Non-mandatory immunization and its potential impact on pertussis epidemiology

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ABSTRACT
In this study, we performed a quantitative analysis of the potential short-term consequences on pertussis of the draft bill on Informed Consent for Immunization proposed in Argentina in 2017, which considers a non-mandatory immunization schedule for minors. We used a mathematical model of pertussis transmission, which had been previously developed by our group. It is considered that the mere presentation of the project causes a reduction in coverage because it creates suspicion on the benefits of immunization. Assuming a 5% annual reduction in coverage for 4 years as of 2018, in the next outbreak, severe cases in infants younger than 1 year will increase more than 100%, with an estimated 101 deaths. With a 10% annual reduction in the coverages for 4 years, the next outbreak would result in an increase of number of cases of more than 200%, with 163 deaths.

Key words: immunization coverage, informed consent, pertussis.

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INTRODUCTION
In spite of the key role played by immunization on infectious disease control, it is occasionally rejected or questioned. In several countries, such as the United Kingdom, Sweden, Japan, etc., crises of confidence in immunization programs have caused a reduction in immunization coverage and/or discontinuation, which has resulted in an incidence of the respiratory disease known as pertussis (or whooping cough) that is 10 to 100 times higher than that reported where immunization programs have not been affected. In general, such crises of confidence are caused by anti-vaccine groups or adverse events following immunization (AEFI), also known as events supposedly attributable to vaccination or immunization (ESAVI). Recommendations have been made on how to manage them in the public opinion.

In Argentina, immunizations have been mandatory and free of charge since 1983, as per Law 22909. However, in June 2017, a draft bill on Informed Consent for Immunization was proposed in Argentina, which considered a non-compulsory immunization schedule by authorizing the possibility of freely deciding to accept or reject immunizations by those who were eligible for immunization or those responsible for the immunization of a minor. The medical and academic community rapidly rejected the draft bill and warned on its catastrophic consequences on the incidence of vaccine-preventable diseases. If this law was passed, its immediate effect would be a reduction in immunization coverage, which would result in the risk for the reintroduction of diseases that have already been eradicated, such as diphtheria, and the worsening of endemic diseases, such as pertussis.

Pertussis is a vaccine-preventable acute respiratory infection that is life-threatening in infants. Since the effectiveness of available vaccines is not enough to eradicate it, even with a high coverage, periodic outbreaks occur every 3-5 years. At present, pertussis is a public health problem. In Argentina, pertussis immunization is indicated at 2, 4, and 6 months...
old (primary schedule, pentavalent DTP-Hib-HB—a combined vaccine against diphtheria, tetanus, pertussis, *Haemophilus influenzae* and hepatitis B—or quadrivalent DTP-Hib), with a booster dose at 18 months old, at the time of starting primary education (triple bacterial DTP), and for adolescents, pregnant women, and health care providers (triple acellular DTPa). According to official data, the primary schedule has reached, in recent years, a coverage of approximately 95%, as recommended by the World Health Organization, although the coverage in some populations is below 80%. The outbreak reported in Argentina in 2011 caused 76 deaths among infants aged 1 year old or younger. As of 2012, and in accordance with international recommendations, a booster dose was introduced for pregnant women for the purpose of protecting newborns until their first dose. The following pertussis outbreak occurred between 2015 and 2016 and caused 43% less severe cases in infants younger than 1 year. According to the Ministry of Health, in 2011 (before introducing the dose for pregnant women), infants younger than 2 months corresponded to 59.2% of deaths, whereas in 2015, they accounted for 22.2%. The lethality rate reduced from 2.6% in 2011 to 0.6% in 2016.

Our hypothesis is that both the proposal of such draft bill and its discussion in the society (even if it has not been approved) imply a loss of trust in immunizations on part of the population and the resulting reduction in coverage.

**OBJECTIVE**

To analyze, using a mathematical model, the potential effects of a reduction in immunization coverage on pertussis.

**METHODS**

The consequences of a potential reduction in immunization coverage on the incidence of severe pertussis cases in infants younger than 1 year were analyzed using a deterministic and aged-structured mathematical model of disease transmission, which is described in Figure 1. This mathematical model, developed by the VacSal Laboratory (Institute of Biotechnology and Molecular Biology [Instituto de Biotecnología y Biología Molecular –IBBM–, La Plata] and the Group for Modeling and Simulation of Infectious Disease Transmission of the Institute of Theoretical and Applied Physicochemical Research [Instituto de Investigaciones Físicoquímicas Teóricas y Aplicadas [INIFTA]], has been presented and validated in advance and was used to assess different

**Figure 1. Schematic of the basic epidemiological model**

*Left:* The children of unvaccinated mothers are born in the susceptible S class, where they remain unless they become infected and enter the infectious I class (which accounts for severe cases) or receive the vaccine when they become 2 months old and enter the lowest partial acquired immunity class (P_{AI1}). However, the children of vaccinated mothers are already born in the P_{AI1} class, where they remain for 2 months while antibody protection lasts. In both cases, with the consecutive effective vaccine doses, individuals will acquire partial immunity (and enter P_{AI2} and P_{AI3} classes) until finally reaching the complete acquired immunity class (C_{AI}). Individuals in partial immunity P_{AI} and P_{AI2} classes may also become infected but they develop a progressively less symptomatic disease (and enter I_{2} and I_{3} classes, respectively). In individuals in the infectious classes, infection disappears after 21 days (i.e., they exit the I_{1}, I_{2}, and I_{3} classes at a rate of $\gamma = 1/21$ [1/day] and enter the recovered R class). Immunity does not last for life because it is lost over time as of the first year of life at a rate of $\tau = \tau' = 1/2$, $\sigma_0 = 1/11$ and $\sigma = 1/100$ in units of 1/year.

*Right:* Detailed vaccine administration. Administered vaccines are not 100% effective. The horizontal arrows represent the effect of administering ineffective doses (in these individuals, the number of administered doses increases but not the protection), whereas the vertical arrows represent the effect of administering effective doses, which increases for individuals receiving them, both in terms of number of doses and level of immunity. For simplicity, mortality corresponding to each compartment was omitted from the figure. See references 10-12 for model details.
pertussis management strategies, such as a booster dose for adolescents, an increased coverage with the primary schedule, a correction in dose administration delays, and looking for the optimal schedule.\textsuperscript{10-13}

In this epidemiological situation, we modeled and performed a quantitative analysis of the effect of the progressive reduction in immunization coverage on pertussis incidence. The number of deaths was estimated based on the estimated outbreak incidence, considering that they are proportional to severe cases and that there were 76 deaths in infants younger than 1 year in 2011.

The effect of maternal immunization on infants was modeled considering that a fraction of individuals were passively immunized acquiring a protection that was equivalent to a vaccine dose that lasted until 2 months old.\textsuperscript{12} The reduction in the source of transmission among infants from having immunized mothers was not included here because the evidence in primates suggests that acellular vaccine confers protection against the disease but does not prevent colonization or transmission.

**Parameters**

The model parameters and epidemiological data used to establish them are described in detail in the study by Pesco P. et al.,\textsuperscript{11} Appendix A, and correspond to the case called CP1A-MDI (Contact Pattern1A- Medium Duration of Immunity).

The parameters of the administration of the primary schedule were established using data from the Hospital Elina de la Serna of La Plata, which reflected the population delay in dose administration.\textsuperscript{13} The coverage is estimated at 95 \% for the primary schedule; and 85 \%, 95 \%, and 85 \% for the subsequent boosters, respectively, and 70 \% for maternal immunization. Each dose shows vaccine effectiveness (VE) = 0.9, except for the first dose, whose VE is considered lower due to the newborn’s immature immune system,\textsuperscript{14} and for the acellular booster dose administered to adolescents (in both cases, VE = 0.5). The parameters of the forces of infection $\lambda$ are established based on the number of cases reported in the pre-vaccine era.\textsuperscript{10}

**RESULTS**

*Figure 2* shows the simulation of severe pertussis cases in Argentina in infants younger than 1 year. The model’s stationary state was altered to emulate an outbreak similar to that of 2011. The administration of a dose to pregnant women started in 2012. The left panel shows the assumption that the draft bill will be discussed in 2018; at that time, a hypothetical reduction in all immunization coverage levels will start for 4 years. Two coverage reduction scenarios are considered: a) a 5 \% annual reduction until reaching a total of 20 \%; b) a 10 \% annual reduction until reaching a total of 40 \%. Scenario a is compatible with the
reduction observed in Chile,\(^\text{15}\) where the anti-vaccine movement is relatively less active, as in Argentina, whereas scenario b is closer to what has been observed in countries where schedules compliance were severely affected.\(^\text{1}\)

According to our model, if the coverage of all doses were reduced as of 2018, as per case a, in the 2020 outbreak, severe cases would increase more than 100 % compared to the previous outbreak (2015), with an estimated of 101 deaths (Figure 2, panel A). In the case of a higher reduction (case b), the next outbreak would be 200 % worse and there would be 163 deaths.

As any intervention in a dynamic system causes a different effect depending on the moment of the cycle when it occurs, panel b of Figure 2 shows the system with a reduction in coverage as of 2020. The increase in the number of cases in the following outbreak (2025) would be 100 % higher compared to the previous outbreak, with an estimated 115 deaths (case a) and more than 300 % higher with an estimated 209 deaths (case b).

**DISCUSSION**

According to our study, and taking into account different possible coverage scenarios and year of initiation for coverage reduction, and even in the case that is considered less unfavorable (i.e., 5 % annual coverage reduction for 4 years as of 2018), in the next pertussis outbreak, the number of cases in infants younger than 1 year would increase more than 100 %, as well as the number of deaths.

The uncertainty in the values of certain parameters, such as transmission between different age groups, is a limitation of this study. The incidence values described here may vary if estimated with other epidemiologically compatible parameters. In previous sensitivity analysis, the variation in the incidence due to a change in the coverage as per different parameter sets has been studied and the conclusion is that predicted trends are robust.\(^\text{10,11}\)

According to our results, reaching –and maintaining– a high coverage level with primary doses and the dose administered to pregnant women is the main strategy to prevent pertussis in infants.\(^\text{10-13}\) However, to maintain a high coverage and the community’s reliability in the immunization schedule, it is necessary to launch campaigns that describe its benefits and warn on the consequences of an incomplete or delayed vaccine administration. In this regard, we believe that this study is useful because it provides the results of a robust, locally parameterized mathematical model that helps to quantify the risk of jeopardizing the mandatory immunization schedule on the incidence of pertussis.\(^\text{7}\)

**REFERENCES**


