Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effectiveness of maternal pertussis vaccination in preventing infection and disease in infants: The NSW Public Health Network case-control study

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ARTICLE INFO

Article history:
Received 27 October 2017
Received in revised form 11 February 2018
Accepted 12 February 2018
Available online xxxx

Keywords:
Pertussis
Maternal vaccination
Vaccination
Australia
dTpa

ABSTRACT

Background: Infants are at the highest risk of severe complications – including death – as a result of pertussis infection. Controlling pertussis in this group has been challenging, particularly in those too young to be vaccinated. Following revised national recommendations in March 2015, the state of New South Wales, Australia, introduced a funded maternal vaccination campaign at 28 – 32 weeks of gestation using a 3-component tetanus-diphtheria-acellular pertussis vaccine (dTpa; Boostrix, GSK). This study aimed to assess the effectiveness of maternal vaccination and add to the growing body of evidence for this strategy.
Methods: A 1:1 matched case-control study was conducted between 16 August 2015 and 17 August 2016. Cases were laboratory or doctor notified, laboratory confirmed (nucleic acid testing or culture) and aged <6 months at onset. Each control infant was randomly selected from public hospital births in the same geographical area in the period up to 3 days before and after the case's birthdate. Odds ratios (OR) were calculated using conditional logistic regression. Vaccine effectiveness (VE) was calculated as 1 – OR.
Findings: In total, 117 cases and 117 controls were recruited. The overall VE estimate was non-significantly protective for infants <6 months old (VE 39%, 95% CI −12 to 66%). Higher VE was observed for infants <3 months old (VE 69%, 95% CI 13–89%) and against hospitalisation (VE 94%, 95% CI 59–99%).
Interpretation: Maternal pertussis vaccination with a 3-component acellular vaccine was found to be highly effective at preventing severe disease in infants, but was less effective at preventing disease which did not require hospitalisation. The overall VE reported in this study was lower than in prior studies and suggests that maternal vaccination, while an effective strategy at preventing severe pertussis, is less effective at protecting against infection or mild disease.

1. Introduction

Despite a vaccination program that has been in existence since the 1950s [1,2], pertussis control in Australia has remained a persistent challenge, with epidemics continuing to occur approximately every three to four years [3]. Epidemics of pertussis can be large and cause significant morbidity and mortality in the

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https://doi.org/10.1016/j.vaccine.2018.02.047
0264-410X/

population, with hospitalisations and deaths increasing during outbreak periods both in Australia and internationally [2,4,5]. Those at highest risk of severe disease are infants [6] who may be too young to receive their first vaccination; as such, protecting infants is the key priority in pertussis public health interventions.

In Australia, infants receive their first pertussis vaccine from 6 weeks of age, and subsequent primary doses at 4 months and 6 months of age [7]. A 3-component diphtheria-tetanus-acellular pertussis vaccine (DTPa) is used. Uptake of the pertussis vaccine in Australia is high, with coverage rates consistently above 90% for both the primary series and booster doses [8].

In addition to timely primary vaccination, other strategies tried in Australia to protect infants include cocooning, where those in contact with infants are vaccinated; however, there is limited evidence for the effectiveness of this strategy [9,10].

In March 2015, advice from the Australian Technical Advisory Group on Immunisation changed from being permissive of maternal vaccination with diphtheria-tetanus-acellular pertussis vaccine (dTpa) to actively recommending pregnant woman be vaccinated in the third trimester of each pregnancy [7]. This recommendation was informed by the growing evidence that suggested maternal vaccination against pertussis was both safe and effective at preventing disease in infants [4,11–14]. The infant is likely to receive protection directly through in utero transfer of antibodies, and indirectly by reducing the likelihood of the mother acquiring and transmitting the disease [4,15].

An upward trend in pertussis notifications in the state of New South Wales (NSW), Australia (the most populous state in Australia), was observed in late 2014. This trend continued until notifications peaked in November 2015. The increase was observed across all age groups and areas of NSW.

Following the update to the national guidelines, and in response to increasing notifications, all Australian states and territories funded the provision of dTpa vaccine to pregnant women, commencing on 30 March 2015 in NSW. To evaluate the effectiveness of maternal vaccination in preventing disease in infants, the NSW Public Health Network (NSW PHN) conducted a case-control study. The primary aim of this study was to estimate the effectiveness of maternal vaccination given in the third trimester of pregnancy at preventing laboratory-confirmed pertussis disease in infants aged <6 months, in an Australian setting.

Given the recent history and epidemiology of pertussis in Australia, the high awareness of pertussis among health care workers and the general public, the cost and commitment involved in implementing a new policy, the wide availability of sensitive diagnostic tools, and an excellent notification system, NSW was well placed to reproduce recent overseas research in an Australian context and place the intervention more firmly within a hierarchy of control strategies.

2. Methods

2.1. Case and control selection

A 1:1 matched case-control study was conducted in NSW between 16 August 2015 and 17 August 2016. Public health unit staff in each local health district (LHD, the administrative divisions of the state health service) collected data on cases and controls. Cases were recruited prospectively through notifications to NSW public health units.

Cases were defined as infants aged <6 months at symptom onset, with laboratory definitive evidence of pertussis – isolation of *Bordetella pertussis,* detection of *B. pertussis* DNA, or seroconversion in paired sera in the absence of recent vaccination (as per national guidelines [16]).

On notification of a confirmed case of pertussis in an infant <6 months of age, local public health unit staff would initiate routine case follow-up with the parent/guardian, generally on the day of notification, and at the same time seek permission to enrol the case into the study. Information on vaccination history, basic clinical presentation and laboratory results is routinely collected into the NSW Notifiable Conditions Information Management System (NCIMS). Where the parent/guardian of the case agreed to participate in the study, an enhanced questionnaire was used to collect information on maternal vaccination, symptoms and demographics, and entered into the case record in NCIMS.

Controls were born in a public hospital in the same LHD where the case was resident. On enrolment of a case into the study, a matching control was selected by producing a list of births in the period up to 3 days before and after the case's birthdate (7 day range) and randomly selecting a single record using a random number function in Microsoft Excel. Once selected, controls were contacted as soon as possible, with three telephone attempts at different times on three consecutive days to contact the control before selecting another control from the birth list. If the control refused participation, further controls were selected in the same manner. Controls were excluded if they had a cough illness within two weeks of the onset of the illness in the matched case.

The parents of both case and control were interviewed by phone by public health unit staff using a standard questionnaire and question guide. Information was collected on maternal vaccination, infant vaccination, household size and demographics, risk factors for pertussis disease, clinical severity for cases, breastfeeding status, and smoking status of household members. Verification of vaccination for both the mother and the infant was obtained through electronic access to the Australian Childhood Immunisation Register (for infants), hospital records (for mothers vaccinated in public hospitals) or by contacting the mother's general practitioner (for vaccinations given in private practice). If the vaccination record could not be verified, it was categorised as recall.

2.2. Sample size calculation

We aimed to recruit a minimum of 39 cases and 39 controls, which would provide 80% power for the study and detect an OR of 0.5 or VE of 50%, using the sample size calculation method described by Woodward [17]. The period of the study overlapped with an increase in pertussis notifications across all age groups. Termination of the study was to be at the guidance of an advisory committee, taking into consideration the burden to public health unit staff collecting study data and the effect on the power of the study.

2.3. Questionnaire variables and statistical methods

Each interviewed parent was asked whether and when the mother was vaccinated against pertussis. For data analysis, the primary variable was vaccination during pregnancy, whether verified or recalled. If the mother was not vaccinated during this pregnancy but had been vaccinated at another time (including preconception, after delivery, with birth of last child or previous pregnancy), they were classified as not vaccinated during pregnancy. The number of infant doses was also collected, including the date the vaccine was given.

To allow for seroconversion and transplacental transfer of maternal antibodies to the fetus, the mother was considered unvaccinated during pregnancy if birth occurred less than 2 weeks after vaccination, and infant vaccinations were only counted if the vaccination occurred at least 2 weeks before disease onset in the case infant.

Please cite this article in press as: Saul N et al. Effectiveness of maternal pertussis vaccination in preventing infection and disease in infants: The NSW Public Health Network case-control study. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.02.047