Assessment of on-time vaccination coverage in population subgroups: a record linkage cohort study

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ABSTRACT

Reported infant vaccination coverage at age 12 months in Australia is >90%. On-time coverage of the 2-4-6 month schedule and coverage in specific populations is rarely reported. We conducted a population-based cohort study of 1.9 million Australian births, 1996-2012, combining individual birth and perinatal records with immunisation records through probabilistic linkage. We assessed on-time coverage across 13 demographic and perinatal characteristics of diphtheria-tetanus-pertussis vaccines (DTP) defined as vaccination 14 days prior to the scheduled due date, to 30 days afterwards. On-time DTP vaccination coverage in non-Aboriginal infants was 88.1% for the 2-month dose, 82.0% for 4-month dose, and 76.7% for 6-month dose; 3-dose coverage was 91.3% when assessed at 12 months. On-time DTP coverage for Aboriginal infants was 77.0%, 66.5%, and 61.0% for the 2-4-6 month dose; 3-dose coverage at 12 months was 79.3%. Appreciable differences in on-time coverage were observed across population subgroups. On-time coverage in non-Aboriginal infants born to mothers with ≥3 previous pregnancies was 62.5% for the 6-month dose (47.9% for Aboriginal infants); up to 23.5 percentage points lower than for first-borns. Infants born to mothers who smoked during pregnancy had coverage 8.7-10.3 percentage points lower than infants born to non-smoking mothers for the 4- and 6-month dose. A linear relationship was apparent between increasing socio-economic disadvantage and decreasing on-time coverage. On-time coverage of the 2-4-6 month schedule is only 50-60% across specific population subgroups representing a significant avoidable public health risk. Aboriginal infants, multiparous mothers, and those who are socio-economically disadvantaged are key groups most likely to benefit from targeted programs addressing vaccine timeliness.

KEY WORDS: vaccine coverage, timeliness, infant, population, diphtheria-tetanus-pertussis

ABBREVIATIONS: ACIR, Australian Childhood Immunisation Register; AIR, Australian Immunisation Register; ARIA, Accessibility/Remoteness Index for Australia; DPT, Diptheria-tetanus-pertussis; IRSAD, Index of Relative Socio-Economic Disadvantage; NSW, New South Wales; PCV, pneumococcal conjugate vaccine; WA, Western Australia

INTRODUCTION

Immunisation is one of the most effective public health prevention strategies worldwide. The National Immunisation Program (NIP) in Australia incorporates a 3-dose infant schedule at 2-4-6 months of age including vaccines against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, *Haemophilus influenzae* type B, pneumococcal disease and rotavirus. The Australian Immunisation Register (AIR), one of only a few population-based vaccine registers worldwide, is used to report immunisation coverage. This is normally assessed at age 12 months using 3-monthly cohorts.[1] Coverage is measured using the 'third dose assumption' which defines a child as fully immunised if a third dose of a particular vaccine course is recorded regardless of whether the first or second doses are recorded.[2] Using this method, coverage rates in Australia of vaccines on the NIP schedule (excluding rotavirus) are reported as over 90%.[3] The population-level coverage of each vaccine at time points closer to the scheduled ages of 2, 4 and 6 months are not routinely examined, but might be an important indicator of on-time vaccination coverage. Delayed vaccination, particularly in high risk children including Aboriginal and/or Torres Strait Islander children (hereinafter referred to as Aboriginal), could be contributing to the continued high rates of some vaccine preventable diseases and the large disparity between Aboriginal and non-Aboriginal children for many infectious diseases.[4, 5]

Linkage of birth and perinatal records to the AIR allows accurate assessment of population-level coverage close to the scheduled vaccination time, using the number of births in the population as the denominator. More importantly, the only demographic information that is recorded on AIR is the child's age, sex, residential postcode and Aboriginal status; therefore calculation of coverage within particular population subgroups (including those born preterm, or from lower socio-economic areas) is only possible through combining information from

multiple datasets with record linkage. The assessment of vaccination coverage in population subgroups might allow identification of specific demographic groups that would benefit most from targeted strategies to improve timeliness. A recent systematic review identified higher birth order, low maternal education and low socio-economic status to be the most cited factors associated with incomplete or delayed vaccination,[6] although factors relating to social determinants of uptake have been shown to be context specific [7] and have not been assessed in minority populations such as indigenous populations. Using an assembled linked dataset of perinatal and birth records linked to immunisation records, we assessed 'on-time' immunisation coverage of the 2-4-6 month schedule in Australia by population subgroup, focusing on the uptake of diphtheria-tetanus-pertussis vaccines (DTP) among Aboriginal and non-Aboriginal infants. We hypothesised that coverage would vary among subgroups and that on-time coverage would be lower than routinely reported coverage at 12 months.

PATIENTS AND METHODS

Study Population

The study population was defined as all live births in Western Australia (WA) and New South Wales (NSW) between 1996 and 2012. WA and NSW together represent 42% of Australia's population. The full details of assembling the linked dataset through probabilistic linkage across three linkage centres are provided elsewhere.[8, 9] In brief, the cohort comprised 1,953,881 infants that had both a registered birth record and a perinatal data record. Aboriginal status was derived using a multi-stage median algorithm, described previously[10] using information from all linked datasets in the study, excluding deaths, and based on Australia's national best practice guidelines for data linkage activities relating to Aboriginal and Torres Strait Islander people.[11] Using this validated algorithm, 5% of our cohort (97,778) were identified as Aboriginal.

Vaccination Records

The AIR (previously known as the Australian Childhood Immunisation Register, ACIR) contains information regarding the date, dose number and types of vaccines given and the type of health service that provided the vaccine. DTP immunisation records for the study cohort between 1996 and 2013 were extracted from AIR and probabilistically linked at the Australian Institute of Health and Welfare as described previously.[8, 9] In brief, immunisation data from AIR were linked to the birth register based on a matched linkage rate of 99.3% (similar to a sensitivity measure) with a corresponding linkage accuracy of 99.0% (similar to a positive predictive value measure). Duplicate immunisation records with the same immunisation date and vaccine dose number were removed. Records with the same immunisation date but different vaccine dose number were combined, retaining the record with the most recent date of recording in AIR. Vaccination records that did not have a corresponding birth cohort record were removed as were records of infants where the date of immunisation was before the child's date of birth on their associated perinatal data record.[9] These exclusions from the cohort equated to 1% of all cohort members (Figure 1). Records pertaining to pneumococcal conjugate vaccines (PCV) for which a national program commenced in 2005 were also analysed with details provided as Supplementary Information.

In order to measure coverage at each scheduled infant dose, we chose time-windows reflecting on-time receipt. A 30-day time period from the expected date of vaccination has been used previously as the standard measure of on-time vaccination.[12] For all infants in the birth cohort, we calculated the age in days at vaccination for each dose at 2, 4 and 6 months of age. A vaccination record within a 3 day window prior to the scheduled date of a 2-month dose up until 30 days after the scheduled date was considered an on-time

vaccination dose. A vaccination record within a 2 week window prior to the expected date up until 30 days after the expected date was considered an on-time vaccination dose for the 4- and 6-month dose. This assessment means that on-time receipt of the 2-month dose was defined as vaccination from age 39 days (the first DTP dose can be administered from 6 weeks and allowing a 3 day grace period) to age 90 days, the window for the 4-month dose was defined as age 106-150 days and the window for the 6-month dose was defined from age 166-210 days.

Population subgroups

We selected maternal, paternal and infant factors from the linked birth register and perinatal datasets *a priori* based on available literature [6]. Maternal and paternal factors included age at time of their child's birth in four discrete age groups, maternal smoking during pregnancy, number of previous births and mother's country of birth (Australia vs overseas). Infant and birth related factors included Aboriginal status, sex, season of birth (summer [December-February], autumn [March-May], winter [June-August], spring [September-November]), mode of delivery (vaginal, caesarean, instrumental), prematurity across three gestational age groups, birthweight across 5 groups, state of birth, socio-economic status measured through the Index of Relative Socio-Economic Advantage and Disadvantage (IRSD) and remoteness as measured through the Accessibility/Remoteness Index of Australia (ARIA). The IRSAD is one of four Socio-Economic Indexes for Areas. Each index measures a different aspect of the socio-economic conditions of the people living in a particular area and ranks different geographical areas across Australia according to a score created from the characteristics in that area.[13] The IRSAD score is derived from 17 variables including income, internet connection, unemployment and education [13] and is grouped into five categories ranging from most disadvantaged (index scores below the 10th percentile) to least disadvantaged

(index scores above the 90th percentile). ARIA is a standard national measure of remoteness and access to services for localities and areas throughout Australia and is classified into 5 groups ranging from major cities to very remote.[14] The IRSAD and ARIA classifications were based on the mother's residential address at the time of delivery. There were minimal missing data for all the population subgroups (7% for maternal country of birth and paternal age at birth; 0-1% for all other factors[9]).

Statistical Analysis

The proportion vaccinated for each scheduled dose was defined as the number of infants with a recorded vaccination within the on-time dose window divided by the number of births eligible for vaccination at that time point. Infants who died before the end of the time window for each dose were excluded. We calculated vaccination uptake by year of birth and by population subgroup for each dose and compare this to coverage assessed by receipt of the third dose by age 12 months, as is defined in published coverage reports. Confidence intervals at the 95% level are not shown for any of the coverage figures as they were very narrow (less than 0.5% change from the point estimate) and represent the population coverage. Analysis was conducted in Stata version 13 and data were accessed through the Secure Unified Research Environment.[15]

Ethical approval

Approval was granted by the Department of Health WA Human Research Ethics Committee, the NSW Population & Health Services Research Ethics Committee, The WA Aboriginal Health Ethics Committee, the NSW Aboriginal Health and Medical Research Council Ethics Committee, The Australian Government Department of Health and Ageing Departmental Ethics Committee and the Australian Institute of Health and Welfare.

RESULTS

The cohort for analysis consisted of 1,953,746 births of whom 97,778 (5.0%) were recorded as Aboriginal (Figure 1). Births from NSW accounted for 76.4% of the cohort (4.6% Aboriginal) and births from WA accounted for 23.6% (6.4% Aboriginal). Most vaccines in NSW were given in general practice (e.g. 83% of 2-month dose) followed by community health centres (13%) and other services (4%) including Aboriginal health services and hospitals; in WA 66% of the 2-month doses were given in general practice, 24% through community health centres and 10% through other services.

Overall DTP vaccine uptake is presented in Figure 2. On-time vaccination for non-Aboriginal infants ranged from 76.7-88.1% and 61.0-77.0% for Aboriginal infants. Coverage for the third dose assessed at age 12 months was 91.3% for non-Aboriginal infants and 79.3% for Aboriginal infants. Thus, on-time vaccination for the 6-month dose was 14.7 percentage points lower for non-Aboriginal infants and 18.3 percentage points lower for Aboriginal infants than coverage assessed at 12 months. Vaccination uptake steadily increased over the study period for all doses (Figure 3). Due to coverage being systematically lower in Aboriginal than in non-Aboriginal infants, analyses of predictors of slow uptake were conducted separately for these populations.

Tables 1 and 2 display on-time coverage for non-Aboriginal and Aboriginal infants for the 2-4-6-month doses across population subgroups. On-time vaccination decreased with each consecutive dose. Similar patterns of differential levels of on-time coverage across population subgroups were seen for Aboriginal and non-Aboriginal infants although the size of

discrepancy differed. The discrepancy between subgroups was most marked for the 4-month and 6-month dose in both non-Aboriginal and Aboriginal infants across all subgroups. The largest discrepancy was seen with maternal parity; on-time uptake for the 6-month dose in infants born to mothers with 3 or more previous pregnancies was only 62.5% in non-Aboriginal infants and 47.9% in Aboriginal infants equating to coverage 20.8 and 23.5 percentage points lower for non-Aboriginal and Aboriginal infants respectively compared with first-borns (Tables 1 and 2). Non-Aboriginal and Aboriginal infants born to mothers who smoked during pregnancy had a vaccine uptake for the 6-month dose approximately 10 percentage points lower than infants born to mothers who did not smoke.

There was a general trend towards a relationship of increasing level of deprivation and decreasing on-time vaccination across the three scheduled doses for all infants, however the discrepancy was greater among Aboriginal than non-Aboriginal infants (e.g. coverage for the 6-month dose was 11.8 percentage points lower in Aboriginal infants living in the most socio-economically disadvantaged areas compared with those living in the least disadvantaged; the discrepancy was only 4.4 percentage points for non-Aboriginal infants; Tables 1 and 2). Infants born to teenage parents had lower on-time coverage, with the 6-month vaccine coverage difference greater in non-Aboriginal infants (7.4 percentage points lower than for infants born to parents aged in their 30s) compared with Aboriginal infants (1.4 percentage points lower). Six month vaccine uptake was lower for infants of low birthweight compared to normal birthweight (6.6-7.2% percentage points lower in infants <1500g when compared with normal birthweight), with similar discrepancies for extreme prematurity (7.2-9.1 percentage points lower compared with term births).

On-time coverage did not vary considerably by remoteness for non-Aboriginal infants but varied considerably for Aboriginal infants; those from regional areas had uptake similar or higher than those in major cities whereas infants from very remote areas had uptake 6.3 percentage points lower than major cities for the 6-month dose. Vaccine uptake was lower in WA than in NSW for all infants, especially for Aboriginal infants in WA.

One-third (34.6%) of the cohort had a mother born overseas. Vaccine uptake was lower for infants of mothers born overseas than infants of mothers born in Australia, most notably for mothers from North America and Oceania (including New Zealand, Pacific Islanders and Papua New Guinea), however the discrepancy was only 1.2 percentage points for the 6-month dose. Both Aboriginal and non-Aboriginal infants born by instrumental delivery had higher on-time coverage than other modes of delivery with the lowest on-time coverage in infants born vaginally. There was minimal difference in vaccine uptake by sex or season of birth. Similar patterns were seen across all subgroups for PCV uptake (Supplementary Information).

DISCUSSION

Through the linkage of perinatal data to immunisation records, we report for the first time, on-time vaccination for the 2-4-6 month infant schedule across population subgroups in a cohort covering >40% of Australia's population. Despite reported coverage assessed at age 12 months in excess of 90%, we have shown that vaccine receipt within acceptable windows of timeliness for each dose is as low as 50-60% in some population subgroups representing a significant avoidable public health risk. Jurisdictions should be encouraged to assess vaccination coverage using both course and narrow age milestones enabling vaccine

programs to benchmark against different jurisdictions and design and implement local interventions to improve vaccination uptake.

Under vaccination or delayed vaccination is a significant avoidable public health risk and can contribute to the overall susceptibility of the population to outbreaks of vaccine preventable diseases. Indeed, a recent study has shown infants with delayed DTP immunisation had a significantly earlier onset of pertussis compared to those vaccinated on time and therefore represent a source of potential disease spread during an outbreak.[16] A recent Australian review of all pertussis-related intensive care unit admissions from 1997-2013 showed that 88.5% of cases occurred in infants before age 6 months,[17] highlighting the importance of on-time vaccination, including for the second dose which has been shown to confer high protection.[18] The importance of on-time vaccination is not likely to be unique to the Australian context with similar observations previously arising from the United States where vaccination uptake at traditional milestones was as high as 85% but with only 34% vaccinated on time.[19] In order to maintain adequate levels of population immunity, on-time receipt of vaccinations funded by national programs should be a public health goal.

A systematic review assessed the factors relating to delayed vaccination included 23 cross-sectional or cohort studies across 13 countries with sample sizes ranging from 187 to 17,295 infants. Higher birth order and low socio-economic status were the most cited factors associated with delayed vaccination.[6] A further recent study using linked data from Wales also found similar results with respect to infants of multiparous mothers.[20] Here we report, on a significantly larger cohort of 1.9 million births through integrating population-based perinatal, birth and immunisation datasets, on-time uptake of DTP infant doses in population

subgroups, many of which also have been previously identified as significant factors for delayed vaccination. Our findings confirm those of the systematic review, with differences in on-time uptake between infants of multiparous versus primiparous mothers as high as 23%.

Apart from high birth order, our population-based study has highlighted other key groups who could benefit from targeted interventions such as regular reminders to address vaccine timeliness. Groups with less than optimal levels of on-time coverage were: premature and low birthweight infants, infants whose mothers smoked during pregnancy, and those who were most socio-economically disadvantaged. The relationship between level of socio-economic disadvantage and morbidity within Aboriginal and non-Aboriginal infants has not been well documented. Here we show a strong association between socio-economic status and on-time vaccination, especially in Aboriginal infants where the difference in uptake between the most socio-economically disadvantaged Aboriginal infants and least disadvantaged Aboriginal infants was up to 13%. On-time vaccine coverage was lower for Aboriginal infants compared to non-Aboriginal infants across all population subgroups. Aboriginal children still experience disproportionately higher rates of many infectious diseases, especially pneumonia and pertussis where rates are up to 15 times higher than non-Aboriginal children.[21] Although vaccine coverage has increased over the past decade, further improvements in vaccine timeliness are needed.

On-time vaccination coverage was lower in WA than in NSW with more marked differences in Aboriginal infants. This may be related to immunisation delivery practices. A far greater proportion of the WA population lives in rural and remote areas than for NSW. Additionally, due to the high morbidity of pertussis in the early weeks of life, the 2-month DTP dose can be

given as early as 6 weeks of age,[3] and this recommendation was promoted earlier (2009) and more actively in NSW than in WA. However, this difference in recommendation only accounts for a small proportion of the study period and for the first dose only so it could only account for a small part of the difference in vaccine uptake observed here. NSW has funded an Aboriginal Immunisation Health Worker Program since 2012, with a focus on timeliness of infant vaccination. Aboriginal health workers work with providers and families to overcome barriers to on-time vaccination. The gap in on-time completion between Aboriginal and non-Aboriginal children of the primary course showed a steady decrease from 17% to 13% in 2016 [22] suggesting Aboriginal health workers have had a positive influence. Further investigation into the differences in coverage by type of vaccine provider, especially for the 2-month dose, may assist in explaining the differences by jurisdiction.

Several other studies have documented the impact of social determinants to delayed vaccination including the social context of the family and parental attitudes to vaccination in various settings.[7, 19, 23, 24] We have indicated here that similar barriers, in particular larger families and those from more socio-economically deprived areas may exist in the Australian context. The importance of maternal vaccination to prevent serious morbidity and mortality due to pertussis and influenza in infants before age 6 months is being realised. It is likely that social determinants of maternal vaccination and other childhood vaccinations could be similar to infant vaccination we have reported here. A systematic review of determinants of maternal vaccination for seasonal influenza identified that women from higher socioeconomic backgrounds and non-smokers were more likely to be vaccinated.[25]

It is highly likely that some maternal, paternal and infant factors we have assessed are co-related. We have not presented any multivariate analyses here. Rather we have presented a descriptive analysis of the absolute on-time uptake in various population subgroups. Our coverage assessed at age 12 months correlates with reported coverage rates using the AIR data alone.[9] Further research to understand the relative importance of maternal, birth and demographic characteristics by degree of vaccine delay are the subject of ongoing analyses.

Our study has some limitations. There are other social factors that may contribute to on-time infant coverage including breastfeeding practices, parental education levels, religious beliefs and maternal immunisation coverage for which information is currently not available from the administrative datasets used in this study. Indigenous status and reporting of immunisation of those living in remote areas has previously been identified as a concern, although the quality of data recording has vastly improved.[26] We do not see this as a significant limitation to our study as we did not rely on the recording of Indigenous status from AIR data alone. Rather we used a validated algorithm using information from all linked datasets to identify Aboriginal and Torres Strait Islander infants.[10] There are still, however, possibly missing vaccination records that have not been entered onto ACIR due to immunisation providers not entering information into patient records or problems with automated software packages from certain general practices.[27] While it is recognised that coverage estimates from AIR may be up to 3% lower than the true coverage[28], this arises from administered doses not transmitted to AIR and other factors including duplicate records, and not the accuracy of recorded dates of vaccination which would affect on-time estimates.

Nevertheless, the strength of these data is the total population-based sample size of 1.9 million births, with minimal missing demographic data and a high level of linkage accuracy[9], and these findings can now be used to inform targeted programs to improve vaccination timeliness. Such programs can be developed utilising the World Health Organization's Tailoring Immunisation Programs approach [29] and may include immunisation recall reminder programs using SMS technology, which have shown some success in parts of Australia [30], for key population groups including larger families and those from lower socioeconomic areas to prompt parents to vaccinate their infants on time, or a case management approach, as in the NSW Aboriginal health worker program.

CONCLUSION

Australia, like other industrialised countries has high vaccination uptake at the reported age milestone of 1 year. However, this population-based analysis, made only possible through linking Australia's immunisation register with perinatal and birth datasets has highlighted a significant avoidable public health risk with delayed vaccination across numerous population groups. These results are likely to be generalizable to international settings, especially to countries with minority populations. Countries with population vaccination programs would benefit from assessing on-time coverage as opposed to traditional age milestones.

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AUTHOR CONTRIBUTIONS

HCM, HFG, CCB conceptualised and designed the study. HCM, PF and HFG cleaned and assembled the linked data. HCM conducted the analysis and drafted the initial manuscript. NdK provided expert statistical advice for the analysis. CCB, BL, TLS, VS, PVE and PM provided expert for the interpretation of findings. All authors critically reviewed the manuscript for intellectual content and approved the final manuscript as submitted.

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CONFLICT OF INTEREST

The authors have no conflict.

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Table and Figure Legends

Table 1: Proportion of non-Aboriginal children with on-time receipt of DTP doses scheduled at 2,4 and 6 months by population subgroup

Table 2: Proportion of Aboriginal children with on-time receipt of DTP doses scheduled at 2,4 and 6 months by population subgroup

Figure 1: Flow chart of datasets and exclusions for DTP infant coverage

Figure 2: Proportion of Aboriginal and non-Aboriginal children born between 1996 and 2012 with on-time receipt of DTP at 2, 4, 6 months and coverage for the third dose assessed at 12 months

Figure 3: On-time vaccination uptake of DTP at 2, 4, 6 months in Aboriginal and non-Aboriginal children by year of birth