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Potential impact of maternal vaccination on life-threatening respiratory syncytial virus infection during infancy ☆

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ABSTRACT

Background: Respiratory syncytial virus (RSV) infection is an important cause of infant mortality. Here, we estimated the potential impact of maternal vaccination against RSV on life-threatening RSV infection in infants.

Methods: We developed a mathematical model for maternal vaccine-induced antibody dynamics and used characteristics of a maternal RSV vaccine currently in phase 3 of clinical development. The model was applied to data from two cohorts of children younger than 12 months with RSV-related paediatric intensive care unit (PICU) admission in the United Kingdom (n = 370) and the Netherlands (n = 167), and a cohort of 211 children younger than 12 months with RSV-related in-hospital death from 20 countries worldwide.

Results: Our model predicted that, depending on vaccine efficiency, maternal vaccination at 30 weeks' gestational age could have prevented 62–75% of RSV-related PICU admissions in the United Kingdom and 76–87% in the Netherlands. For the global mortality cohort, the model predicted that maternal vaccination could have prevented 29–48% of RSV-related in-hospital deaths. Preterm children and children with comorbidities were predicted to benefit less than (healthy) term children.

Conclusions: Maternal vaccination against RSV may substantially decrease life-threatening RSV infections in infants.

1. Introduction

Respiratory syncytial virus infection (RSV) is an important cause of morbidity and mortality in young children [1,2]. Globally, it is estimated that 48,000–74,500 children aged younger than five years died in-hospital with RSV-related lower respiratory tract infection in 2015 [2]. About 99% of RSV-related childhood mortality occurs in developing countries [2]. Most RSV-related mortality occurs during the first year of life [3–6]. In our recent global case series study of 358 children with RSV-related in-hospital death, median age at death varied from 4 to 7 months depending on income region (upper middle-income vs. high-income countries, respectively) [6]. Preterm children and children with comorbidities such as congenital heart disease or chronic lung disease are at increased risk for severe RSV infection or even fatal RSV infection [7–10].

Maternal vaccination is currently being considered for RSV prevention in young children [11]. Maternal vaccination will only provide temporary protection due to an age-dependent decrease of maternally-acquired protective antibodies after birth [12,13]. For example, serological studies from Bangladesh and Kenya reported maternally-acquired protective antibodies against RSV to be present only up to four months after birth [14–16]. Similarly, maternal

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vaccination against influenza and pertussis provides protection during the first two to three months of life [12,17]. As transplacental antibody transfer becomes efficient only from the third trimester of pregnancy onward, maternal vaccination may provide limited protection for preterm infants [18–20]. To date, the potential impact of a maternal RSV vaccine on RSV-related mortality in young children is unknown. In this observational, retrospective study, we developed a mathematical model for maternal vaccine-induced antibody dynamics, taking into account transplacental antibody transfer rates and antibody decline after birth [15,18,21–24]. We applied this model to data from two retrospective cohorts of children with RSV-related paediatric intensive care unit (PICU) admission and a previously published cohort of children with RSV-related in-hospital death [6] and predicted the percentage of life-threatening RSV infections potentially prevented by maternal vaccination.

2. Methods

To predict the percentage of life-threatening RSV infections potentially prevented by maternal vaccination we developed a mathematical model for maternal vaccine-induced antibody dynamics, taking into account transplacental transfer rates of protective antibodies during pregnancy and antibody decline in newborn children.

2.1. Maternal vaccine-induced antibodies

Vaccination of pregnant women against RSV infection induces an increase in maternal anti-RSV antibodies. For simplicity, maternal vaccine-induced RSV-specific antibody levels were modelled as an exponential increase between day 7 and day 21 post-vaccination, and were assumed to stay constant afterward [15,21,22]. We hence modelled maternal vaccine-induced RSV-specific antibody levels (a_m in μg/ml) as follows (Fig. 1A):

$$if \;\; t < 7, \quad a_m(t) = a_{m0}$$

$$if \;\; 7 \le t \le 21, \quad a_m(t) = a_{m0} \;\; e^{(t-7)\log(f)/14}$$

$$if \;\; t > 21, \quad a_m(t) = a_{m0} \;\; f$$

where t is the time in days since vaccination, a_{m0} the natural level of maternal RSV-specific antibodies in μg/ml, and f the vaccine-induced fold increase in maternal RSV-specific antibodies (later referred to as vaccine efficiency).

2.2. Transfer of maternal antibodies

During pregnancy, maternal immunoglobulin G (IgG) antibodies are transferred to the foetus by transplacental transport. Transplacental transfer is thought to increase during pregnancy to become most efficient during the third trimester, and at term foetal IgG concentrations typically even exceed maternal IgG levels [18–20,25]. Based on published data on maternal and foetal IgG antibody levels at different time points during pregnancy (Section 5 and Fig. 3 (IgG1) of Palmeira et al. [26] which are based on Fig. 2 of Malek et al. [18]), we chose to model maternal IgG antibody transfer with an exponential function, as it gave the best description of the experimental data [18]. The parameters of this function were estimated using the function *lm* in R software (version 3.3.2) after a log-transformation of the data and the best fit of this model to the experimental data was found for:

$$r(t) = e^{-4.97+0.13t}$$

where r is the foetus-to-mother IgG transfer ratio and t is time in days since the beginning of pregnancy (Fig. 1B).

2.3. Foetal antibody levels after birth

We assumed that maternally-derived RSV-specific antibody levels in umbilical cord blood at birth (a_{cb} in μg/ml) can be calculated directly from the RSV-specific antibody levels in the mother and the foetus-to-mother IgG transfer ratio at time t_b, the gestational age (i.e. time of birth) in days, using the following function:

$$a_{cb}(t_b) = a_m(t_b).r(t_b)$$

After birth, maternally-acquired RSV-specific antibody levels in the new-born were assumed to decrease with a half-life $t_{1/2}$. The RSV-specific antibody levels of new-born children (a_c in μg/ml) can therefore be described as follows (Fig. 1C):

$$a_c(t) = a_{cb}(t_b)\left(\frac{1}{2}\right)^{t/t_{1/2}}$$

where t is the age of the new-born child in days after birth.

2.4. Model parameterization

Similar antibody dynamics for maternal vaccine-induced RSV-specific IgG and palivizumab competing antibody (PCA) have been reported [21,27] and as more data are available for PCA we decided to parameterize our model on PCA. A natural PCA level a_{m0} of 33 μg/ml was used based on the phase-2 trial studying the safety and immunogenicity of a recombinant RSV fusion protein nanoparticle vaccine (RSV F vaccine) candidate in non-pregnant women of childbearing age [21]. PCA levels after vaccination against RSV have been reported to be 6.9–7.9-fold higher than the natural PCA level, depending on vaccine dosing [21]. Based on these values, we considered two vaccine efficiencies (f) of 5 and 10 in our simulations. RSV-specific antibody half-life after birth was reported to be 41 days by maternal RSV F vaccine manufacturers [23], which is in close agreement with reported values of 36–38 days in clinical studies measuring cord blood and infant maternally-acquired RSV-specific antibody levels [15,28]. A child PCA level of 40 μg/ml was considered as the protective threshold against life-threatening RSV infection [24,29,30].

2.5. Study population

We applied our model to three independent, retrospective cohorts of patients. Anonymised secondary patient data were obtained through retrospective review of medical records. The first and second cohort consisted of children aged younger than 12 months with community-acquired RSV infection admitted to the PICU for mechanical ventilation, who all survived. The first cohort consisted of 370 children admitted to a PICU in the United Kingdom (UK) between 2002 and 2014 and the second cohort consisted of 167 children admitted to two PICUs in the Netherlands between 2008 and 2015. None of the children had received palivizumab during infancy. In the third cohort, children were selected from a retrospective case series study describing global, in-hospital, RSV-related mortality in 358 children aged younger than five years [6]. All children aged younger than 12 months with available data for prematurity were included. This resulted in a study population of 211 children with RSV-related in-hospital death from 20 countries. In the second and third cohort, when the exact gestational age was missing (i.e. for 60 term children in the Dutch PICU cohort and for 19 preterm and 85 term children in the mortality cohort) it was imputed to 34 or 40 weeks of gestation for preterm or term children respectively, based on median values of children with complete gestational age data.

For each cohort, we defined the following subgroups: children with comorbidities, healthy term children (born without

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