Effectiveness of nirsevimab immunisation on invasive pneumococcal disease in children nationwide in France: an observational cohort study

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Summary

Background Invasive pneumococcal diseases (IPDs) remain a leading cause of morbidity and mortality in children worldwide, despite the widespread use of pneumococcal conjugate vaccines. Respiratory syncytial virus (RSV) disease is suspected to be associated with an increased risk of IPD. We assessed whether immunisation with nirsevimab, a monoclonal antibody targeting RSV, reduced the risk of IPD in children.

Methods This population-based, retrospective cohort study used data from the French National Health Data System. All liveborn children in metropolitan France between Feb 6, 2023, and Jan 31, 2024, for whom nirsevimab immunisation status was available, were included. The date of nirsevimab immunisation defined the inclusion date of immunised children and their birth-month-matched non-immunised children. Children immunised with nirsevimab during the first year of life constituted the immunised group, whereas children non-immunised with nirsevimab constituted the non-immunised group. The primary outcome was hospitalisation for IPD within 6 months after inclusion. Propensity score analysis using inverse probability of treatment weighting (IPTW) was conducted to adjust for differences in baseline characteristics between the two groups. Immunisation effectiveness was calculated with the use of the following equation: effectiveness=100% × (1 – odds ratio [OR]), with the OR reflecting the association between nirsevimab and IPD.

Findings Of the 608 641 children born in France during the study period, 527 971 were included, of whom 119 435 (22·6%) received nirsevimab. During the 6-month follow-up period, 112 cases of IPD occurred: 17 (14·2 per 100 000) in the immunised group versus 95 (23·3 per 100 000) in the non-immunised group. After IPTW, nirsevimab was associated with a 36% reduction in the odds of hospitalisation for IPD 6 months after immunisation (OR 0·64, 95% CI 0·46–0·82). 9 months after immunisation, effectiveness remained consistent with a 34% reduction (0·66, 0·51–0·85).

Interpretation Nirsevimab immunisation in children younger than 12 months was associated with a lower risk of IPD for at least 6 months following immunisation. These findings suggest an additional benefit of nirsevimab implementation beyond RSV disease prevention, but further studies are needed to confirm these findings.

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Introduction

Despite the implementation of pneumococcal conjugate vaccines (PCVs) worldwide, *Streptococcus pneumoniae* remains a leading cause of morbidity and mortality, accounting for over 300 000 deaths annually in children younger than 5 years.[1] The near disappearance of vaccine serotypes in nasopharyngeal carriage following PCV implementation led to replacement with non-vaccine serotypes, resulting in a subsequent increase of invasive pneumococcal disease (IPD) due to non-vaccine serotypes in numerous countries.[2,3] This serotype replacement highlights the need for complementary strategies beyond PCVs to further reduce the burden of IPD in children.

Human respiratory syncytial virus (RSV) disease is suspected of facilitating the transition from pneumococcal nasopharyngeal colonisation to IPD. This hypothesis is supported by a range of epidemiological and in-vitro studies.[4–6]

Nirsevimab, a long-acting monoclonal antibody targeting RSV, has shown efficacy in preventing RSV-related lower respiratory infections in children younger than 12 months.[7,8] Nirsevimab was implemented for the first time in France during the 2023–24 RSV season. In this context, we hypothesised that preventing RSV disease through nirsevimab immunisation in children younger than 12 months would lead to a reduced risk of IPD afterwards. The aim of this study was to assess the

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Research in context

Evidence before this study

We searched PubMed for articles published from database inception to April 1, 2026, using the MeSH terms "respiratory syncytial virus infections" or "pneumococcal infections" without language restrictions. Several fundamental studies suggested that respiratory syncytial virus (RSV) disease might facilitate the transition from pneumococcal nasopharyngeal carriage to invasive pneumococcal disease (IPD) by increasing bacterial adhesion, impairing mucociliary clearance, and enhancing local inflammation. Epidemiological studies have suggested a temporal association between RSV circulation and IPD. However, to date, no population-based study has assessed whether preventing RSV disease could reduce the incidence of IPD in children. The recent implementation of nirsevimab, a monoclonal antibody providing passive immunisation against RSV, offers the first opportunity to assess whether RSV immunisation could also reduce the risk of IPD in children.

Added value of this study

This study is the first to assess the association between nirsevimab immunisation and IPD. Using nationwide data from over half a million children in France and a propensity score-weighted approach, we found that immunisation with nirsevimab was associated with a 36% reduction in hospitalisations for IPD within 6 months after immunisation (odds ratio 0·64, 95% CI 0·46–0·82), with consistent findings across sensitivity and subgroup analyses. Similar findings were obtained when extending the follow-up to 9 months after immunisation.

Implications of all the available evidence

Our findings suggest that nirsevimab immunisation has a broader effect in childhood infections, potentially reducing not only RSV disease but also IPD. In the context of the evolving epidemiology of pneumococcal infections due to serotype replacement, RSV immunisation may provide a complementary tool to address the burden of IPD in children. Further studies with longer surveillance in the context of higher-valency pneumococcal conjugate vaccines are needed to confirm these findings.

effectiveness of nirsevimab immunisation in preventing IPD in children.

Methods

Study design and participants

We conducted a national retrospective population-based cohort study using propensity score-based inverse probability weighting to estimate nirsevimabh effectiveness in preventing IPD via logistic regression. During the 2023–24 RSV season, French guidelines recommended administration of a single dose of nirsevimab to all children born in France between Feb 6, 2023, and Jan 31, 2024.[9] The nirsevimab immunisation campaign was conducted in metropolitan France between Sept 15, 2023, and Jan 31, 2024, and was defined as the dispensing of nirsevimab either in maternity units or in outpatient settings. A single intramuscular dose of 50 mg was recommended for children weighing less than 5 kg, and 100 mg for those weighing at least 5 kg.

All children born in metropolitan France between Feb 6, 2023, and Jan 31, 2024, affiliated with the French national health insurance system, with available information regarding nirsevimab immunisation, were included in the study. As some maternity units did not report data on nirsevimab immunisation, children born during the nirsevimab campaign in those maternity units and who had not received immunisation in ambulatory settings were not included. Exclusion criteria were as follows: (1) same-sex twins, who could not be individually identified in the database, (2) children immunised with palivizumab, (3) children who died before the inclusion date, (4) children hospitalised for IPD before the inclusion date, and (5) children who died during follow-up before an IPD had occurred. Children immunised with nirsevimab during their first year of life within the 2023–24 nirsevimab immunisation campaign constituted the immunised group, whereas children non-immunised with nirsevimab constituted the non-immunised group.

The reporting of this study followed the RECORD guidelines (appendix 2 p 45). Our research group has permanent regulatory access to data from the French National Health Data System (SNDS) under French Decree number 2016–1871 of Dec 26, 2016, governing the processing of personal data in the SNDS, and under articles R.1461–1 and R.1461–14 of the French public health code. This study was registered on the Health Data Hub (reference 22277495) as part of an ongoing mission of public health using pseudonymised data for public health purposes; therefore, ethical committee approval and written informed consent were not required.

Data source

This study used data from the SNDS, an exhaustive French claims database that includes individuals affiliated with the national health insurance system, covering approximately 99% of the French population. For each individual, the SNDS contains pseudonymised information on sociodemographic characteristics, reimbursement data for outpatient visits, and inpatient data from both public and private hospitals in France, including medical diagnoses and procedures.[10] These

data are recorded uniformly in the SNDS regardless of the health-care provider or location. Except for the maternity units that did not report nirsevimab dispensation data at birth, each nirsevimab dispensed, whether in maternity units or in outpatient settings, generates a reimbursement claim within the national health insurance system. This process ensures exhaustive capture of nirsevimab dispensations for all children included in the main analysis. Loss to follow-up was identified when children no longer interacted with the French health-care system.

For each child included in the study, we extracted data regarding sociodemographic and perinatal characteristics, comorbidities, pneumococcal vaccination and nirsevimab immunisation status, and clinical outcomes that were identified through ICD-10 codes. PCV in children has been mandatory in France since 2018. Until June, 2024, 13-valent PCV (PCV13) was the sole PCV recommended for both primary and booster immunisation in children in France, using a 2+1 schedule (injection at 2 months, 4 months, and 11 months). In June, 2024, 15-valent PCV (PCV15) was introduced into the national immunisation programme using the same schedule.

Data were extracted in the SNDS system, hosted by the national government, using SAS version 9.4 and managed with R version 4.0.2. Quality control was done by the investigators (ZV, NO, RB, FK, and IF) using guidelines specified by the SNDS.

Microbiology

Isolates from IPD were routinely serotyped at the French National Reference Centre for Pneumococci (NRCP), which receives strains from children younger than 15 years as part of the French national surveillance programme of pneumococcal infections. Only the NRCP performs serotyping at the national level, using latex agglutination with antisera provided by Statens Serum Institute (Copenhagen, Denmark).[2,11] Serotyping data in the NRCP could be related to IPD cases in the SNDS using individual participant data.

Outcomes

The primary outcome was hospitalisation for IPD among immunised children versus non-immunised children within 6 months following inclusion in the study. IPDs were identified through the following discharge diagnoses: pneumococcal meningitis, pneumococcal bacteraemia, bacteraemic pneumococcal pneumonia, pneumococcal pneumonia with pleural effusion, pneumococcal osteoarticular infection, pneumococcal intra-cranial abscesses, or pneumococcal mastoiditis (ICD-10 codes G001, A403, J13, M001, or B953 combined with one of the following: G00, G01, G06, A40, A41, I330, J13, J15, J17, J18, J90, J91, J840, M86, M01, M13, M462, and H700). Codes for specific diagnoses are provided in appendix 2 (pp 3–4).

Secondary outcomes were hospitalisation for IPD among immunised versus non-immunised children within 9 months following inclusion; hospitalisation for IPD in immunised versus non-immunised children within 6 months following inclusion according to prematurity (birth <37 *vs* ≥37 weeks of gestation); and hospitalisation for IPD among immunised versus non-immunised children within 6 months following inclusion according to birthweight (<2500 g *vs* ≥2500 g).

Statistical analysis

A total sample size of 510 696 children (immunised and non-immunised) were required to detect a 30% reduction in the odds of IPD among children immunised with nirsevimab, assuming an expected incidence of 20 IPD cases per 100 000 non-immunised children,[2] with 80% power and an alpha risk value of 0·05.

Immunised children entered the cohort on the date of nirsevimab immunisation, which defined their inclusion date.[12–14] On each day of recruitment during the nirsevimab immunisation campaign, for each newly immunised child, we randomly selected one or more non-immunised children matched with the immunised child on birth month. Finally, to define the immunised-to-non-immunised ratio (ie, the number of non-immunised children to match with immunised

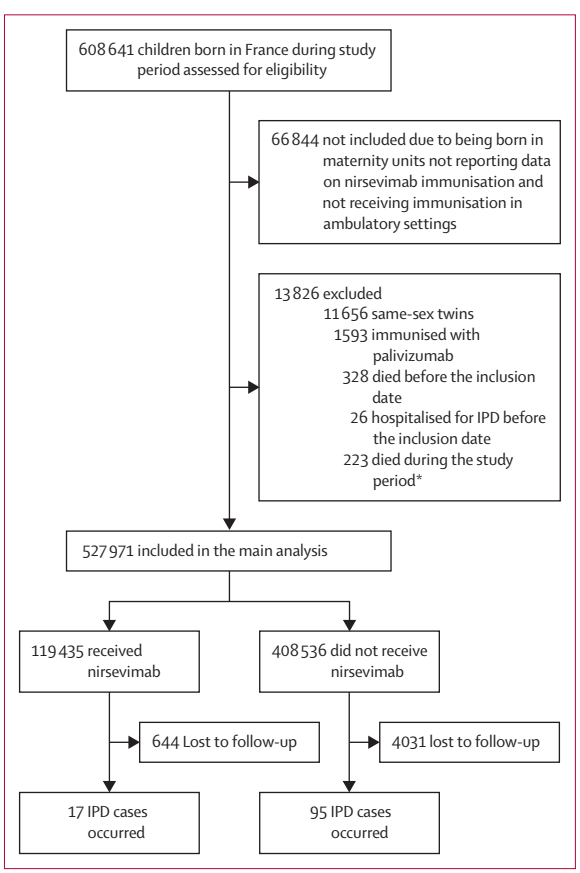


Figure 1: **Study population**
IPD=invasive pneumococcal disease. *Children who died during follow-up before an IPD had occurred.

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See **Online** for appendix 2

children), we applied the immunisation coverage rate corresponding to the birth month of each pair, taking temporal variation into account. By varying the immunised-to-non-immunised ratio, we could optimise the overall number of children included in the main analysis, thereby preventing bias due to the exclusion of unmatched non-immunised children.[15] Furthermore, matching immunised and non-immunised children on birth month allowed us to avoid imbalance in the inclusion date distribution and follow-up timeline between the two groups,[12–14] as recommended to account for survival bias.[12] Finally, defining the inclusion date for non-immunised children in the cohort according to birth month allowed us to account for both age-related and seasonal variation in the risks of RSV infections and IPD,[16] along with the varying probability of nirsevimab immunisation over time.[17]

	Immunised with nirsevimab (n=119 435)	Not immunised with nirsevimab (n=408 536)	SMD before IPTW	SMD after IPTW
Age at inclusion	..	..	−0·6967	0·0975
Median (IQR), months	0 (0–3)	4 (0–6)	..	..
<3 months	85 101 (71·3%)	165 524 (40·5%)	..	..
≥3 months	34 334 (28·7%)	243 012 (59·5%)	..	..
Sex	..	..	−0·0340	0·0003
Male	61 699 (51·7%)	207 767 (50·9%)	..	..
Female	57 736 (48·3%)	200 769 (49·1%)	..	..
Region of birth	..	..	..	..
Île-de-France	24 682 (20·7%)	96 462 (23·6%)	−0·0295	−0·0001
Auvergne-Rhône-Alpes	14 463 (12·1%)	50 919 (12·5%)	0·0052	−0·0001
Hauts-de-France	14 108 (11·8%)	39 347 (9·6%)	−0·0044	−0·0032
Provence-Alpes-Côte d'Azur	9243 (7·7%)	33 723 (8·3%)	0·0097	−0·0002
Occitanie	8790 (7·4%)	32 564 (8·0%)	0·0218	−0·0015
Nouvelle-Aquitaine	9556 (8·0%)	30 856 (7·6%)	0·0007	0·0040
Grand Est	8907 (7·5%)	30 188 (7·4%)	−0·0111	0·0042
Pays de la Loire	5683 (4·8%)	23 954 (5·9%)	0·0186	−0·0034
Bretagne	7841 (6·6%)	19 207 (4·7%)	0·0045	0·0025
Normandie	6910 (5·8%)	19 673 (4·8%)	−0·0061	−0·0034
Bourgogne-Franche-Comté	3990 (3·3%)	15 447 (3·8%)	−0·0035	0·0019
Centre-Val de Loire	4810 (4·0%)	14 334 (3·5%)	−0·0052	0·0008
Corse	452 (0·4%)	1862 (0·5%)	−0·0008	−0·0014
Gestational age at birth, weeks	..	..	−0·0411	−0·0120
≤32	1215 (1·0%)	2898 (0·7%)	..	..
>32 and <37	6358 (5·3%)	17 329 (4·2%)	..	..
≥37	111 862 (93·7%)	388 309 (95·0%)	..	..
Birthweight, g	..	..	−0·0340	−0·0090
Median (IQR)	3300 (2980–3610)	3300 (3000–3610)	..	..
<2500 g	8140 (6·8%)	22 836 (5·6%)	..	..
≥2500 g	111 295 (93·2%)	385 700 (94·4%)	..	..
French Social Deprivation Index*	..	..	..	..
Quintile 1	37 535 (31·4%)	116 583 (28·5%)	0·0289	0·0282
Quintile 2	22 107 (18·5%)	73 833 (18·1%)	0·0044	0·0034
Quintile 3	20 563 (17·2%)	69 848 (17·1%)	0·0012	−0·0033
Quintile 4	18 322 (15·3%)	65 576 (16·1%)	−0·0071	−0·0107
Quintile 5	20 908 (17·5%)	82 690 (20·2%)	−0·0274	−0·0175
Data missing	0	6 (0·0%)	..	..

(Table 1 continues on next page)

The primary analysis relied on a propensity score analysis using the inverse probability of treatment weighting (IPTW) method.[18] First, we estimated the probability of receiving nirsevimab for each child using a logistic regression model that included baseline covariates (sociodemographic and clinical data). These probabilities served as propensity scores. To adjust for baseline covariate imbalances between the immunised and non-immunised groups, we created a pseudo-randomised population by attributing a stabilised weight to each child derived from the inverse probability of receiving nirsevimab based on the estimated propensity scores. Weights were stabilised by multiplying the inverse probability weights by the marginal probability of the exposure (being immunised *vs* not immunised). All covariates were defined at baseline (ie, at the date of inclusion in the cohort). These covariates, selected a priori based on the existing literature and their potential to influence the likelihood of receiving nirsevimab or the risk of IPD,[8,11,17,19,20] included: age at inclusion, sex, month of birth, region of birth, gestational age at birth in weeks of gestation, birthweight (grams), the French Social Deprivation Index that is a marker of the socioeconomic level of the household, bronchopulmonary dysplasia, neonatal respiratory distress, cystic fibrosis, lung surgery, congenital heart defects and diseases, congenital anomalies of the upper aerodigestive tract, nervous system anomalies, other congenital malformations, genetic disorders, bleeding disorders, congenital immunodeficiencies, perinatal exposure to HIV, sickle cell disease, functional asplenia or splenectomy, osteo-meningeal breach, cochlear implant recipients, and diabetes. Month of birth and region of birth were included as covariates in the propensity score, based on previously published studies showing their influence on IPD epidemiology.[4,16,21] Month of birth was included despite immunised and non-immunised children being matched on birth month because varying the immunised-to-non-immunised ratio meant that some birth months were over-represented in the control group (resulting in the control group appearing older than the immunised group). Detailed definitions of each covariate included in the propensity score are provided in appendix 2 (p 5). Covariates were considered well balanced between the two groups if the absolute standardised mean difference after IPTW was more than −0·1 and less than 0·1.[18]

In all analyses, the effectiveness of nirsevimab against hospitalisation for IPD was estimated by computing the marginal average treatment effect by use of a logistic regression model on the pseudo-randomised population. Due to an expected low rate of missing data, complete case analysis was performed. For all models, immunisation

effectiveness was calculated with the use of the following equation: effectiveness=100%×(1−odds ratio [OR]), with the OR reflecting the association between nirsevimab and IPD.

To assess the robustness of our findings, several sensitivity analyses were performed. First, we performed two sensitivity analyses based on alternative definitions of the outcome: a more restrictive definition of IPD (without unspecified pneumococcal diseases) and exclusion of IPD cases identified as associated diagnoses. Second, we performed two sensitivity analyses based on time-dependent analyses: death was analysed as a competing event (instead of excluding children who died before IPD was documented) and pneumococcal vaccination was modelled as a time-dependent confounder. Third, we performed four sensitivity analyses based on alternative definitions of covariates in the propensity score: history of previous severe infection included in the propensity score; other acquired immunodeficiencies included in the propensity score; model with age considered as a categorical covariate instead of continuous; and age modelled using restricted cubic splines in the propensity score model. Fourth, we performed four sensitivity analyses based on changes in inclusion, exclusion, or exposure definitions: assignment of inclusion dates to non-immunised children regardless of month of birth; previous nirsevimab receipt considered with a 7-day delay; exclusion of children immunised in ambulatory settings and born in maternity units that did not report nirsevimab dispensation data; and exclusion of children with incomplete follow-up.

Fifth, we performed seven sensitivity analyses with modelling variants of the propensity score framework: 1:2 matching between immunised and non-immunised children (based on age, sex, and region of birth); double-robust adjustment on region of birth and age;[22] mixed-effects regression model with a random intercept for region;[23] estimation of the average treatment effect in the treated population;[24] propensity score matching approach as an alternative method to IPTW;[18,24] overlap-weighting approach;[14,25] and trimming at the 5th percentile for immunised children and the 95th percentile for non-immunised children, with extreme stabilised weights.[26] Detailed definitions of and rationale for each sensitivity analysis are provided in appendix 2 (p 13).

To explore a potential unmeasured confounding bias, we performed a post-hoc analysis considering invasive group B streptococcal disease as a negative control outcome, following the same statistical approach as the main analysis. Statistical analyses were performed with SAS version 9.4 and R version 4.0.2.

Role of the funding source

The funders of the study had no role in data collection, data analysis, data interpretation, or writing of the manuscript.

	Immunised with nirsevimab (n=119 435)	Not immunised with nirsevimab (n=408 536)	SMD before IPTW	SMD after IPTW
(Continued from previous page)				
Bronchopulmonary dysplasia	392 (0·3%)	812 (0·2%)	0·001	0·0002
Neonatal respiratory distress	9396 (7·9%)	25 966 (6·4%)	0·0151	0·0020
Cystic fibrosis	54 (0·0%)	77 (0·0%)	0·0003	0·0000
Lung surgery	62 (0·1%)	82 (0·0%)	0·0004	0·0000
Congenital heart defects and diseases	1406 (1·2%)	3303 (0·8%)	0·0040	0·0013
Congenital anomalies of the upper aerodigestive tract	100 (0·1%)	189 (0·0%)	0·0004	0·0001
Nervous system anomalies	483 (0·4%)	1274 (0·3%)	0·0009	0·0004
Other congenital malformations	2300 (1·9%)	6921 (1·7%)	0·0023	0·0010
Genetic disorders	136 (0·1%)	380 (0·1%)	0·0002	0·0001
Bleeding disorders	275 (0·2%)	815 (0·2%)	0·0003	0·0004
Congenital immunodeficiencies	58 (0·0%)	139 (0·0%)	0·0001	0·0000
Perinatal exposure to HIV	78 (0·1%)	386 (0·1%)	–0·0003	0·0000
Sickle cell disease	69 (0·1%)	232 (0·1%)	0·0000	0·0000
Functional asplenia or splenectomy	17 (0·0%)	38 (0·0%)	0·0000	0·0000
Osteo-meningeal breach	1234 (1·0%)	4323 (1·1%)	–0·0002	0·0007
Cochlear implant recipient	23 (0·0%)	74 (0·0%)	0·0000	0·0000
Diabetes	52 (0·0%)	159 (0·0%)	0·0000	..

Data are n (%), unless otherwise specified. All covariates were defined at baseline (ie, at the date of inclusion in the cohort), except for pneumococcal vaccination status that also covered the follow-up period. Covariates included in the propensity score were continuous (age at inclusion, in months), categorical (sex, region of birth, gestational age at birth, birthweight, and French Social Deprivation Index), or dichotomous (bronchopulmonary dysplasia, neonatal respiratory distress, cystic fibrosis, lung surgery, congenital heart defects and diseases, congenital anomalies of the upper aerodigestive tract, nervous system anomalies, other congenital malformations, genetic disorders, bleeding disorders, congenital immunodeficiencies, perinatal exposure to HIV, sickle cell disease, functional asplenia or splenectomy, osteo-meningeal breach, cochlear implant recipient, diabetes, and pneumococcal vaccination uptake). SMD=standardised mean difference. IPTW=inverse probability of treatment weighting. *French Social Deprivation Index is a marker of socioeconomic level based on the residence area's median household income, percentage of high school graduates in the population aged 15 years or older, percentage of manual workers in the labour force, and level of unemployment; it is categorised into quintiles, with Q1 representing the least deprived (ie, the highest socioeconomic level) and Q5 representing the most deprived (ie, the lowest socioeconomic level).

Table 1: **Baseline characteristics of included children**

Results

Among the 608 641 children born in metropolitan France between Feb 6, 2023, and Jan 31, 2024, who were eligible for inclusion, 527 971 children representing 89% of the target population were included in the main analysis, of whom 119 435 (22·6%) received nirsevimab and 408 536 (77·4%) did not receive nirsevimab (figure 1). Children born in non-reporting facilities but immunised with nirsevimab in ambulatory settings represented 505 (0·4%) of 119 435 children in the immunised group. Baseline characteristics are presented in table 1. Details regarding PCVs administered in this cohort are provided in appendix 2 (p 19). After applying IPTW, all baseline covariates used to generate the propensity score were well balanced between groups, with a standardised mean difference of less than 0·1 (table 1; appendix 2 p 20). After IPTW, median age at inclusion was 3 months (IQR 0–3 in the immunised group and 0–6 in the non-immunised group) and the sex ratio of male to female was 1·04 in

	Immunised with nirsevimab*	Not immunised with nirsevimab*	Adjusted OR (95% CI)
Hospitalisation for IPD within 6 months of inclusion (primary analysis)	17/119 435 (14·2/100 000)	95/408 536 (23·3/100 000)	0·64 (0·46–0·82)
Sensitivity analyses			
Alternative, more restrictive definition of IPD (without unspecified pneumococcal diseases)	17/119 435 (14·2/100 000)	81/408 536 (19·8/100 000)	0·61 (0·45–0·83)
Attribution of inclusion dates for non-immunised children regardless of birth month	17/119 435 (14·2/100 000)	91/408 522 (22·3/100 000)	0·66 (0·50–0·88)
Previous severe infections included in the propensity score	17/119 435 (14·2/100 000)	95/408 536 (23·3/100 000)	0·60 (0·45–0·80)
Other acquired immunodeficiencies included in the propensity score	17/119 435 (14·2/100 000)	95/408 536 (23·3/100 000)	0·61 (0·46–0·82)
Nirsevimab receipt considered with a 7-day delay	17/119 435 (14·2/100 000)	91/408 526 (22·3/100 000)	0·65 (0·49–0·86)
Age categorised as <3 months or ≥3 months	17/119 435 (14·2/100 000)	95/408 536 (23·3/100 000)	0·59 (0·44–0·79)
Non-linear age term (splines with 3 knots)	17/119 435 (14·2/100 000)	95/408 536 (23·3/100 000)	0·67 (0·51–0·89)
Excluding of children with incomplete follow-up	17/118 791 (14·3/100 000)	95/404 474 (23·5/100 000)	0·60 (0·45–0·81)
Cox model with death as a competing event	17/118 791 (14·3/100 000)	95/404 474 (23·5/100 000)	0·65 (0·49–0·86)
Cox model with pneumococcal vaccination as a time-dependent variable	17/118 791 (14·3/100 000)	95/404 474 (23·5/100 000)	0·62 (0·47–0·82)
Excluding children immunised in ambulatory settings but born in excluded maternity units†	17/118 930 (14·2/100 000)	95/408 536 (23·3/100 000)	0·62 (0·47–0·83)
Excluding IPDs in associated diagnosis only	13/119 431 (10·9/100 000)	69/408 504 (16·9/100 000)	0·72 (0·52–0·99)
Secondary analyses			
Hospitalisation for IPD within 9 months of inclusion	23/119 425 (19·3/100 000)	113/408 501 (27·7/100 000)	0·66 (0·51–0·85)
Weight groups			
Birthweight <2500 g	2/8140 (24·6/100 000)	15/22 836 (65·7/100 000)	0·29 (0·11–0·74)
Birthweight ≥2500 g	15/111 295 (13·5/100 000)	80/385 700 (20·7/100 000)	0·66 (0·51–0·90)
Gestational age, weeks			
<37 (preterm birth)	2/7573 (26·4/100 000)	10/20 227 (49·4/100 000)	0·39 (0·14–1·06)
≥37 (term birth)	15/111 862 (13·4/100 000)	85/388 309 (21·9/100 000)	0·65 (0·48–0·87)

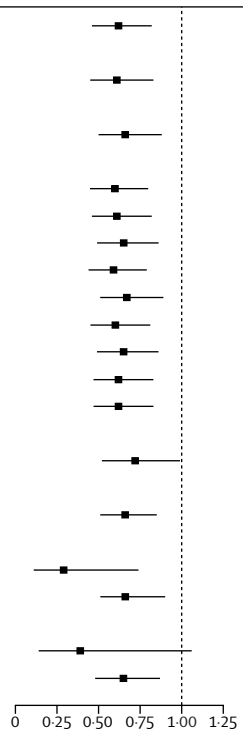


Figure 2: **Effectiveness of nirsevimab against hospitalisation for IPD**
On the graph, circles indicate point estimates and horizontal lines indicate 95% CIs. The primary analysis involved a propensity score using the inverse probability of treatment weighting method. All analyses were performed using a logistic regression model, except for the sensitivity analysis with a random intercept for the region (mixed-effects logistic regression model). All analyses excluded six patients, for whom the French Social Deprivation Index was missing. Detailed definitions of sensitivity analyses are provided in appendix 2 (p 13). IPD=invasive pneumococcal disease. OR=odds ratio. *Crude incidence. †Maternity units that did not report nirsevimab dispensation data at birth.

	Incidence rate of invasive pneumococcal disease, number of cases per 100 000 (95% CI)	Odds ratio (95% CI)*
Crude data		
Immunised with nirsevimab	14·2	..
Non-immunised with nirsevimab	23·3	..
Primary analysis		
Immunised with nirsevimab	14·7	0·64 (0·46–0·82)
Non-immunised with nirsevimab	23·1	1 (ref)

The primary analysis involved a propensity score using the inverse probability of treatment weighting method. The primary outcome was the occurrence of an invasive pneumococcal disease among children who were immunised versus not immunised within 6 months following inclusion. All analyses were done with a logistic regression model, except for the sensitivity analysis with a random intercept for the region (mixed-effects logistic regression model). The analyses excluded six patients, for whom the French Social Deprivation Index was missing.

Table 2: **Invasive pneumococcal disease among children who were immunised with nirsevimab versus not immunised (crude and adjusted data)**

both groups. The proportion of preterm births after IPTW was 6·0% in the immunised group and 5·2% in the non-immunised group. Characteristics of excluded children are provided in appendix 2 (p 16). Details regarding deaths, loss to follow-up, and inclusion dates among immunised versus non-immunised children are provided in appendix 2 (pp 17–18, 21–22).

During the 6-month follow-up period, 112 cases of IPD occurred: 17 (14·2 cases per 100 000) in the immunised group versus 95 (23·3 cases per 100 000) in the non-immunised group (figure 2; appendix 2 p 24). 6 months after immunisation, the primary analysis based on IPTW found that nirsevimab was associated with a 36% reduction in the odds of hospitalisations for IPD (OR 0·64, 95% CI 0·46–0·82; figure 2, table 2). Results from all sensitivity analyses yielded effectiveness estimates consistent with the main analysis (figure 2; appendix 2 p 38). The negative control outcome analysis found no association between nirsevimab immunisation and invasive group B streptococcal disease (appendix 2 p 40).

Extending the follow-up period to 9 months after inclusion in the cohort, 136 cases of IPD occurred: 23 (19·3 cases per 100 000) in the immunised group and 113 (27·7 cases per 100 000) in the non-immunised group. 9 months after immunisation, nirsevimab was associated

with a 34% reduction in the risk of hospitalisation for IPD (OR 0·66, 95% CI 0·51–0·85; figure 2). In subgroup analyses of the primary endpoint by gestational age at birth and birthweight, nirsevimab effectiveness appeared similar (figure 2); however, due to low number of observations, subgroup analyses should be considered as exploratory and interpreted with caution.

Among 112 cases of IPD up to 6 months, 20 (18%) were meningitis, 11 (10%) were bacteraemia without source, 72 (64%) were bacteraemic pneumococcal pneumonia or pneumococcal pneumonia with pleural effusion, and nine (8%) were other infections. Regarding disease severity, 36 (32%) cases required admission to the intensive care unit, and 47 (42%) cases required ventilatory support. Death occurred in six (5%) cases, all in the non-immunised group (table 3).

Pneumococcal serotypes were available for 41 (37%) of 112 IPD cases. Four (10%) cases were caused by PCV13 serotypes, six (15%) cases by serotypes in PCV15 not included in PCV13, 13 (32%) cases by serotypes in 20-valent PCV (PCV20) not included in PCV15, and 18 (44%) cases by non-PCV20 serotypes. Serotypes 24F (nine [22%] of 41 cases) and 15B/C (six [15%] of 41 cases) were the main non-PCV13 serotypes involved. Serotype distribution appeared similar in immunised versus non-immunised groups. A single pneumococcal vaccine breakthrough was identified. We found no cases of pneumococcal vaccine failure (table 3).

Discussion

In this real-world cohort study, nirsevimab immunisation in children younger than 12 months was associated with a 36% reduction in the risk of hospitalisation for IPD (OR 0·64, 95% CI 0·46–0·82) at 6 months after immunisation. This association remained at 9 months of follow-up and was supported by concordant sensitivity and secondary analyses.

These findings should be put into perspective with a growing body of evidence suggesting interactions between RSV and *S pneumoniae*. Indeed, RSV is suspected of increasing pneumococcal adhesion to the respiratory epithelium, altering the local immune response, and impairing ciliary function, leading to reduced bacterial clearance and thereby enabling pneumococcal

	Immunised with nirsevimab (n=17)	Not immunised with nirsevimab (n=95)
Age, months	4 (3–7)	6 (4–9)
Sex		
Male	13 (76%)	58 (61%)
Female	4 (24%)	37 (39%)
IPD by clinical entity		
Meningitis	5 (29%)	15 (16%)
Bacteraemia without source	1 (6%)	10 (11%)
Bacteraemic pneumonia or pneumonia with pleural effusion	10 (59%)	62 (65%)
Other*	1 (6%)	8 (8%)
Underlying conditions†	3 (18%)	13 (14%)
Pneumococcal serotypes‡		
PCV13 serotypes	2 (20%)	2 (6%)
Serotype 3	2	0
Serotype 19F	0	2
PCV15–non-PCV13 serotypes	1 (10%)	5 (16%)
Serotype 22F	1	0
Serotype 33F	0	5
PCV20–non-PCV15 serotypes	3 (30%)	10 (33%)
Serotype 8	2	1
Serotype 15B/C	1	5
Serotype 10A	0	4
Non-PCV20 serotypes	4 (40%)	14 (45%)
Serotype 24F	3	6
Serotype 35F	0	2
Serotype 29	0	2
Other§	1	4
(Table 3 continues in next column)		
(Continued from previous column)		
Pneumococcal vaccine failure¶	0 (0%)	0 (0%)
Pneumococcal vaccine breakthrough¶	0 (0%)	1 (3%)
Paediatric intensive care unit	7 (41%)	29 (31%)
Ventilatory support‖	8 (47%)	39 (41%)
Death	0 (0%)	6 (6%)

Data are median (IQR), n (%), or n. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine. *Other IPD included osteoarticular infections and mastoiditis. †Underlying conditions were defined as at least one of the following diagnoses: congenital immunodeficiencies, perinatal exposure to HIV, sickle cell disease, functional asplenia or splenectomy, osteo-meningeal breach, cochlear implant recipient, other causes of acquired immunodeficiency (including immunosuppressive treatment, organ transplantation, chronic renal failure, or nephrotic syndrome), congenital heart defects and diseases, or diabetes. ‡Serotyping data were available for ten isolates in the immunised group and 31 isolates in the non-immunised group; PCV13 serotypes include 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F; PCV15–non-PCV13 serotypes were 22F and 33F; PCV20–non-PCV15 serotypes were 8, 10A, 11A, 12F, and 15B; all remaining pneumococcal serotypes were classified as non-PCV20 serotypes. §Other serotypes included serotypes 21, 23A, 31, and a serotype that cannot be named. ¶Pneumococcal vaccine failure was defined as a case of IPD caused by a pneumococcal serotype included in PCV13, occurring in a child who had completed their full vaccination schedule; a pneumococcal vaccine breakthrough was defined as a case of IPD caused by a pneumococcal serotype included in PCV13, occurring in a child age-appropriately vaccinated with PCV13 but with an incomplete vaccination schedule prior to IPD, according to the national vaccination schedule; a 2-week interval between vaccine administration and the occurrence of an IPD was required to consider a vaccine failure or a breakthrough. ‖Ventilatory support included both invasive and non-invasive ventilatory support.

Table 3: **Characteristics of IPD cases up to 6 months according to nirsevimab immunisation status**

overgrowth.[27–29] Additionally, mucosal inflammation might facilitate the transition from pneumococcal colonisation to invasive disease.[27] These hypotheses are supported by epidemiological studies, suggesting that RSV infections and IPD follow strikingly similar seasonal patterns.[4] An interaction between RSV and *S pneumoniae* was further supported by diseases following similar epidemiological dynamics during the COVID-19 pandemic.[6] Our study adds new quasi-experimental evidence in support of a key role for RSV in inducing IPD. Our findings indicate that RSV prevention through nirsevimab immunisation could contribute to alleviating the burden of IPD in young children. Further studies are needed to assess whether similar associations are observed with different prevention modalities (eg, maternal immunisation).

Previous studies have suggested that RSV might be more frequently associated with pneumococcal pneumonia than non-pneumonia IPD,[30] and that some pneumococcal serotypes might have a stronger association with RSV.[31] These observations suggest that the effectiveness of nirsevimab against IPD could vary by clinical entity or pneumococcal serotype. In our study, we were not able to identify substantial differences in the distribution of IPD by clinical entity or serotype across groups, but interpretation was limited by the small number of events and availability of serotyping data. Non-PCV13 serotypes were predominant in both groups, serotypes 24F and 15B/C being the main serotypes involved, aligning with previously observed trends among children younger than 2 years in France.[2] Further studies with larger numbers of IPD cases will help investigate whether nirsevimab effectiveness might differ by clinical entity or pneumococcal serotype.

Several limitations should be discussed. First, IPD cases were identified using ICD-10 codes recorded as either the primary or an associated diagnosis. While this approach ensures comprehensive capture of IPD cases, it might introduce some misclassification. However, the results remained consistent in a sensitivity analysis using a more restricted definition of IPD, excluding those defined by the association of ICD-10 code B953 (*S pneumoniae*) combined with invasive disease, which might be more subject to misclassification, and in a sensitivity analysis excluding IPD cases identified as associated diagnoses. Additionally, the incidence rates of IPD observed in our cohort, as well as the proportion of IPD cases requiring admission to the intensive care unit, align with recent data.[2,32] Additionally, pneumococcal serotyping was available for 41 (**37%**) of the 112 IPD cases identified, an expected proportion, consistent with data previously reported in France.[2,33] Of note, based on the available ICD-10 codes, it was not possible to distinguish pneumococcal meningitis cases identified by PCR from those confirmed by culture. However, PCR testing for *S pneumoniae* in cerebrospinal fluid is well validated and has high sensitivity and specificity.

Second, nirsevimab shortages experienced during the first national immunisation campaign might have led to differential uptake of nirsevimab depending on the date and region of birth, which might have introduced bias. To address this, we included region and month of birth as covariates in the propensity score model, and inclusion dates in the non-immunised group were based on birth month. Moreover, double-robust adjustment including region and month of birth, as well as the matching of non-immunised children with immunised children according to age, sex, and region of birth, provided similar results in sensitivity analyses. Third, the main analysis allowed a varying immunised-to-non-immunised ratio, to optimise the number of children included in the analysis. As residual bias related to differential weighting of participants could not be excluded, a sensitivity analysis using matching with a fixed 1:2 ratio between immunised and non-immunised children was conducted and provided similar results. Fourth, subgroup analyses based on age groups, clinical entity, disease severity or pneumococcal serotype were small and should be interpreted with caution. In addition, maternal RSV immunisation has shown efficacy in preventing RSV-related lower respiratory infections in children.[34] As maternal RSV vaccination was not implemented in France during the study period, we could not assess its effectiveness against IPD in children. Fifth, follow-up after inclusion in the cohort was limited to 9 months. Longer-term surveillance in older children is needed to determine how long nirsevimab effectiveness against IPD is maintained. Sixth, the effectiveness of nirsevimab was estimated in a context where almost all children had received PCV13 with a national coverage of more than 90%. Although pneumococcal vaccination coverage was slightly higher in the immunised group, sensitivity analyses modelling pneumococcal vaccination as a time-dependent variable yielded similar results, suggesting that this minor imbalance is unlikely to have influenced our findings. The recent introduction of PCV15 and PCV20, covering additional serotypes, might modify IPD epidemiology. Therefore, further studies are needed to assess nirsevimab effectiveness in the context of this evolving pneumococcal vaccine landscape. Seventh, children who were lost to follow-up were considered free of disease in the main analysis, which might have introduced bias. To explore this, we conducted a sensitivity analysis excluding children with incomplete follow-up (0·9% of the whole cohort), which provided similar results to the main analysis.

In conclusion, this real-world cohort study indicated that nirsevimab immunisation in children younger than 12 months of age was associated with a lower risk of IPD for at least 9 months following immunisation. Nirsevimab might help reduce the burden of IPD in children beyond PCVs. Further studies with longer surveillance in the context of higher-valency PCVs are needed to confirm these findings.

Contributors

IF, ZV, FK, RB, and NO made substantial contributions to the conception or design of the work. IF, RB, and NO drafted the manuscript. IF, ZV, FK, and NO had access to the data in the study and directly accessed and verified the data. All authors provided critical revision of the manuscript for important intellectual content. NO, RB, FK, IF, and ZV were responsible for the decision to submit the manuscript for publication.

Declaration of interests

NO reports travel grants from GSK, Pfizer, and Sanofi. CL reports grants to the institution ACTIV from GSK, Sanofi, Pfizer, and MSD, and personal fees and non-financial support from Pfizer and MSD, outside the conduct of the study. RC reports grants to the institution ACTIV, personal fees, and non-financial support from GSK, Sanofi, Pfizer, and MSD, outside the submitted work. EV reports grants to the institution Centre Hospitalier Intercommunal de Créteil, from Pfizer and Merck, outside the conduct of the study. CG-LG reports honoraria from One Biomerieux conference. ABo reports consulting fees from Jazz Pharma. FA reports payments to their institution and an educational event from Sanofi. LDP reports support for attending meetings from MSD and Pfizer. RB reports consulting fees from Sanofi and support for lectures or presentations from Sanofi, MSD, and Oral B. All other authors declare no competing interests.

Data sharing

The clinical codes, data management (R script), and analysis codes used in this study are available on request from the corresponding author. A data dictionary defining each field can be found at: https://health-data-hub.shinyapps.io/dico-snds/. Anonymised data can be granted only upon request to the SNDS platform.

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