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Using age-stratified incidence data to examine the transmission consequences of pertussis vaccination

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ABSTRACT

Pertussis is a highly infectious respiratory disease that has been on the rise in many countries worldwide over the past several years. The drivers of this increase in pertussis incidence remain hotly debated, with a central and long-standing hypothesis that questions the ability of vaccines to eliminate pertussis transmission rather than simply modulate the severity of disease. In this paper, we present age-structured case notification data from all provinces of Thailand between 1981 and 2014, a period during which vaccine uptake rose substantially, permitting an evaluation of the transmission impacts of vaccination. Our analyses demonstrate decreases in incidence across all ages with increased vaccine uptake – an observation that is at odds with pertussis case notification data in a number of other countries. To explore whether these observations are consistent with a rise in herd immunity and a reduction in bacterial transmission, we analyze an age-structured model that incorporates contrasting hypotheses concerning the immunological and transmission consequences of vaccines. Our results lead us to conclude that the most parsimonious explanation for the combined reduction in incidence and the shift to older age groups in the Thailand data is vaccine-induced herd immunity.

1. Introduction

Pertussis, or whooping cough, is a highly infectious respiratory disease that remains a major public health concern (Wood and McIntyre, 2008; Domenech de Celles et al., 2016). Despite the initial success of pediatric vaccination programs, pertussis is currently responsible for an estimated 300,000 deaths per year worldwide (Crowcroft and Pebody, 2006). In addition, it has undergone a resurgence in many countries – including the United States (Rohani and Drake, 2011; Magpantay and Rohani, 2015) – despite maintaining high levels of vaccine uptake (Wood and McIntyre, 2008). While many plausible mechanisms driving these dynamics has been proposed (Jackson and Rohani, 2014; Domenech de Celles et al., 2016), the protective immunity elicited by both whole cell (wP) and acellular (aP) vaccines has long been questioned (Preston and Stanbridge, 1972; Blennow et al., 1988; Ausiello and Cassone, 2014). The absence of a reliable serological marker for protection has meant that much of the discussion regarding the consequences of vaccination for immunity have focused on epidemiological patterns (Lavine et al., 2011).

The ability of whole cell vaccines to prevent pertussis transmission has been discussed for more than fifty year (Preston, 1965) and was famously called into question by Fine and Clarkson (1982), who argued based on patterns of periodicity in pertussis incidence that whole cell vaccines likely prevented disease rather than transmission. If true, this would lead to significant silent circulation of pertussis (Águas et al., 2006; Kretzschmar et al., 2010), posing a major threat to unvaccinated or partially immunized infants, who are at highest risk of pertussis-related complications and death. More recently, the debate regarding the mechanisms behind pertussis resurgence and the potential role played by has centered on acellular vaccines (Aoyama et al., 1985; Ausiello and Cassone, 2014; Domenech de Celles et al., 2014). Two modeling studies have concluded that pertussis resurgence may be the natural consequence of widespread switch to the aP vaccine (Gambhir et al., 2015) and its inability to generate protective immunity (Edwards, 2014; Althouse and Scarpino, 2015). This conclusion is supported by animal transmission models, in baboons (Warfel et al., 2014) and

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mice (Smallridge et al., 2014), where the experimental challenge of aP-vaccinated animals indicates the potential for a transmissible infection.

To better understand the extent of the cross-over between individual-level animal challenge experiments to population-level pertussis incidence in humans and the consistency between epidemiological evidence in different countries, we examined incidence reports from Thailand. Specifically, we scrutinized age-stratified incidence data from different provinces in Thailand from 1981 to 2000. During this period, vaccine uptake systematically increased from ∼26% in the early 1980s to greater than 95% by mid-1990s. We explored the epidemiological consequences of this vaccine ramp-up to assess the protective effects of wP vaccination. We paid particular attention to changes in incidence among "high risk" groups – such as unvaccinated infants – as uptake increased. Epidemiological theory predicts that vaccination programs that successfully protect vaccinees from infection should induce herd immunity, thereby minimizing transmission to unprotected high risk groups (Gay and Miller, 2000). Tracking incidence in these age-groups is therefore an essential component to quantifying the success of vaccination in reducing circulation (Keeling and Rohani, 2008; Domenech de Celles et al., 2016). For this reason, we also examined pertussis incidence reports from 2003 to 2014 in infants younger one month and those between 1 and 12 months.

The analyses of age-incidence patterns were allied to two age-structured transmission models, which were used to distinguish among competing hypotheses about the role of vaccine-protection as a driver of observed age-structured incidence (ex. Riolo et al., 2013; Lavine et al., 2011; Rohani et al., 2010). We challenged these models to capture the qualitative epidemiological transition observed in Thailand when contrasting assumptions were made regarding the immunological impacts of infant immunization. In previous analyses, we reported that there is an increase in herd immunity with vaccine uptake in Thailand and we supported these claims through the use of statistical inference to select a best-fitting model of pertussis dynamics (Blackwood et al., 2013). However, that analysis primarily considered the aggregate data independent of age. Here, we provide additional corroboration via a study of age-structured dynamics. Consistent with our prior analyses, we find empirical support for increased herd immunity with vaccine uptake in Thailand, a finding that is re-inforced by our transmission modeling.

2. Pertussis incidence data, 1981–2000

Thailand adopted the National Expanded Programme on Immunization (EPI) in 1977 for infant vaccination. Initially, two doses of the diptheria–tetanus–pertussis (DTP) whole cell vaccine was administered until a third dose was added to the schedule in 1982 (Bhunbhu, 1989). Beginning in 1992, the schedule included 5 doses of DTP at 2, 4, 6, and 18 months with the final booster dose at 4–6 years. The whole cell vaccine was used exclusively until 1998. Since then, the DTP-HiB has been favored in government clinics and the acellular vaccine (DTaP) in private clinics. We obtained the corresponding annual national vaccine uptake estimates for 1981–1996 and 1999 from the Vaccine Coverage Survey of Thailand. Missing years (1997–1998, 2000) were assumed to have attained the same uptake as the most recently reported year.

Annual case notification data from each of Thailand's 72 provinces between 1981 and 2000 were obtained from the Ministry of Public Health (Bureau of Epidemiology, 1981–2000). From 1981 to 2000, the case notification data were also available annually for the following age groups: under 1 year, 1–4, 5–9, 10–14, 15–24, 25–34, 35–44, 45–54, 55–64, and older than 65 years of age. In 1985 these data were also available for one-year age groups up to age seven. In our analysis we assumed the age of cases were uniformly distributed between all ages within each age group. We obtained age-stratified population data for 1980, 1990, and 2000 from the National Statistical Office of Thailand censuses and log-linear fits between census years were used to estimate annual population sizes from 1981 to 2000 (National Statistical Office of Thailand, 1980, 1991, 2001).

3. Age-structured incidence dynamics

In this section, we present the age-structured incidence data from Thailand during the time period 1981–2000. To paint a general picture of pertussis in Thailand, in Fig. 1A we present aggregated monthly incidence in addition to the annual vaccine uptake. Three clear epidemics are observed in 1981, 1982, and 1983 followed by a rapid decline from 1984 to 1990 and stable low incidence throughout the 1990s. These dynamics coincide with the rapid rise in vaccine uptake, which consistently exceeds 95% beginning in 1996.

Fig. 1A also includes two shaded regions: 1981–1983 (gray) and 1996–2000 (green). These two time periods display dramatically different incidence patterns corresponding to changes in vaccine uptake. Namely, incidence was highest from 1981 to 1993 when vaccine uptake was the lowest, and incidence remained very low from 1996 to 2000 when vaccine uptake remained above 95%. A comparison of the age-specific incidence patterns during these two "eras" is presented in Fig. 1B, depicting the percentage of reported cases attributed to five different age groups (under 1 year, 1–4, 5–9, 10–15, and 15+ years). The figure indicates a shift in incidence to older age groups in the later era.

To observe the age-stratified dynamics at a finer temporal resolution, in Fig. 1C we display the percentage of annual cases in four age classes. During the early through mid-1980s, the age distribution of cases remains relatively stable with between 13% and 23% of all cases attributed to infants. The percent of cases in infants then rises briefly and drops again in the early 1990s. The decline in the percent of cases in infants coincides with a dramatic increase in vaccine uptake. While this is indicative of reduced transmission to infants – who are more susceptible to disease because they are less likely to be fully immunized against pertussis – it should be noted that the incidence is very low throughout the 1990s. As a consequence, variability in the age-distribution is to be expected and such variation is indeed observed during the years post-1995.

To determine whether these observations are consistent at finer spatial resolutions, Fig. 2B–G replicates Fig. 1B for each of the six distinct geographic regions of Thailand (as developed by the National Geographical Committee in 1978). In Fig. 2B–G, the percent of cases in each age group from 1981 through 1983 are represented by gray bars and the percent of cases in each age group from 1996 to 2000 are in color. The bars are colored by region, and Fig. 2A provides a map of Thailand such that the provinces in each region are colored accordingly. These data are consistent with those for Thailand as a whole (Fig. 1B), with a higher percentage of cases attributed to older age classes during 1996–2000. While the Western (Fig. 2C, pink) region appears to contradict this observation, it only accounts for 5.3% of the total cases in Thailand and therefore has minimal impact on the overall age-structured dynamics in the country as a whole.

Previous work has shown that an increase in the mean age of infection may correspond to decreasing transmission to infants (e.g. Skowronski et al., 2002). We therefore estimated the mean age of infection for the early (1981–1983) and late (1996–2000) vaccine eras, assuming that cases are uniformly distributed within age classes (see Supplementary information for details). To test