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Mathematical modeling of delayed pertussis vaccination in infants

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ABSTRACT

Pertussis is an acute vaccine-preventable respiratory disease that remains a public health problem. In an attempt to improve the control of the disease, many countries have incorporated new boosters in their vaccination schedule. Since the incorporation of these boosters is relatively recent, there are not enough data about their impact to support and/or universalize their use. Alternative strategies such as the improvement in vaccine coverage and reduction in vaccination delays, in addition to the incorporation of boosters, could be implemented. Though these strategies are not new, they have not been adequately evaluated in order to be implemented and/or prioritized. To evaluate the potential impact of these alternative strategies on pertussis incidence, we developed a methodology that involves the use of data collected from vaccination centers and an age-structured deterministic mathematical model for pertussis transmission. The results obtained show that strategies that avoid delays in vaccination have a strong impact on incidence reduction in the most vulnerable population (infants less than 1y). In regions with high vaccination coverage (95%) the elimination of delays in the three primary doses decreases pertussis incidence in infants by approximately 20%. In regions where delays in the administration of vaccines are higher, the combined action to reduce delays and improve coverage leads to a significant improvement in disease control in infants. By repeating the calculations using different sets of parameters that describe different possible epidemiologic scenarios, we determined the robustness of our results.

All the results presented highlight the importance of having high vaccine coverage and shorter delays in vaccine administration in order to reduce the impact of the disease in infants.

1. Introduction

Pertussis is a highly contagious respiratory disease mainly caused by *Bordetella pertussis*. This disease, which causes uncontrollable violent coughing, most commonly affects infants and young children and can be fatal, especially in babies less than 1 year of age [1,2].

The best way to prevent pertussis is to get vaccinated. In fact, the introduction of massive pertussis vaccination in the fifties dramatically reduced the morbidity and mortality associated with the disease. However, in the last years the incidence rates of the disease have increased in many countries [3–6]. The World Health Organization estimates that about 16 million cases occur per year in the world with approximately 200,000 deaths [7]. Though most of these cases have been reported in countries with low vaccination coverage, pertussis outbreaks were also detected in countries with high vaccination coverage [3,4]. In the Americas, the number of cases varies between 1500 and 49,000 among countries, where Argentina, Brazil, Mexico, Chile, Colombia, Paraguay, Peru, and the United States have reported the highest number of cases [8–10]. In Argentina, the last outbreak occurred in 2011 when 76 deaths were reported mainly in children under 6 months [11]. In 2012, in the US 48,778 cases (the highest outbreak since 1955) including 20 pertussis-related deaths were reported. Incidence rates were very high in infants but also in the population of children (7–10 years) and adolescents (13–14 years) [12].

This epidemiological situation has forced health systems to revise their control actions to strengthen and/or implement short-term strategies to improve the situation, at least for the most vulnerable population represented by infants. Before the resurgence of the disease, recommended immunization schedules consisted of a primary series of 3 doses during the first year of life and a booster between 1 and 6 years of age, preferably during the second year of age. With the disease resurgence, more boosters

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were added following recommendations of international organizations [13–15]. In fact, the number of boosters increases year by year in many countries, probably as a consequence of failures in the used vaccines, in particular in acellular vaccines [16,17]. In this context, the evaluation of other alternative strategies, instead of the addition of the current acellular booster doses, is important for controlling the disease in the short term. In previous work, using an age-structured deterministic mathematical model for pertussis transmission designed by us, we estimated that improvements in the coverage of the first dose would lead to a larger reduction in the 0–1y disease incidence than that caused by the addition of an 11y booster [18]. The population dynamics of our model was described by transferring individuals among 9 epidemiological classes that differ in immune status and infectiousness. In the present work we evaluate the potential impact of shorter delays in the administration of the first three doses of pertussis vaccine on infants younger than 1y. With this aim, we developed a calculation method that involves the introduction of new epidemiological classes to keep track of the number of doses administered to the population in each epidemiological class. This method also allows us to accurately incorporate the vaccination coverage for each dose in the model.

The results obtained with our model and data gathered from vaccination centers in urban and suburban areas in an Argentine city show that a reduction in delayed vaccination would decrease the incidence of the disease in infants by at least 20%. The results from the model reveal that efforts to improve the administration of the first doses of the immunization schedule, either by enhancing coverage or strictly complying with the recommended scheduled age, would significantly decrease pertussis incidence in infants.

2. Materials and methods

2.1. Vaccination schedule and epidemiological data

In Argentina, the immunization schedule against pertussis includes three primary doses at 2, 4 and 6 months old, one booster dose at 18 months old, and another at 6 years (school entry) [19]. For all these doses, whole-cell pertussis vaccine is used (DTwP). According to the Ministry of Health, DTP3 coverage (DTP3-cov) for infants under 1y old was higher than 90%, but there are some regions with coverage below 80% [11]. Over the last few years, since the resurgence of pertussis, different protection strategies have been included in Argentina: immunization of adolescents, pregnant women and health workers with acellular vaccines.

The epidemiological data included in this work, consisting of 29,845 records of pertussis vaccination for children aged 0–12 months, are from La Plata (654,324 inhabitants), an Argentinian city located in Buenos Aires province. Specifically, we used retrospective data (January 2005–May 2012) on the distribution of applied DTP doses by age provided by the vaccination center of Elina de la Serna Hospital. At this center, which is one of the 10 vaccination centers located in the urban region of La Plata city, approximately 13% of La Plata population is vaccinated. Children whose age was undefined or unclear were excluded. Fig. 1A shows the number of vaccinated individuals per dose by age from January 2005 to May 2012.

In Fig. 1B we represent the same data as in Fig A, but as a fraction of vaccinated individuals at age a_i with dose d (hereafter referred to as f_{di}). These profiles were obtained by performing histograms with the data of Fig. 1A, where each histogram interval is taken as a month divided by four (a "week"), ages a_i are assigned to the middle of the interval, and f_{di} are normalized to one for each dose, d. The f_{di} profiles and the vaccination coverages for each dose DTP-cov$d$ are the parameters that determine vaccine administration in our mathematical model.

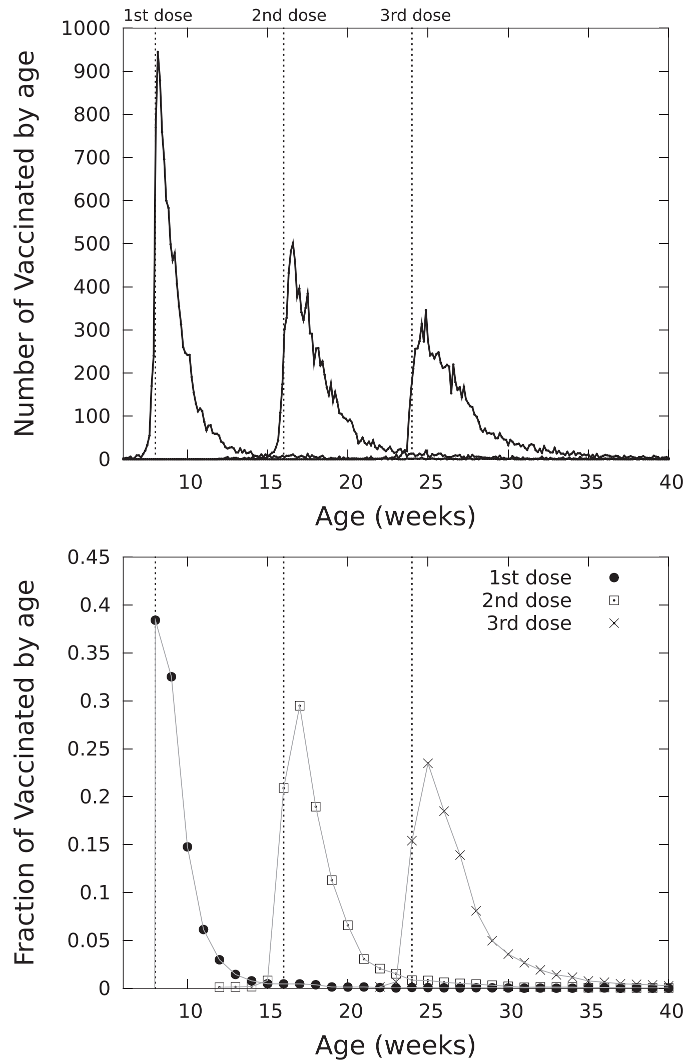

Fig. 1. (A) Number of vaccinated individuals per dose by age, between January 2005 and May 2012 (continuous lines). Data are from Elina de la Serna Hospital. (B) Fraction of vaccinated individuals with dose d, at age a_i (in weeks), f_{di} (gray lines are to guide the eye). Data are obtained from (A). In both figures dotted lines indicate the recommended age for primary doses of pertussis vaccination schedule in Argentina.

For comparison purposes, we also included epidemiological data from the periphery of La Plata city, where the population is younger than that from downtown, with 23% and 14% of inhabitants younger than 14 years old, respectively. There are 3.7 individuals per household on average, instead of the 2.7 individuals registered in the downtown area [20].

2.2. Mathematical model

The model used here to evaluate the effect of vaccination delays on pertussis transmission is based on a deterministic age-structured compartmental model developed previously by us [18]. The population dynamics of this model is described transferring individuals among 9 epidemiological classes at given rates as is shown in Fig. 2A. Each one of the 9 epidemiological classes is divided into age groups. To study the effect of delays in vaccination we have introduced modifications into the model that allow us to take into account the actual age at which the population receives the three primary doses of the pertussis vaccine, regardless of the age recommended by the national vaccination schedule.

On the other hand, the fact that vaccination does not have a 100% effectiveness is considered assuming that only a fraction of