Communicable Disease New Zealand*. 1992;92:1-13.

48. Ministry of Health. Immunisation Coverage National and DHB Data for 12 months ending Dec 2013. Wellington: Ministry of Health; 2014.

49. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet*. 2014;384:1521-1528.

50. Lopez MA, Cruz AT, Kowalkowski MA, Raphael JL. Trends in hospitalizations and resource utilization for pediatric pertussis. *Hosp pediatr*. 2014;4:269-275.

51. Groom AV, Santibanez TA, Bryan RT. Vaccination coverage among American Indian and Alaska native children, 2006-2010. *Pediatrics*. 2012;130:e1592-1599.

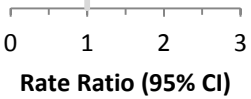
Figure Legends

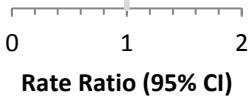
Figure 1. Pertussis immunization schedule in New Zealand 1991 to 2013.

Figure 2. Pertussis disease burden in New Zealand (1991-2013), as shown by number of infant pertussis deaths; infant pertussis admissions to the Pediatric Intensive Care Unit (PICU); infant pertussis hospitalization rates; and from 1997-2013, pertussis notification rates for all ages.

Table 1. Associations of annual infant pertussis mortality and Pediatric Intensive Care Unit (PICU) admission rates with changes in (i) pertussis identification through notification and use of polymerase chain reaction; (ii) pertussis vaccine coverage and number of booster doses in the national immunization schedule and; (iii) type of pertussis vaccine used in New Zealand (1991-2013).

	Infant pertussis deaths			Infant pertussis PICU admissions		
Variable	**Average annual infant mortality rate from pertussis per 100,000 live-births-per-year**	**Rate ratio (95%CI)**	**Forest Plot**	**Average annual infant PICU admission rate for pertussis per 100,000 live-births-per-year**	**Rate ratio (95% CI)**	**Forest Plot**
Pertussis disease identification						
Pertussis notification						
Not a notifiable disease and PCR not available (1991-1996)	0.05	1.00		1.38	1.00	
Notifiable disease and PCR available (1998-2013)	0.06	1.23 (0.82-1.35)		0.84	1.12 (1.02-1.19)	
Pertussis vaccine coverage and immunization schedule						
Pertussis immunization coverage*						
Less than 80% (1991-2007)	0.04	1.00		0.64	1.00	
80% or more (2008-2013)	0.18	1.46 (0.61-2.51)		2.33	1.19 (0.94-1.47)	
Number of boosters in schedule						
0 (1991-1995)	0.00	-		1.51	1.00	
1 (1997-2001)	0.14	1.00		3.27	1.38 (1.14-1.58)	
2 (2003-2013)	0.08	1.07 (0.58-1.32)		1.02	1.11 (0.98-1.22)	
Type of pertussis vaccine used in national immunization schedule						
Type of pertussis vaccine used*						
Whole-cell (1991-1999)	0.02	1.00		0.86	1.00	
Acellular (2001-2013)	0.08	1.48 (0.94-1.63)		1.00	1.19 (1.06-1.31)	





* For comparisons of the changes that occurred in pertussis becoming a notifiable disease, in pertussis PCR being available, in number of booster doses of pertussis vaccine and the timing of these doses and in the type of pertussis vaccine used the year in which that change occurred was not included in the analysis.

CI - confidence interval

PCR - polymerase chain reaction

Table 2 . Demographics, immunization status, and household cough contacts of infants with pertussis admitted to the Pediatric Intensive Care Unit **(**PICU): comparison between time intervals defined by pertussis identification capacity and type of vaccine used in the national immunization schedule.

			Time interval defined by pertussis identification capacity			Time interval defined by type of pertussis vaccine used		
Variable	**n**	**All infants admitted to PICU with pertussis from1991 to 2013**	**Not a notifiable disease, PCR not available (1991-1996) n_1=29**	**Notifiable disease and PCR available (1998-2013) n_2=127**	***P*-value**	**Whole-cell pertussis vaccine (1991-1999) n_3 = 40**	**Acellular pertussis vaccine (2001-2013) n_4 = 100**	***P*-value**
Age in months, median (IQR)	159	1.5 (1.0-2.1)	1·7 (1·1-2·1)	1·5 (0.9-2·1)	0·10	1.7 (0.9-2.2)	1.4 (1.0-2.0)	0.19
Female gender, n (%)	159	76 (48)	14 (48)	62 (49)	0·96	18 (45)	49 (49)	0.67
Weight in kg, mean (SD)	154	4.49 (1.40)	4·71 (1·78)	4·44 (1·46)	0·12	4.59 (1.33)	4.45 (1.33)	0.60
Gestation < 37 weeks, n (%)	159	44 (28)	9 (31)	34 (27)	0.64	14 (35)	27 (27)	0.35
Comorbidity* present, n (%)	159	20 (13)	6 (21)	14 (11)	0·16	6 (15)	12 (12)	0.63
Household deprivation, n (%)†	151				0.08			0.10
1		8 (5)	3 (11)	5 (4)		3 (8)	3 (3)	
2		12 (8)	1 (4)	11 (9)		2 (5)	10 (10)	
3		18 (12)	0 (0)	18 (15)		1 (3)	16 (16)	
4		37 (25)	7 (26)	28 (23)		11 (30)	19 (18)	
5		76 (50)	16 (59)	60 (49)		20 (54)	52 (50)	
Ethnicity, n (%)‡	155				0.40			0.22
European		38 (25)	9 (31)	27 (22)		12 (30)	22 (22)	
Maori		60 (39)	11 (38)	48 (39)		16 (40)	37 (37)	
Pacific		47 (30)	9 (31)	38 (31)		12 (30)	23 (23)	
Other		9 (6)	0 (0)	9 (7)		0 (0)	9 (9)	

Number of pertussis vaccine doses received, n (%)	159				0.36				0.28
0		116	(73)	20 (69)	93	(73)	28	(70)	73 (73)
1		33	(21)	9 (31)	24	(19)	10	(25)	19 (19)
2		4	(2)	2 (0)	4	(3)	2	(5)	2 (2)
3		6	(4)	0 (0)	6	(5)	0	(0)	6 (6)
Other household members with cough, n (%)[§]	125	87	(70)	15 (68)	71	(70)	0·85	21 (70)	58 (69) 0.92
Child in household coughing, n (%)[‖]	89	51	(57)	12 (63)	39	(57)	0·60	15 (63)	28 (52) 0.38
Adult in household coughing, n (%)[¶]	87	49	(56)	5 (41)	43	(59)	0·26	9 (50)	37 (59) 0.51

* Congenital heart disease (n=4), chronic lung disease (n=9), other co-morbidity (n=10)

† n_1=27, n_2=122, n_3 = 37, n_4 = 97. Area-level socio-economic deprivation was measured using the NZ Index of Deprivation (NZDep06), grouped as quintiles.[1]

‡ n_1=29, n_2=122, n_3 = 40, n_4 = 100

§ n_1=22, n_2=101, n_3 = 30, n_4 = 84

‖ n_1=19, n_2=69, n_3 = 24, n_4 = 54

¶ n_1=12, n_2=73, n_3 = 18, n_4 = 63

IQR – interquartile range

SD – standard deviation

1. Salmond C, Crampton P, Atkinson J. NZDep2006 Index of Deprivation. Wellington: Department of Public Health, University of Otago; 2007.

Table 3. Clinical characteristics of illness on hospital presentation for infants with pertussis admitted to the Pediatric Intensive Care Unit (PICU): comparison between time intervals defined by pertussis identification capacity and type of vaccine used in the national immunization schedule.

Variable	n	All infants admitted to PICU with pertussis (1991-2013)	Time interval defined by pertussis identification capacity			Time interval defined by type of pertussis vaccine used		
			Not a notifiable disease, PCR not available (1991-1996) n_1=29	Notifiable disease and PCR available (1998-2013) n_2=127	*P*-value	Whole-cell pertussis vaccine (1991-1999) n_3 = 40	Acellular pertussis vaccine (2001-2013) n_4 = 100	*P*-value
Cough duration pre-admission (days), median (IQR)*	156	6(3-12)	5 (2-7)	7(3-12)	0.22	5(2-10)	7(4-12)	0.11
Number of case-defining symptoms, n (%)	159				0.18			0.28
0		15 (9)	3 (10)	12 (9)		4 (10)	8 (8)	
1		59 (37)	7 (24)	51 (40)		11 (27)	40 (40)	
2		57 (36)	11 (38)	45 (35)		15 (38)	39 (39)	
3 or 4		28 (18)	8 (28)	19 (15)		10 (25)	13 (13)	
Presence of any case-defining symptom, n (%)								
Paroxysmal cough	159	113 (71)	20 (69)	91 (72)	0.77	26 (65)	78 (78)	0.11
Apnea	159	106 (67)	25 (86)	78 (61)	0.01	35 (88)	57 (57)	<0.001
Post-tussive vomit	159	28 (18)	6 (21)	21 (17)	0.59	8 (20)	17 (17)	0.68
Whoop	159	13 (8)	3 (10)	9 (7)	0.70	4 (10)	6 (6)	0.47
Laboratory Findings								
Peripheral leukocyte count ($x10^9$/L), median (IQR)†	154	21.7 (12.7-31.6)	17.0 (11.1-27.2)	22.3 (12.9-32.0)	0.18	17.2 (11.6-32.4)	22.1 (13.1-29.7)	0.52
Peripheral lymphocyte count ($x10^9$/L), median (IQR)‡	150	12.3 (7.1-19.2)	10.8 (6.0-16.7)	12.4 (7.1-19.4)	0.47	11.4 (7.1-19.3)	12.3 (6.6-18.9)	0.94

Laboratory confirmation of *Bordetella pertussis* infection, n (%)	159	101 (64)	9 (31)	90 (72)	<0.001	14 (35)	77 (77)	<0.001
Culture positive for *B. pertussis*, n (%)	159	43 (27)	6 (21)	36 (28)	0.41	7 (18)	35 (35)	0.04

* n_1=29, n_2=124, n_3=40, n_4=97
† n_1=29, n_2=124, n_3=38, n_4=97
‡ n_1=29, n_2=120, n_3=38, n_4=94
IQR – interquartile range

Table 4. Severity of pertussis disease in infants admitted to the Pediatric Intensive Care Unit (PICU): comparison between time intervals defined by pertussis identification capacity and type of vaccine used in the national immunization schedule.

Variable	n	All infants admitted to PICU with pertussis from 1991 to 2013	Time interval defined by pertussis identification capacity			Time interval defined by type of pertussis vaccine used		
			Not a notifiable disease, PCR not available (1991-1996) n_1=29	Notifiable disease and PCR available (1998-2013) n_2=127	*P*-value	Whole-cell pertussis vaccine (1991-1999) n_3 = 40	Acellular pertussis vaccine (2001-2013) n_4 = 100	*P*-value
Pediatric Index of Mortality (PIM) score, median (IQR)*	150	0.008 (0.000-0.028)	0.009 (0.008-0.043)	0.008 (0.000-0.024)	0.006	0.010 (0.008-0.049)	0.000 (0.000-0.013)	<0.001
Total days in PICU, median (IQR)	159	7(3-12)	4 (2-7)	7 (4-13)	0.02	4 (3-7)	8 (4-14)	0.002
Assisted ventilation								
CPAP, n (%)	159	33 (21)	3 (10)	29 (23)	0.13	5 (13)	21 (21)	0.24
Mandatory ventilation, n (%)	159	69 (43)	9 (31)	59 (47)	0.13	13 (33)	45 (45)	0.18
Duration of mandatory ventilation (days)†, median (IQR)	69	4 (2-9)	3 (2-4)	4 (2-10)	0.11	3 (2-4)	4 (2-10)	0.12
Complications in PICU, n (%)								
Pneumonia	159	55 (35)	12 (41)	43 (34)	0.44	16 (40)	27 (27)	0.13
Seizures	159	8 (5)	3 (10)	5 (4)	0.17	3 (8)	4 (4)	0.41
Shock	159	8 (5)	0 (0)	8 (6)	0.35	0 (0)	6 (6)	0.18
Pulmonary hypertension	159	14 (9)	0 (0)	14 (11)	0.07	0 (0)	11 (11)	0.03
Died in intensive care unit	159	8 (5)	0 (0)	8 (6)	0.35	0 (0)	7 (7)	0.19

* percentage probability of death at the time of first contact with the PICU team[1]

† n_1=9, n_2=59, n_3=13, n_4=45

IQR – interquartile range

CPAP – continuous positive airway pressure

1. Straney L, Clements A, Parslow RC, et al. Paediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care. *Pediatr Crit Care Med*. 2013;14:673-681.

Figure 1. Pertussis immunization schedule in New Zealand 1991 to 2013

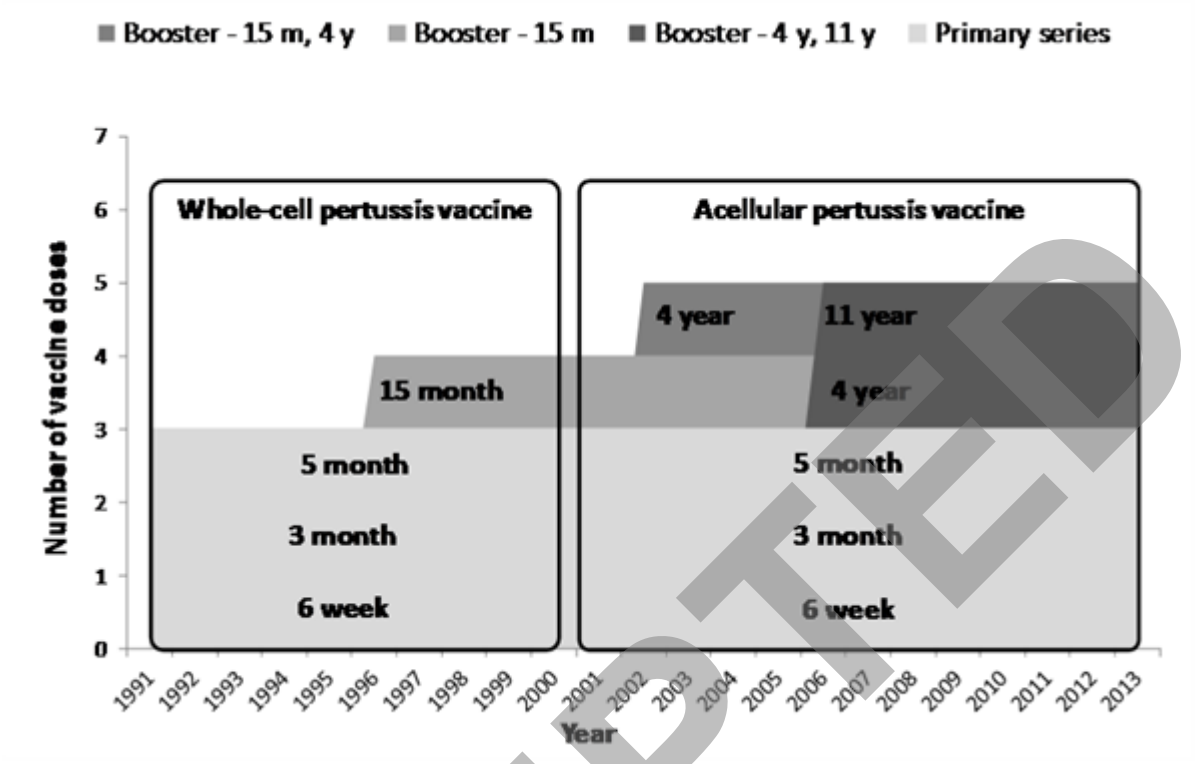


Figure 2. Pertussis disease burden in New Zealand (1991-2013), as shown by number of infant pertussis deaths; infant pertussis admissions to the Pediatric Intensive Care Unit (PICU); infant pertussis hospitalization rates; and from 1997-2013, pertussis notification rates for all ages.