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Respiratory syncytial virus immunization program for the United States: Impact of performance determinants of a theoretical vaccine☆

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ABSTRACT

Objectives: To inform strategic decisions on respiratory syncytial virus (RSV) vaccine development and identify critical endpoints likely to drive the vaccine's medical and economic impact.
Design: A decision-analysis model populated using healthcare utilization data and costs from the literature; vaccine efficacy and duration based on assumptions.
Setting: Vaccination in the physician office setting in the USA.
Participants: A hypothetical cohort of newborn infants.
Intervention: Vaccination of children at low and high risk of respiratory sequelae with a theoretical RSV vaccine vs palivizumab prophylaxis for children at high risk.
Outcome measures: Medical and economic value of RSV vaccination, including cost per quality adjusted life-year (QALY) gained.
Results: Using base-case assumptions (efficacy 50% at birth; half-life 12 months), RSV vaccination would prevent 23,069 hospitalizations and 66 deaths per vaccinated birth cohort in the USA. Excluding vaccination costs, direct medical costs for RSV would reduce by $236 million, and income and productivity losses by $134 million. Assuming a vaccine cost per course similar to Rotarix® in the USA ($232 including administration fees), the cost per QALY gained would be $93,401 (95% CI: $65,815-$126,060) from the healthcare system perspective and $65,115 (95% CI: $41,003–$93,679) from the societal perspective. The net cost (healthcare system perspective) per life-year saved would be $216,120 (95% CI: $161,184–$263,981); the cost per hospitalization averted would be $19,172 (95% CI: $14,679–$22,093). Aside from efficacy, the vaccine's impact is sensitive to the start of protective immunity and the duration of protection.
Conclusions: Development of an RSV vaccine would substantially reduce inpatient hospitalizations and outpatient visits. It would also have an impact on infant mortality. To demonstrate the full medical and economic value of the vaccine, appropriate endpoints or endpoint surrogates for hospitalization, mortality, and total case reductions should be collected during vaccine development.

1. Introduction

Respiratory syncytial virus (RSV) is the most common cause of severe lower respiratory tract disease among infants and young children [1]. 69% of infants are infected during the first year of life and 83% during the second [2]; typically, <3% experience severe symptoms and require hospitalization [3].

Globally, there are 34 million (95% CI 19.3–46.2) new RSV infections annually in children < 5 years old, with at least 3.4 million (95% CI 2.8–4.3) infections necessitating hospital admission, leading to 66,000–199,000 deaths [4]. Infants and children who suffer from severe RSV infections may be susceptible to the development of respiratory sequelae such as wheezing or asthma [5]. Groups particularly at risk include premature infants and children < 2 years old with chronic lung disease or congenital heart disease [6].

In the USA, 2 million children require medical care for RSV annually [7]. This includes 1.7 million office visits [8], 180,000 emergency room (ER) visits for infants aged < 1 year [9], and 400,000 ER visits for children < 5 years old [8]. Between 60,000 and 144,000 infants are hospitalized annually because of RSV [3,5,9,10]; over half of these are <6 months old [8]. The average length of stay is 3.4–3.9 days [8,9].

The American Academy of Pediatrics recommends that infants at particularly high risk of severe RSV disease receive prophylaxis, e.g. administration of palivizumab (approved in 1998 in the USA) [11]. There are currently no approved vaccines to prevent RSV

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disease. Three vaccine candidates are in Phase I or II development [12]: MEDI-559 and MEDI-534 (MedImmune) and one from Novavax. To date, only seroconversion data have been reported for these vaccines [13,14]. The vaccination of pregnant women is a potential way to protect full-term infants from RSV disease during the first few months following birth, based on antibodies passed transplacentally late in pregnancy [15]. In July 2012, Novavax announced partnership with PATH to fund clinical trials of its RSV vaccine candidate for immunization of pregnant women [16].

The literature evaluating the impact of an RSV vaccine is limited and no article has modeled the impact of RSV vaccination of children in the USA [17–20]. In this article, we developed a decision-analysis model to compare the impact of a hypothetical RSV vaccine for children at low and high risk of respiratory sequelae in the USA with the current standard of care (palivizumab prophylaxis for children at high risk). In addition, this article provides strategic information for policy-makers and vaccine manufacturers. In particular, our model aims to identify the critical endpoints that determine a vaccine's value.

2. Methods

2.1. Model

The monthly costs and outcomes of RSV disease were estimated for a hypothetical infant cohort from birth until a defined time point. Vaccination and no-vaccination scenarios were analyzed (Fig. 1). For each scenario, the number of events (e.g. hospitalizations, death) attributed to RSV was calculated based on information from the literature and vaccine assumptions. The model's time horizon was 5 years after birth for healthcare utilization (as 98% of pediatric RSV-related hospitalizations occur during this period [8]), 10 years for the impact on asthma, and lifetime for loss of productivity due to premature death. The cohort size (4.23 million) was calculated using the average cohort size for 2007, 2008 and 2009 [21–23].

Two perspectives can be taken to analyze the vaccination program. In the analysis conducted from the healthcare system perspective, only direct medical costs are included. For the societal perspective, direct nonmedical costs (travel, meals, and lodging) and productivity losses are also included. More specifically, the incremental cost effectiveness ratio (ICER) from the societal perspective was calculated using the formula:

$$\mathrm{ICER} = [Co * Ra * (Pc + Ad) - Ms - NMs - Ps]/Qg$$

where *Co* is the cohort size, *Ra* the vaccination rate, *Pc* the price per course, *Ad* the administration fees per course, *Ms* the medical cost savings from vaccination, *NMs* the direct nonmedical costs, *Ps* the productivity savings from vaccination (if societal perspective is taken), and *Qg* the number of QALYs gained from vaccination. Rotarix® price per course was used for *Pc* (see sensitivity analysis). A vaccination rate of 69% was assumed (see supplementary material). Note that no wastage and no advertising or adverse-event costs were assumed.

It is unknown whether an RSV vaccine would be administered to pregnant women or to infants. However, the model can be used to provide insight into both vaccination strategies by adjusting the onset and the duration of protection (see Discussion).

2.2. Medical assumptions

2.2.1. Vaccine efficacy and safety

Because no efficacy data are available for any vaccines in development, the base case assumed that vaccination would reduce the probability of RSV-associated events by 50%. Equal effectiveness against RSV subgroups A and B was assumed. The start of protective immunity from the RSV vaccination is also unknown. The base case assumed a vaccination and a protective effect at birth. An exponential distribution was assumed for the duration of protection. The base case assumed a half-life of 12 months, which is lower than that for vaccines with known low persistence (eg., meningococcal, pertussis) [26,27]. The vaccine was assumed not to increase the incidence of medically attended events.

2.2.2. Resource utilization

Table 1 shows key assumptions for healthcare utilization due to RSV. Data from Paramore et al. [8] were used to estimate the risk by age of inpatient hospitalization and of hospital outpatient visits due to RSV infection. The age distribution of hospital outpatient visits was assumed to be similar to that of inpatient hospitalization. The risk by age of visits to the ER and to physicians' offices was based on data from Hall et al. [28].

2.2.3. Mortality

Published estimates of RSV-associated deaths in the USA range from 130 to 390 annually for infants <1 year old (mortality rate range, 3.1–9.4 per 100,000), and reach 510 for children <5 years old [9,29,30]. The model used estimates of 5.4/100,000 for children <1 year old and 0.9/100,000 for children aged <5 years [29].

2.2.4. Increased risk of asthma/wheezing

The average prevalence of asthma used in the model was 6% for children <5 years old and 10.5% for those aged 5–11 years [31]. Severe RSV disease in the first year of life was assumed to increase the risk of asthma/wheezing with a pooled odds ratio of 3.84 (95% CI: 3.23–4.58) [32]. Several studies have shown that the association between RSV and asthma decreases with age in children [33–35], and no higher prevalence of asthma was assumed once children reached 10 years old.

2.2.5. Quality of life

The assumptions made of QALYs lost as a result of RSV disease are summarized in Table 2. The QALYs lost due to premature death were calculated by using the average utility value per age group and life expectancy [36,37]. The utility value is 0.03 lower for individuals with asthma compared with healthy people [38].

It was assumed that visits to pediatrician and hospital outpatient settings were associated with Lee's definition of mild cough [39]. ER visits and inpatient stays were assumed to be triggered by severe cough and by respiratory complications, respectively. Episodes of RSV infection were assumed to last 10 days [40], with a resulting loss in utility value of 0.005–0.010 per attack. More details regarding the QALY calculations can be found in the supplemental materials. After an ER visit, the probability of being admitted to hospital or of making an office visit was assumed to be 29% and 30%, respectively [9].

2.2.6. Cost assumptions

Cost estimates (Table 2) were derived from published sources and adjusted to 2011 US dollars, based on the Consumer Price Index (CPI) [46]. Costs rather than charges were used to better reflect the opportunity cost to society [47].

2.2.7. Medical costs

Hospitalization costs for RSV were assessed using International Classification of Diseases, Ninth revision codes 079.6 (RSV), 466.11 (acute bronchiolitis due to RSV), and 480.1 (pneumonia due to RSV) for the principal diagnosis.