

# Impact of RSV Immunization on the Rate of Pediatric Acute Otitis Media: A Time-series Analysis

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**Background.** Acute otitis media (AOM) is the leading cause of antibiotic prescription in children. Respiratory syncytial virus (RSV) is suspected to play an important role in AOM. The aim of this study was to estimate the impact of RSV immunization on the rate of subsequent AOM in children, as this effect remains unknown.

**Methods.** We conducted an interrupted time-series analysis based on a French network involving 110 ambulatory pediatricians, trained in pediatric infectious diseases (PARI network). All ambulatory visits for AOM, from June 2017 to February 2025 were included. The main outcome was the monthly rate of pediatric ambulatory visits for AOM in infants aged < 12 months per 1000 pediatric ambulatory visits over time, assessed by a seasonally adjusted quasi-Poisson regression model. Bronchiolitis and urinary tract infections (UTI) were analyzed over the same period, as positive and negative controls, respectively.

**Results.** We included 70 452 cases of AOM, 13 284 bronchiolitis and 814 UTI. The rate of AOM per 1000 visits in infants aged < 12 months significantly decreased after RSV immunization implementation (−23.7%, 95% CI −37.6 to −9.7,  $P = .0014$ ), whereas no significant change was observed in older age groups. We observed similar trends for bronchiolitis. The monthly rate of UTI did not significantly decrease.

**Conclusions.** RSV immunization led to a strong reduction of AOM rate in infants aged < 12 months. Beyond its efficacy in preventing RSV-related lower respiratory infections in infants aged < 12 months, RSV immunization may contribute to reduce the burden of AOM in children.

**Keywords.** acute otitis media; nirsevimab; time-series analysis.

Acute otitis media (AOM) accounts for 391 million cases worldwide annually, and is particularly frequent in infants aged < 2 years [1]. AOM is the first cause of antibiotic prescription in children, highlighting the huge burden of this disease in pediatrics [2].

AOM is often a complication following viral upper respiratory infections (URIs), and could be caused by bacteria, viruses or a

combination of both [3]. The role of both respiratory viruses and some bacteria from the nasopharyngeal flora is highly suspected, but difficult to confirm due to the lack of reliable microbiological sampling during most episodes of AOM. Samples taken from otorrhea and nasopharyngeal carriage during some episodes of AOM suggest a significant role of *Streptococcus pneumoniae*, even after pneumococcal conjugate vaccines [4, 5].

Among respiratory viruses, the human respiratory syncytial virus (RSV) has been identified as the most commonly detected virus during AOM episodes [6], even if its involvement in the disease remains difficult to confirm. Moreover, RSV is also suspected to trigger the transition from pneumococcal nasopharyngeal colonization to pneumococcal infection [7]. Thus, RSV may play a significant role in the occurrence of AOM, either directly or indirectly by triggering a pneumococcal infection.

Nirsevimab is a monoclonal antibody against RSV that has demonstrated its efficacy in reducing RSV-related lower respiratory infections (LRIs) in infants aged < 12 months [8, 9]. Maternal RSV immunization during pregnancy has been also

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implemented in mainland France to prevent RSV-related LRIs in infants [10]. To date, the impact of RSV immunization on the rate of AOM in children is unknown.

In this context, the aim of this study was to estimate the impact of RSV immunization (nirsevimab or maternal vaccine) on the rate of AOM in children in ambulatory settings.

## METHODS

### Study Design

We conducted an interrupted time-series analysis using ambulatory-based French national surveillance of AOM in children from June 2017 to February 2025.

### Settings

The Pediatric and Ambulatory Research in Infectious diseases (PARI) network, is a national surveillance system created in 2017 involving 110 pediatricians located across the French territory that are specifically trained in the diagnosis and management of community-acquired pediatric infectious diseases [11, 12]. The reliability of this network has been previously shown through several studies based on other surveillance systems of LRIs in children [13]. AOM is the leading infectious diagnosis and by far the leading cause of antibiotic prescription.

### Inclusion Criteria

We included all children aged < 18 years visiting an ambulatory pediatrician of the PARI network for AOM, bronchiolitis, or urinary tract infection (UTI) from June 2017 to February 2025.

### Study Periods

To reduce the risk of LRIs caused by RSV in infants, national French guidelines recommended RSV immunization during the 2024–25 season: (1) A single-dose of nirsevimab, a monoclonal antibody implemented in metropolitan France on 15 September 2024 for infants born between 6 February 2024 and 31 January 2025 [14] or (2) A single-dose maternal vaccination with Abrysvo, indicated between 32 and 36 weeks of gestational age from 15 September 2024 to 31 January 2025 [15]. Based on the implementation period of these two products, the post-RSV immunization period was considered from October 2024 to February 2025.

During the 2023–24 nirsevimab immunization campaign in France, national shortages were observed, leading to prioritize immunization with nirsevimab at birth in maternity units, while immunization coverage in ambulatory settings was low. Furthermore, maternal immunization campaign was not conducted during the 2023–24 season. Due to the low nirsevimab immunization coverage during the first 2023–24 season in French ambulatory settings, data covering the period between September 2023 and September 2024 were excluded from the analysis. The RSV immunization period was considered from October 2024.

Because URIs and AOM epidemiology have been influenced by the coronavirus disease 2019 (COVID-19)-related nonpharmaceutical interventions (NPI) implemented worldwide, we used a model accounting for the NPI implementation period. According to the stringency index developed in France to estimate the degree of proximity among individuals [16] and as previously published [17], the NPI implementation period was defined from April 2020 to March 2021.

### Outcomes

RSV immunization with nirsevimab in France was indicated for infants aged < 12 months.

Therefore, the main outcome was the monthly rate of ambulatory visits for AOM per 1000 visits for children aged < 12 months. To calculate the rate of AOM per 1000 visits, we used the total number of ambulatory visits reported by the PARI network as the denominator and the number of visits for AOM as the numerator.

The 2024–25 RSV immunization campaign in France led to a high coverage in infants aged < 6 months. Therefore, we performed a secondary analysis of AOM by age groups (<6 months, 6–11 months, 1 to <2 years, and  $\geq 2$  years).

To explore the potential bias due to hidden cointerventions, the monthly rate of ambulatory visits for UTI per 1000 visits for children aged < 18 years was analyzed as a negative control outcome over the same period. Additionally, we considered AOM in children aged  $\geq 12$  months as a second negative control group, since they were not targeted by the RSV immunization program. The rate of ambulatory visits for bronchiolitis, defined as the first wheezing attack with respiratory symptoms before 12 months of age or the second attack in infants without a personal or family history of asthma or atopy [18], per 1000 visits was analyzed as a positive control outcome and was also assessed by age groups (<6 months and 6–11 months).

### Statistical Analysis

Outcomes were analyzed using a quasi-Poisson regression model, accounting for seasonality by including harmonic terms (sines and cosines with 12-, 6-, and 3-months periods), with the time unit set to 1 month [19–21].

First, the observed monthly rate of ambulatory visits for AOM was fitted by the model for each time-point of the study period, with the RSV immunization implementation included as an explanatory variable. Then, according to the pre-RSV immunization implementation trend and seasonality, and setting the intervention terms to zero, the model enabled us estimate the expected values of the outcome without RSV immunization implementation. Based on this model, we estimated changes in the rate of ambulatory visits for AOM following RSV immunization implementation, compared to the expected values of the outcome based on the pre-RSV immunization implementation trend.

**Table 1. Baseline Characteristics of Ambulatory Visits of Children Aged < 18 y between June 2017 and February 2025 in France**

Characteristics	Children, No. (%)			
	Pre-RSV Immunization Period	Transitional Period	Post-RSV Immunization Period	All Study Periods
AOM < 12 m	12 957 (72.3)	3359 (18.7)	1607 (9.0)	17 923
AOM by other age groups				
<6 m	1819 (75.2)	442 (18.3)	159 (6.5)	2420
6–11 m	11 138 (71.9)	2917 (18.8)	1448 (9.3)	15 503
1 to <2 y	16 406 (70.1)	4772 (20.4)	2217 (9.5)	23 395
≥2 y	18 804 (64.6)	6798 (23.3)	3532 (12.1)	29 134
Overall AOM				
No. of cases	48 167 (68.4)	14 929 (21.2)	7356 (10.4)	70 452
Sex ratio (H/F)	59.2/40.8	59.4/40.6	56.9/43.1	59.0/41.0
Age, median (IQR), months	18.8 (11.5–35.5)	21.4 (12.6–42.7)	23.1 (12.8–42.5)	19.8 (11.9–37.8)
Bronchiolitis				
No. of cases	9630 (72.5)	2506 (18.9)	1148 (8.6)	13 284
Sex ratio (H/F)	66.0/34.0	65.6/34.4	64.1/35.9	65.8/35.2
Age, median (IQR), months	6.4 (4.7–8.6)	6.6 (4.9–8.9)	6.6 (4.9–8.9)	6.5 (4.8–8.7)
UTI				
No. of cases	603 (74.1)	150 (18.4)	61 (7.5)	814
Age, median (IQR), months	46.4 (20.8–80.6)	50.5 (23.4–77.4)	51.7 (32.3–79.9)	47.2 (21.8–79.4)
Total no. of nonurgent ambulatory visits	2 352 884 (77.3)	512 014 (16.8)	181 040 (5.9)	3 045 938
Total no. of ambulatory visits for infectious diseases	224 795 (69.1)	66 896 (20.5)	33 810 (10.4)	325 501
Total no. of ambulatory visits	2 577 679 (76.4)	578 910 (17.2)	214 850 (6.4)	3 371 439

Qualitative data are presented as numbers (%), and quantitative data (age) as medians (IQR). Pre-RSV immunization period: June 2017 to August 2023. Transitional period: September 2023 to September 2024 (data excluded from the analysis, due to the very low immunization coverage in French ambulatory settings during the 2023–24 RSV immunization season). Post-RSV immunization period: October 2024 to February 2025.

Abbreviations: AOM, acute otitis media; IQR, interquartile range; RSV, respiratory syncytial virus; UTI, urinary tract infections.

The validity of the quasi-Poisson regression models was assessed by visual inspection of correlograms and residuals analysis.

To assess the robustness of the study findings, we performed the following sensitivity analyses: (1) a quasi-Poisson regression model adjusted for nonurgent ambulatory visits. Indeed, urgent ambulatory visits are often related to infectious diseases, some of which may have been influenced by RSV immunization implementation. Thus, this sensitivity analysis aimed at accounting for any potential reduction in the rate of overall ambulatory visits due to the impact of RSV immunization on urgent ambulatory visits. (2) a quasi-Poisson regression model including harmonic terms with only 12-month periods, (3) a segmented linear regression model including a combination of harmonic terms (sines and cosines) with 12-month periods, (4) a segmented linear regression model including a combination of harmonic terms (sines and cosines) with 12-, 6-, and 3-month periods to explore different seasonal patterns, (5) a segmented linear regression using an additive model, (6) a negative binomial regression model, and (7) a quasi-Poisson regression model adjusted for the negative control outcome (rate of UTI/1000 ambulatory visits over the same period) to explore the possibility that potential changes observed in the rate of AOM may have been related to another intervention.

All statistical tests were two-sided, with  $P < .05$  considered statistically significant. Analyses were performed using R version 4.2.2 ([www.R-project.org](http://www.R-project.org)).

## RESULTS

### General Characteristics

In total, 70 452 pediatric ambulatory visits for AOM were included between June 2017 and February 2025. The median [IQR] age was 19.8 [11.9–37.8], with 41 577 (59%) boys and 28 875 (41%) girls. AOM in infants aged < 12 months accounted for 17 923 cases (25.4% of total AOM). Bronchiolitis accounted for 13 284 cases (4.1% of the total number of ambulatory visits for infectious diseases) and UTI for 814 cases (0.3% of the total number of ambulatory visits for infectious diseases). The general characteristics are presented in [Table 1](#).

### Association of RSV Immunization with the Rate of AOM

The rate of AOM per 1000 visits significantly decreased after RSV immunization implementation in infants aged < 12 months (estimated cumulative change;  $-23.7\%$ , 95% CI  $-37.6$  to  $-9.7$ , [Table 2](#) and [Figure 1](#)). This decrease was particularly marked in infants aged < 6 months (estimated cumulative change;  $-47.8\%$ , 95% CI  $-76.4$  to  $-19.3$ ) ([Table 2](#) and [Figure 1](#)). Correlograms and residuals analyses indicated a

**Table 2. Association of RSV Immunization with the Monthly Rate of Ambulatory Visits for AOM in France**

Outcome	Post-RSV Immunization Period	
	Estimated Cumulative Change in the Rate of AOM, % (95% CI)	P value
AOM in infants aged < 12 m <sup>a,b</sup>	-23.7% (-37.6 to -9.7)	.0014
Sensitivity analyses <sup>a</sup>		
Quasi-Poisson regression adjusted for nonurgent ambulatory visits	-22.9% (-36.5 to -9.2)	.0016
Quasi-Poisson regression (12 m)	-22.8% (-32.4 to -2.4)	.0262
Segmented linear regression with trigonometric function (12 m)	-13.3% (-22.2 to -4.4)	.0046
Segmented linear regression with trigonometric function (3-6-12 m)	-13.7% (-20.0 to -7.3)	< .0001
Segmented linear regression without trigonometric function	-20.7% (-22.7 to -18.7)	.0130
Quasi-Poisson regression adjusted for the monthly rate of UTI	-23.7% (-36.7 to -10.6)	.0007
Negative binomial regression (3-6-12 m)	-23.7% (-46.6 to -0.7)	.0433
AOM among other age groups <sup>a,b</sup>		
<6 m	-47.8% (-76.4 to -19.3)	.0016
6-11 m	-19.6% (-31.5 to -7.5)	.0023
1 to <2 y	-14.4% (-37.2 to 8.4)	.2201
≥2 y	-16.3% (-34.7 to 10.9)	.3083
Control outcomes		
UTI <sup>a,b</sup>	-9.3% (-19.7 to 1.1)	.0845
Bronchiolitis <sup>a,b</sup>	-42.7% (-70.7 to -14.7)	.0038
<6 m	-49.1% (-78.1 to -20.0)	.0015
6-11 m	-37.5% (-65.9 to -9.1)	.0118

Post-RSV immunization period: October 2024 to February 2025.

Abbreviations: AOM, acute otitis media; CI, confidence interval; RSV, respiratory syncytial virus; UTI, urinary tract infections.

<sup>a</sup>Expressed as the monthly rate per 1000 ambulatory visits.

<sup>b</sup>Analysis using a quasi-Poisson regression model with 12-, 6-, and 3-month periods.

satisfactory quality of the final model (Supplementary eFigure 1) and sensitivity analyses provided similar results (Table 2; Supplementary eFigure 4).

#### Positive and Negative Control Outcomes

We observed similar patterns for the monthly rate of bronchiolitis per 1000 visits after the implementation of RSV immunization (estimated cumulative change; -42.7%, 95% CI -70.7 to -14.7). This decrease was particularly marked in infants aged < 6 months (estimated cumulative change; -49.1%, 95% CI -78.1 to -20.0) (Table 2 and Figure 2). By contrast, we didn't find any change in the rate of UTI per 1000 visits over the same period (Table 2; Supplementary eFigure 3), nor in the rate of AOM in infants aged 1 to < 2 years and infants aged ≥ 2 years, not targeted by RSV immunization (Table 2; Supplementary eFigure 2).

#### DISCUSSION

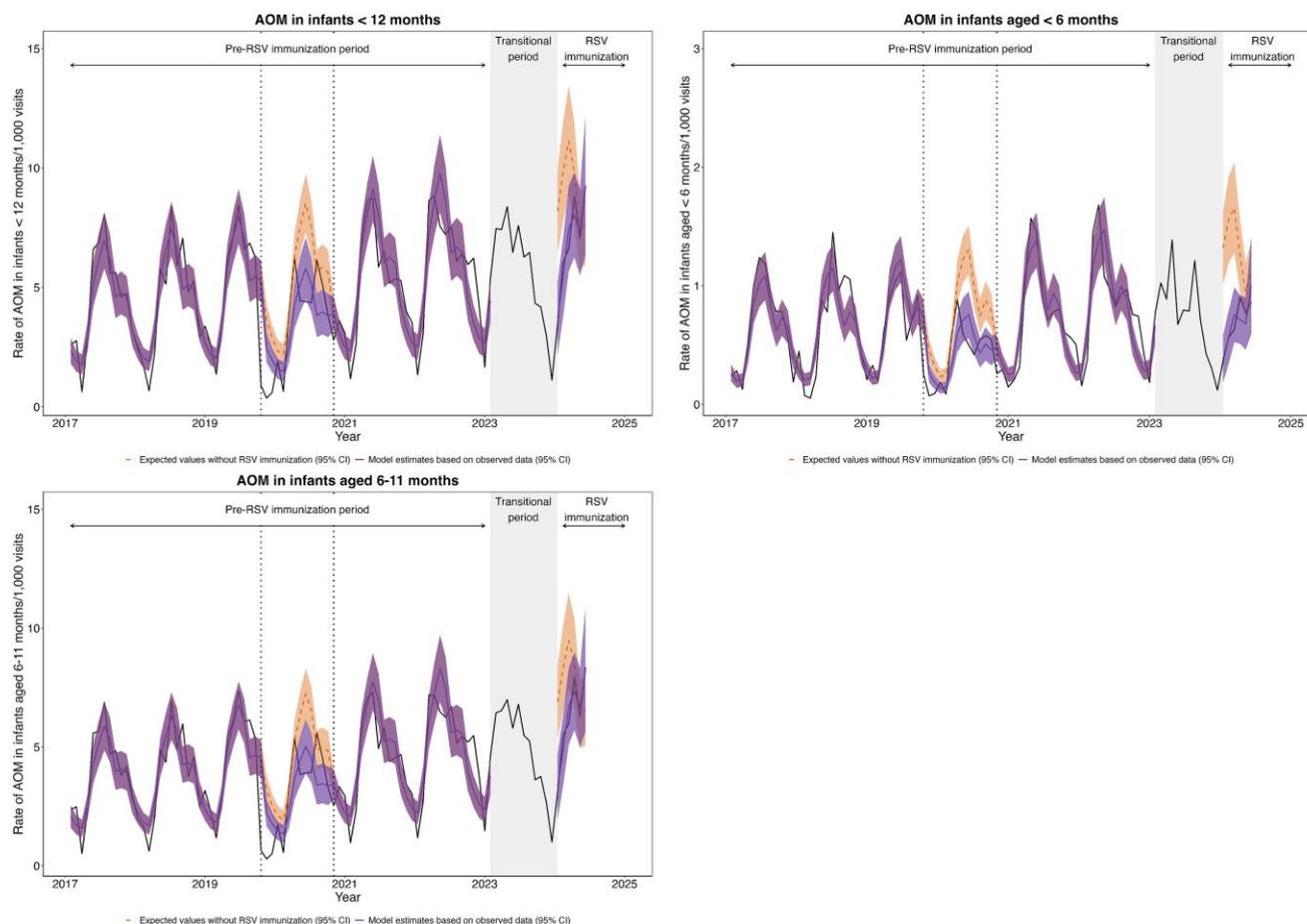
We observed a significant reduction in the rate of AOM in infants aged < 12 months.

This result was reinforced by several sensitivity analyses and the control outcomes analyses. Indeed, the evolution of the rate

of bronchiolitis as a positive control outcome showed similar results, whereas the rate of UTI as a negative control outcome did not significantly decrease over the same period. Interestingly, we did not observe any significant change in the rate of AOM among children aged ≥ 12 months, who were not targeted by RSV immunization. These preliminary findings reinforce the hypothesis of a causal relationship between RSV immunization and the reduction in AOM rates among infants aged < 12 months.

Several hypotheses can be considered to explain this decreased rate of AOM in infants aged < 12 months. The observed decrease may be attributable to a reduced rate of RSV infections, as RSV is a known potential trigger for AOM. However, viral testing is rarely conducted during AOM episodes, making the role of RSV in the pathogenesis of AOM difficult to ascertain [1].

Second, *S. pneumoniae* is one of the main bacterial pathogens involved in AOM, particularly in infants aged < 6 months [22]. RSV being highly suspected to trigger the transition from pneumococcal nasopharyngeal colonization to pneumococcal infection [7], RSV immunization may limit the transition from asymptomatic pneumococcal carriage to AOM through

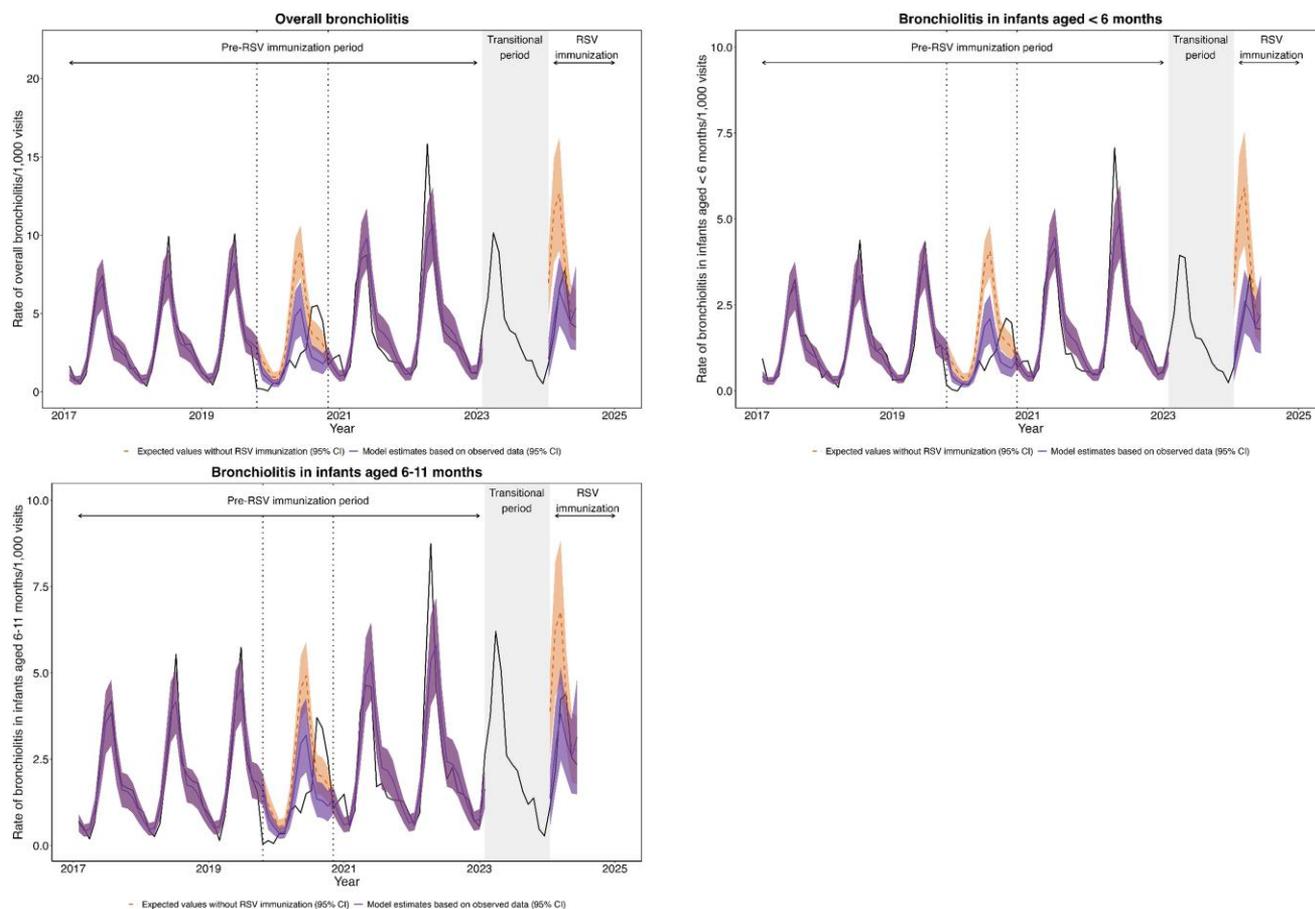


**Figure 1.** Impact of RSV immunization implementation on the monthly rate of AOM from June 2017 to February 2025 in France, in children aged: (A) <12 m ( $N = 17\,923$ ), (B) <6 m ( $N = 2420$ ), (C) 6–11 m ( $N = 15\,503$ ). The rate is expressed as the number of ambulatory visits for AOM per 1000 ambulatory visits per month. The black line shows the observed data. The purple line shows the model estimates based on observed data using the quasi-Poisson regression. The dashed orange line shows the expected values assuming RSV immunization was not implemented using the same quasi-Poisson model. The purple and orange shading indicates the 95% CIs. Vertical black dashed lines indicate the COVID-19 pandemic period. Pre-RSV immunization period: June 2017 to August 2023. Transitional period: September 2023 to September 2024 (data excluded from the analysis, due to the very low immunization coverage in French ambulatory settings during the 2023–24 RSV immunization season). Post-RSV immunization period: October 2024 to February 2025. COVID-19 pandemic period from April 2020 to March 2021 (delimited by vertical black dashed lines); quasi-Poisson regression model accounting for this period, as AOM epidemiology have been influenced by the implementation of nonpharmaceutical interventions. Abbreviations: AOM, acute otitis media; COVID-19, coronavirus disease 2019; RSV, respiratory syncytial virus.

RSV-pneumococcus interactions [23], resulting in a decreased rate of AOM particularly in infants aged < 6 months. However, the impact of RSV immunization on pneumococcal carriage and pneumococcal infections is still unknown and further studies are needed.

Previous studies have suggested that the prevention of early episodes of AOM in infants aged < 6 months, often related to *S. pneumoniae*, could reduce the risk of subsequent recurrent AOM [24], which is often polymicrobial and secondary to non-vaccine pneumococcal serotypes [25, 26]. In this study, we found a strong impact of nirsevimab immunization on early AOM in infants aged < 6 months. These results suggest that RSV immunization with nirsevimab may contribute to reduce the risk of recurrent AOM in older children in the future, in countries implementing nirsevimab.

Several limitations should be discussed. First, the role of RSV in AOM remains challenging to ascertain, as respiratory testing is infrequently performed during AOM episodes [1]. Second, the diagnosis of AOM remains challenging, thereby introducing a potential diagnostic bias. However, the pediatricians within the PARI network are trained in the diagnosis and management of pediatric infectious diseases, making the established diagnoses reliable [11]. Third, given the timing of Abrysvo implementation in 2024–25 in France, we were not able to assess the impact of Abrysvo implementation on AOM. Indeed, Abrysvo implementation started in 15 September 2024 and was administered during the third trimester of pregnancy. Most infants whose mothers had been vaccinated were aged  $\leq 3$  months during the post-RSV immunization period [27] that ended in February 2025 in this study. Given the rare occurrence of AOM in infants



**Figure 2.** Impact of RSV immunization implementation on the monthly rate of bronchiolitis from June 2017 to February 2025 in France, in children aged: (A) <12 m ( $N = 13\,284$ ). (B) <6 m ( $N = 5621$ ). (C) 6–11 m ( $N = 7663$ ). The rate is expressed as the number of ambulatory visits for bronchiolitis per 1000 ambulatory visits per month. The black line shows the observed data. The purple line shows the model estimates based on observed data using the quasi-Poisson regression. The dashed orange line shows the expected values assuming RSV immunization was not implemented using the same quasi-Poisson model. The purple and orange shading indicates the 95% CIs. Vertical black dashed lines indicate the COVID-19 pandemic period. Pre-RSV immunization period: June 2017 to August 2023. Transitional period: September 2023 to September 2024 (data excluded from the analysis, due to the very low immunization coverage in French ambulatory settings during the 2023–24 RSV immunization season). Post-RSV immunization period: October 2024 to February 2025. COVID-19 pandemic period from April 2020 to March 2021 (delimited by vertical black dashed lines): quasi-Poisson regression model accounting for this period, as AOM epidemiology have been influenced by the implementation of nonpharmaceutical interventions. Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; RSV, respiratory syncytial virus.

aged < 3 months, the decreased rate of AOM in infants aged < 12 months may not be attributable to Abrysvo, but rather to nirsevimab implementation. Further studies are required to assess the impact of maternal RSV vaccine in AOM. Fourth, during the 2024–25 campaign in France, the immunization coverage was estimated at 70% among infants born during the nirsevimab immunization campaign, compared with 50% among those born before its initiation. Therefore, the impact of RSV immunization could be further optimized through improved coverage in future seasons. Fifth, as for any observational study relying on temporal associations, a causal relationship between RSV immunization implementation and the evolution of the rate of AOM in ambulatory settings cannot be assumed. The benefit of RSV immunization on the burden of AOM in infants aged < 12 months needs to be confirmed in further studies, including effectiveness studies.

## CONCLUSION

RSV immunization led to a strong reduction of the rate of AOM in infants aged < 12 months.

Beyond its efficacy in preventing RSV-related LRIs in infants aged < 12 months, these preliminary data suggest that RSV immunization may also contribute to reduce the overall burden of AOM.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

**Author Contributions.** I. F., R. C., and N. O. made substantial contributions to the conception or design of the work. I. F.,

R. C., and N. O. drafted the manuscript. All authors were involved in the acquisition, analysis, or interpretation of data. All authors provided critical revision of the manuscript for important intellectual content. Other contributions: We are grateful to the investigators of the PARI study Network: Drs Akou'Ou Marie-Hélène, Auvrignon Anne, Bakhache Pierre, Barrois Sophie, Batard Christophe, Beauflis-Philippe Florence, Bellemin Karine, Berquier Juliette, Bled Jérémie, Boulanger Sophie, Cambier Nappo Eliane, Chartier Albrech Chantal, Cheve Anne, Cornic Muriel, Coudy Caroline, Courtot Hélène, Delavie Nadège, Delobbe Jean-François, Desvignes Véronique, Elbez Annie, Gelbert Nathalie, Gorde-Grosjean, Stéphanie, Goulamhousen Salim, Guiheneuf Cécile, Hassid Frédéric, Hennequin Stéphanie, Jouty Cécile, Kampf Maupu Flaviane, Kherbaoui Louisa, Langlais Sophie, Legras Cécilia, Lemarie Dominique, Lubelski Patricia, Minette Delphine, Moore Wipf Solange, Pruvost Dussart Isabelle, Ravilly Sophie, Salaun Jean-François, Salomez Sophie, Sangenis Marta Inès, Savajols Elodie, Seror Elisa, Starynkevitch Anne, Thollot Franck, Vigreux Jean-Christophe, Werner Andreas, Wollner Alain, and Zouari Morched. N. O. and R. C. take responsibility for the content of the manuscript, including the integrity of the data and the accuracy of the data analysis.

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