Burden of Respiratory Syncytial Virus Disease in Infants and the Potential Value of Maternal Immunization in Greece.

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Introduction

- Respiratory syncytial virus (RSV) is the leading cause of viral bronchiolitis and pneumonia in children under 5 years of age, with infants under 6 months being at the highest risk for severe disease, including bronchiolitis and pneumonia, where respiratory distress is a key feature (1-2).
- RSV is associated with considerable direct healthcare use and costs, which has been estimated at approximately €4.8 billion globally per year in children <5 years of age (3).
- The recently licensed bivalent RSV prefusion F protein-based vaccine (RSVpreF) has the potential to fulfill an unmet medical need(4) having demonstrated efficacy, safety, and immunogenicity against RSV in infants born to women vaccinated during pregnancy in a pivotal placebo-controlled Phase III MATISSE clinical trial (4).

Objective

The objective of present study was to evaluate the health and economic burden of RSV disease and the cost-effectiveness of maternal immunization with RSVpreF vaccine for the prevention of RSV among infants in Greece.

Methods

Model overview

- The current published model(5) employs a cohort framework and Markov-type process to depict health outcomes and economic costs of infections in newborn infants from birth to 1 year of age.
- The model population was initially characterized based on gestational age in weeks(full-term, ≥37; late preterm, 32-36; early preterm, 28-31; extreme preterm, ≤27) at birth and infants may be assumed to be protected against RSV due to maternal vaccination or would remain unvaccinated against RSV (no intervention received).
  - Health outcomes: Cases of medically attended RSV-RTD by care setting (hospital [H], emergency department [ED], outpatient visit [OV]), attributable deaths, and QALYs.
  - Economic outcomes: Direct medical costs of treatment for RSV are generated based on event rates and unit costs in relation to the setting of care (hospital, ED and OV).

Estimation of Model Inputs

- The model population included infants (n=76,541) born to 76,500 women during a one-year period. Estimates of born infants, number of women giving birth and the distribution of births by term status in a single year was provided by Hellenic Statistical Authority (EL. STAT.).
- Annual incidence rates of RSV by month of age and by care setting (i.e., hospital, ED, and OV) were derived based on age-specific values from a published study (5) and local experts (Table1).
- Age- specific relative rates of RSV by term status were derived based on the study by Rha et al.(6)and were assumed to apply for all care settings.
- Case fatality rate (CFR) due to RSV-Hospital was assumed to be 0.1 per 100 cases for full term infants based on a published study (7). Given limited research on CFR related to RSV, CFR for preterm infants was derived based on the number of RSV-related deaths among children aged <1 year according to recently published estimates (8).
- Distribution of RSV cases were allocated across calendar months using data from local experts.
- Vaccine effectiveness (VE) estimates were derived using the cumulative efficacy data for the primary endpoints from MATISSE clinical trial(4).

Table 1: Incidence rates for RSV by care setting and age and associated direct medical costs

Incidence rates for RSV (per 1000) by care setting and age				
Age	**Hospital**	**Emergency Department**	**Outpatient Visit**	**Source**
<1 month	137.9	124.1	124.1	
1 - <2 months	164.3	166.3	168.3	(5)
2 - <3 months	94.3	101.4	102.9	
3 - <6 months	56.9	76.6	98.4	
6 - <12 months	34.9	85.5	146.0	

Cost of RSV requiring hospitalization by age and term status(9)				
Terms status	**Age**			
	<1 Month	**1 - <2 Months**	**2 - <6 Months**	**6 - <12 Months**
Full term (≥37 wGA),	11,273 €	4,149 €	2,595 €	1,907 €
Late preterm (32-36 wGA),	13,441 €	11,273 €	4,149 €	2,595 €
Early preterm (28-31 wGA),	18,265 €	15,768 €	8,984 €	6,104 €
Extreme preterm (≤27 wGA).	31,460 €	23,575 €	15,768 €	11,864 €
Cost of RSV treated in Emergency department by age¥				
All infants	203 €	203 €	203 €	203 €
Cost of RSV treated in outpatient by age ¥				
All infants	123 €	123 €	123 €	123 €

¥Source: Drug price bulletin issued by the Greek Ministry of Health(9) , official website of EOPYY(10), and local experts .

Methods

- The age/ term status -specific direct medical costs associated with RSV hospitalization were obtained from the Diagnosis-Related Group (9)(Table1).
- While the cost of ED and OV cases were estimated by combining the resources consumed, as provided by local experts, with the corresponding unit costs obtained from official sources (9-10) (Table 1).
- The bivalent RSVpreF unit cost per dose was estimated at €205.98 according to the price bulletin issued by the Greek Ministry of Health (9).
- Utilities data for infants with RSV-LRTI, based on published study (11).
- The annual uptake of RSVpreF was 19.5%, in line with the influenza vaccination rates for pregnant women reported in a recent Greek study (12), and this rate was assumed to be stable/constant across all months.

Analysis

- Incremental cost-effectiveness ratios are calculated by comparing vaccination strategy and no vaccination and calculating the additional cost per additional health benefit in terms of cost per QALY gained, cost per LY gained and cost per hospitalization avoided.
- Deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) evaluated impact of changes in key model parameters and assumptions.
- The perspective of the analysis was that of a Greek public payer (EOPYY) and an annual discounting of 3.5% was applied for future health outcomes and costs as often used in such studies in Greece.

Results

- Model analysis indicated that without RSV vaccination there would be 4,884 hospitalizations, 7,155 ED encounters, 9,896 OV and 11 deaths related to RSV among Greek infants resulting in direct medical costs of circa €26 million (Table 2).
- Year-round RSVpreF vaccination with 19.5% coverage, was projected to reduce hospitalizations by 484, ED encounters by 335, OV by 389 and deaths by 1 during a period of 1 year. The effectiveness benefits associated with RSVpreF translate in RSVpreF accruing more 31 QALYs than the no vaccination strategy (Table 2).
- The incremental analysis showed that RSVpreF was estimated to be a cost-effective vaccination strategy and resulted in ICERs of €12,082 per LY gained, €8,280 per QALY gained and €528 per RSV hospitalized case avoided compared to no vaccination (Table 2).
- The results of DSA indicated that the base case model results are robust to changes in parameter inputs.
- The PSA confirmed the base case results.

Table 2:Base case model results

Parameters	Maternal vaccination strategy	No vaccination strategy	Incremental
Health Outcomes			
No. of RSV cases			
Hospital	4,401	4,884	-484
Emergency department	6,820	7,155	-335
Outpatient visit	9,507	9,896	-389
Total	20,727	21,935	**-1,208**
No. of RSV-related deaths	10	11	**-1**
Total QALYs	1,863,469	1,853,558	**31**
Total LYs	2,064,605	2,053,508	**21**
Economic Outcomes (in millions)			
Direct cost of vaccine (€)	3.15	-	3.15
Direct RSV medical care cost (€)	22.98	25.87	-2.89
Total cost (€)	26.13	25.87	**0.26**
Cost-effectiveness analysis (Maternal vaccination vs No vaccination)			
ICER per QALY gained (€)			**8,280**
ICER per LY gained (€)			**12,082**
ICER per RSV hospitalized case avoided (€)			**528**

Conclusion

▪The maternal RSVpreF vaccination, providing protection from the first day of life, has the potential to significantly reduce RSV-related disease in infancy.

▪ Year-round maternal RSVpreF vaccination was estimated to be a cost-effective option compared to no intervention from the payer perspective, demonstrating its value as a preventive strategy against RSV.

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