

Effectiveness and impact of nirsevimab in Chile during the first season of a national immunisation strategy against RSV (NIRSE-CL): a retrospective observational study

Juan Pablo Torres*, Denis Sauré*, Marcel Goic, Charles Thraves, Jorge Pacheco, Javiera Burgos, Natalia Trigo, Felipe Del Solar, Ignasi Neira, Gonzalo Díaz, Miguel O’Ryan*, Leonardo J Basso*



Summary

Background Nirsevimab for the prevention of respiratory syncytial virus (RSV) was introduced in some countries in the northern hemisphere in 2023. Chile was the first to implement a universal strategy in the southern hemisphere. We aimed to evaluate the effectiveness and impact of nirsevimab during the 2024 RSV season in Chile.

Methods Roll-out of the strategy began on April 1, 2024, and ended on Sept 30, 2024, targeting infants born between April 1, 2024, and Sept 30, 2024 (seasonal newborn cohort), and infants born between Oct 1, 2023, and March 31, 2024 (catch-up cohort). Using historical surveillance and hospital discharge data from ten hospitals that perform universal RSV testing for all patients admitted due to lower respiratory tract infection (LRTI), we identified a set of ICD-10 codes most closely related to RSV admissions during the 2019, 2022, and 2023 RSV seasons. These codes were applied to a national database of three consolidated nationwide government registries to identify RSV-related LRTI hospitalisations (primary endpoint) among infants who received or did not receive nirsevimab. Secondary endpoints were RSV-related intensive care unit (ICU) admission, all-cause LRTI hospitalisation, and all-cause hospitalisation occurring at least 7 days after birth. Nirsevimab effectiveness was estimated using a stratified Cox proportional hazards model, calculated as $(1 - \text{hazard ratio})$ multiplied by 100, with 95% CIs. We also assessed the impact of nirsevimab by estimating, compared with a counterfactual scenario in which nirsevimab was never introduced, the averted number and relative reduction of cases, and the number needed to immunise to avoid one case. This study was registered with ClinicalTrials.gov, NCT06511687 (completed).

Findings Data for 157 709 infants with complete records were extracted from the consolidated database. After excluding 1247 infants with missing or corrupt data and 2289 infants whose immunisation status could not be determined, 154 173 infants were included in the primary analysis. The median age of infants was 6·27 months (IQR 3·20–9·17). 76 045 (49·32%) infants were female and 78 128 (50·68%) were male. 145 087 infants were immunised by the end of the strategy roll-out, with 72 246 (49·79%) in the catch-up cohort and 72 841 (50·21%) in the seasonal cohort. After controlling for age, sex, geographical area, and weeks of gestational age, combined effectiveness of nirsevimab (for catch-up and seasonal cohorts) against RSV-related LRTI hospitalisations was 76·41% (95% CI 72·57–79·72), against RSV-related ICU admissions was 84·94% (79·47–88·95), against all-cause LRTI hospitalisations was 66·50% (61·97–70·50), and against all-cause hospitalisations was 47·90% (44·35–51·21). We estimated a relative reduction of 77·46% in RSV-related LRTI hospitalisations, 30·05 averted cases per 1000 infants, and a number needed to immunise to prevent one RSV-related LRTI hospitalisation of 35.

Interpretation Chile’s nirsevimab immunisation strategy significantly reduced RSV-related LRTI hospitalisations and more severe cases requiring intensive care. Our findings indicate a broader public health impact, with reductions also observed in all-cause LRTI hospitalisations. These results might encourage other countries to advance RSV prevention efforts.

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Introduction

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection (LRTI) worldwide, disproportionately affecting young children.^{1,2} In Chile,³ RSV primarily affects infants younger than 1 year (appendix 2 p 5). A prophylactic strategy targeting high-risk groups for RSV prevention was followed until 2023, based

on the use of palivizumab (AstraZeneca, Cambridge, UK), a monoclonal antibody directed against site II of the fusion (F) protein of RSV. Because palivizumab has a short half-life and high cost, the strategy targeted only a small number of high-risk infants who received a monthly dose throughout the RSV season, typically from mid-April to mid-September (appendix 2 p 6).

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*Contributed equally

For the Spanish translation of the abstract see Online for appendix 1

Departamento de Pediatría y Cirugía Infantil, Facultad de Medicina (J P Torres MD PhD), Departamento de Ingeniería Industrial, Facultad de Ciencias Físicas y Matemáticas (D Sauré PhD, M Goic PhD, C Thraves PhD, Prof L J Basso PhD), Instituto de Ciencias Biomédicas (Prof M O’Ryan MD), and Universidad de Chile, Santiago, Chile; Instituto Sistemas Complejos de Ingeniería, Santiago, Chile (J P Torres, D Sauré, M Goic, C Thraves, Prof L J Basso, N Trigo MSc, F Del Solar BSc, I Neira MSc, G Díaz MSc, Prof M O’Ryan); Departamento de Estadísticas e Información de Salud, Ministerio de Salud de Chile, Santiago, Chile (J Pacheco MD MSc, J Burgos MSc)

Correspondence to: Prof Leonardo J Basso, Departamento de Ingeniería Industrial, Facultad de Ciencias Físicas y Matemáticas, Universidad de Chile, Santiago 8370456, Chile lbasso@uchile.cl

or

Prof Miguel O’Ryan, Instituto de Ciencias Biomédicas, Universidad de Chile, Santiago 8370456, Chile moryan@uchile.cl

See Online for appendix 2

Research in context

Evidence before this study

Before the introduction of nirsevimab, respiratory syncytial virus (RSV) prophylaxis relied on palivizumab, which was limited to high-risk infants due to its high cost and short half-life. Nirsevimab, a long-acting monoclonal antibody, was approved in 2023 for the broader infant population and showed significant efficacy in clinical trials (MELODY [NCT03979313] and MEDLEY [NCT03959488]). We searched PubMed for studies published in English from database inception to March 6, 2025, using the terms “RSV”, “nirsevimab”, “monoclonal antibody”, “passive immunization”, “effectiveness”, and “impact”. Data on real-world effectiveness and population-level impact of nirsevimab are recent (beginning in 2023), support the trial data, and mostly represent subnational estimates. Two registered studies (ENVIE [NCT06030505] and EPINIR-BRONC [NCT06185647]) reported results from France, the only country that followed a nationwide universal strategy, but neither study used the full national data, and no information has been reported for the southern hemisphere.

Added value of this study

This study provides the first evidence of nirsevimab effectiveness and impact in a real-world setting using all

national-level data from a universal national programme in Chile, with the first data for the southern hemisphere. By analysing data from a universal immunisation strategy with a large number of eligible participants ($n=155\,000$), we found significant reductions in RSV-related lower respiratory tract infection (LRTI) hospitalisations, with effectiveness estimates aligning closely with those observed in clinical trials. We also provided estimates for intensive care unit admissions and further analysed factors affecting nirsevimab effectiveness and impact (such as preterm birth, rurality, and climate).

Implications of all the available evidence

Our results show the potential of nirsevimab to significantly reduce the RSV burden in infants when implemented at a national level. Additionally, our findings indicate a broader public health impact, with reductions observed not only in RSV-related LRTI hospitalisations but also in all-cause LRTI hospitalisations. These findings offer insights for other countries considering similar programmes and emphasise the importance of continued monitoring and research to optimise immunisation strategies for RSV prophylaxis.

In 2024, through the National Immunization Program, Chile introduced a nationwide prophylactic strategy with nirsevimab (AstraZeneca, Cambridge, UK and Sanofi, Paris, France) on the basis of a cost-saving analysis.⁴ This monoclonal antibody binds to site 0 of the prefusion F protein of RSV. Because of its extended half-life and lower cost compared with palivizumab, a single dose of nirsevimab was made available free of charge to all infants born up to 6 months before the beginning of the RSV season in Chile.⁵ This strategy was similar to those adopted by various countries and regions in the northern hemisphere during the 2023–24 RSV season, reporting promising results.^{6,7} As of March, 2025, 19 studies had evaluated nirsevimab effectiveness and/or impact;^{8–26} nine were done in Spain, six in France, and four in the USA.

The NIRSE-CL study, named after the NIRSE-GAL study in Galicia, Spain,^{27,28} is a collaborative effort between the Ministry of Health of Chile (MOH), the Instituto Sistemas Complejos de Ingeniería, and the Faculty of Medicine at the University of Chile, with the primary aim of evaluating the effectiveness and impact of nirsevimab against RSV-related LRTI hospitalisations and other RSV-related health outcomes in infants, during the 2024 RSV season in Chile. Our study combines nationwide closed-access records on hospitalisations, immunisation, and births to track and compare outcomes between infants who received nirsevimab, infants who were eligible to receive but did not receive nirsevimab, and non-eligible individuals. We present effectiveness and impact data

until Sept 30, 2024, the official end of the 2024 season in Chile. Follow-up of these cohorts is planned for the 2025 RSV season.

Methods

Immunisation strategy and participants

Roll-out of the national prophylactic strategy began on April 1, 2024, approximately 1 month before the beginning of the RSV season in Chile, and ended on Sept 30, 2024; both dates were decided by the MOH based on RSV circulation during previous years (appendix 2 p 6). The strategy targeted infants born between April 1, 2024, and Sept 30, 2024 (seasonal newborn cohort); infants born between Oct 1, 2023, and March 31, 2024 (catch-up cohort); and infants with high-risk conditions who previously would have been eligible for prophylaxis with palivizumab (high-risk cohort).²⁹ Infants in the seasonal cohort were immunised at birth in maternity wards after parental consent had been obtained, before hospital discharge. Parents or guardians of infants in the catch-up cohort were invited to bring infants to vaccination centres for immunisation through a national communications campaign led by the MOH (appendix 2 p 8). Health authorities contacted parents or guardians of infants in the high-risk cohort outside the seasonal and catch-up cohorts. In our analysis, we included only infants in the seasonal and catch-up cohorts, since accurately identifying infants at high risk who were born before Oct 1, 2023, was not possible with the data that were available.

The Chilean Government routinely collects the data used in this study. Approval for the use of the anonymised data was granted by the MOH. This study was registered with ClinicalTrials.gov, NCT06511687 (completed).

Study design and data collection

We accessed three nationwide government registries for retrospective collection of data. The national immunisation registry records information on the date and place of immunisation of all individuals receiving nirsevimab and any other vaccine in Chile. Records from the National Registry and Identification Service (NRIS) contain gestational age in weeks, weight, length at birth, and sex for all newborns in Chile, as well as their mother's county of residence, level of education, and nationality. The NRIS also provides a date and probable cause for all deaths. The MOH's Department of Statistics and Information (DEIS) database provides hospital discharge records for all hospitalisations in Chile, including a registry of hospital bed occupancy (by day and type of bed—eg, ward or intensive care unit [ICU]) and discharge diagnoses based on ICD-10 codes. Each registry identifies individuals by a unique national identifier number assigned at birth. Using routine procedures, experts from DEIS used identifiers of infants (or of mothers if, for example, hospital discharge occurred before birth registration at the NRIS) to combine data from all governmental sources into a consolidated registry, which was then anonymised before analysis.

In Chile, comprehensive RSV tests are mandated at health-care facilities associated with a nationwide sentinel surveillance programme. Ten hospitals (appendix 2 p 7) throughout the country test all patients admitted due to LRTI (using immunofluorescence and confirmation by real-time PCR). Using historical surveillance and hospital discharge data from these ten hospitals, we identified a set of ICD-10 codes most closely related to RSV admissions during the 2019, 2022, and 2023 RSV seasons (the 2020 and 2021 seasons were not considered due to anomalies in RSV epidemiology caused by the COVID-19 pandemic; appendix 2 pp 9–11). A hospital admission was defined as an RSV-related LRTI if it occurred at least 7 days after birth, during the RSV season, and if the hospital discharge record contained any of five codes as the primary diagnosis: J12·1 (pneumonia due to RSV), J20·5 (acute bronchitis due to RSV), J21·0 (acute bronchiolitis due to RSV), J21·9 (acute bronchiolitis, unspecified), and B97·4 (RSV as the cause of diseases classified elsewhere [according to the ICD-10 code]). In our secondary analysis, we did not associate primary diagnosis code J21·9 with RSV.

Outcomes

The primary endpoint was RSV-related LRTI hospitalisation among infants who received or did not receive nirsevimab. Secondary endpoints were severe

RSV-related LRTI hospitalisation requiring ICU admission (RSV-related ICU admission); all-cause LRTI hospitalisation (defined as admission occurring at least 7 days after birth with a discharge record containing ICD-10 codes J-209 to J-229 as the primary diagnosis, and those associated with RSV); and all-cause hospitalisation occurring at least 7 days after birth.

Statistical analysis

All eligible infants with complete data on RSV-associated LRTI hospitalisation episodes were considered in the primary endpoint analysis. Infants with missing or corrupt data were excluded from the analysis; we excluded data for individuals with abnormal immunisation (eg, date of immunisation before the date of birth) or birth data (ie, improbable weight or gestational age; appendix 2 p 15), unlikely age of the mother (<12 years or >51 years), and sex reported as intersex. We excluded infants with mismatched immunisation data (ie, infants in the seasonal cohort whose immunisation status could not be determined) from the primary analysis; a secondary analysis imputed immunisation status according to the coverage level among the seasonal cohort at birth.

For each outcome, all eligible infants in the seasonal cohort were followed up from birth until the first occurrence of the outcome, death, or end of the immunisation strategy (Sept 30, 2024), whichever occurred first. Eligible infants in the catch-up cohort were followed up from the beginning of the strategy (April 1, 2024) until the first occurrence of the outcome, death, or end of the immunisation strategy, whichever occurred first. Nirsevimab effectiveness was determined by estimating the hazard ratio (HR) between immunised and non-immunised infants. We considered infants to be immunised starting 7 days after receipt of nirsevimab to account for the possibility that infants were already infected with the virus at the time of immunisation. Thus, eligible infants with RSV-related hospitalisation in the first 7 days after immunisation were considered non-immunised. We used a stratified Cox proportional hazards model, considering several potential confounding factors for stratification (sex, gestational age in weeks, age in months, rurality [urban vs rural], and region). These confounders were selected using a directed acyclic graph to analyse the potential relationships among the covariates, access to treatment, and the primary outcome (appendix 2 pp 12–13), and were used in a stratified procedure rather than being included directly in the model because the proportional hazards assumption was not fulfilled, according to Schoenfeld residuals test. We also ran a negative-control test with these variables, considering hospital admission due to intestinal infectious diseases (ICD-10 codes A08·0 to A08·5, A09·0, and A09·9) as the outcome. To explore the impact of sociodemographic factors on nirsevimab effectiveness, we conducted stratified Cox models for subsets of the data according to

sex, cohort, prematurity, rurality, and macrozones clustered according to climate and viral activity patterns (appendix 2 p 14). Further analysis examining the interaction of prematurity and cohort was conducted. The effectiveness of nirsevimab against the various outcomes was calculated as $(1 - \text{HR})$ multiplied by 100, with 95% CIs. Records from infants with an outcome before April 1, 2024, were excluded from the analysis for that outcome. Kaplan–Meier survival curves were used to assess the model's underlying assumptions.

The impact of the strategy was computed as the ratio of RSV-related LRTI hospitalisations between infants facing their first RSV season and those facing their second RSV season (first-to-second RSV ratio), which was calculated for seasons 2019, 2022, and 2023 (eg, infant faces their second season during 2023 when born between Oct 1, 2022, and Sept 20, 2023). Then, using the observed number of RSV-related hospitalisations in 2024 among infants facing their second RSV season, we estimated as a counterfactual the number of RSV-related hospitalisations among infants

facing their first season had there been no immunisation strategy with nirsevimab, assuming that the first-to-second RSV ratio for 2024 was the same as observed during 2019, 2022, or 2023. Then, we computed the averted number and relative reduction of cases, by comparing the counterfactual scenario with the real-world data, and estimated the number needed to immunise to avoid one case for each estimate (2019, 2022, and 2023). We also compute the SD for each of these metrics.

We report the number of infants discharged from hospital whose secondary diagnosis ICD-10 codes were RSV-related, which were considered primarily to be nosocomial infections (others could have been infected, admitted due to trauma, and presented symptoms while hospitalised). We compared length of stay between immunised and non-immunised infants using the Mann–Whitney *U* test, otherwise comparisons of means between two groups were performed using a two-sided Student *t* test (5% α level). Proportion comparisons between multiple groups were performed using χ^2 tests

	Immunised infants (n=145 087)	Non-immunised infants (n=9086)	Overall (n=154 173)	p value*
Median age, months	6.07 (3.13–9.00)	8.87 (6.27–10.93)	6.27 (3.20–9.17)	<0.0001
<3	34 443 (23.74%)	1378 (15.17%)	35 821 (23.23%)	..
3–6	37 436 (25.80%)	746 (8.21%)	38 182 (24.77%)	..
>6	73 208 (50.46%)	6962 (76.62%)	80 170 (52.00%)	..
Sex	0.80
Female	71 551 (49.32%)	4494 (49.46%)	76 045 (49.32%)	..
Male	73 536 (50.68%)	4592 (50.54%)	78 128 (50.68%)	..
Nationality of the infant's mother	<0.0001
Foreign national	15 800 (10.89%)	1118 (12.30%)	16 918 (10.97%)	..
Chile	119 291 (82.22%)	7902 (86.97%)	127 193 (82.50%)	..
Unknown	9996 (6.89%)	66 (0.73%)	10 062 (6.53%)	..
Cohort	<0.0001
Catch-up	72 246 (49.79%)	6937 (76.35%)	79 183 (51.36%)	..
Seasonal	72 841 (50.21%)	2149 (23.65%)	74 990 (48.64%)	..
Median time to immunisation, days†	<0.0001
Catch-up	24 (10–44)
Seasonal	1 (0–2)
Mean gestational age, weeks	38.21 (1.75)	38.29 (1.83)	38.21 (1.76)	<0.0001
Mean weight at birth, grams	3275.01 (532.66)	3302.53 (539.79)	3276.64 (533.12)	<0.0001
Preterm	<0.0001
No (≥ 37 weeks)	130 913 (90.23%)	8306 (91.42%)	139 219 (90.30%)	..
Yes (<37 weeks)	14 174 (9.77%)	780 (8.58%)	14 954 (9.70%)	..
Macrozones of Chile‡	<0.0001
North	14 285 (9.85%)	1233 (13.57%)	15 518 (10.07%)	..
Center	86 112 (59.35%)	4327 (47.62%)	90 439 (58.66%)	..
South	42 709 (29.44%)	3429 (37.74%)	46 138 (29.93%)	..
Austral	1976 (1.36%)	96 (1.06%)	2072 (1.34%)	..

Data are n (%), median (IQR), or mean (SD). *p values compare the immunised population with the non-immunised population, except the p value for median time to immunisation that compares the catch-up with seasonal cohorts. †The number of days between birth and immunisation date for the seasonal cohort and between April 1, 2024, and immunisation date for the catch-up cohort. ‡Macrozones are shown in the appendix (p 6); climate and respiratory syncytial virus circulation characteristics are also shown in the appendix (p 14).

Table 1: Baseline characteristics at the end of the national immunisation strategy roll-out (Sept 30, 2024)

(5% α level). Safety was assessed by the Comité de Farmacovigilancia en Vacunas registry. Adverse events possibly attributable to immunisation were monitored, and reported events were reviewed for causality by the Subdepartment of Vaccine Pharmacovigilance of the Institute of Public Health (MOH, Chile).

Role of the funding source

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

Results

The national immunisation strategy, which targeted around 155 000 eligible infants during the 6-month 2024 RSV season, had a coverage of more than 94%.³⁰ Data for 157 709 infants with complete records were extracted from the consolidated database; records for infants with improbable weight or gestational age ($n=636$), reported intersex ($n=6$), unlikely age of the mother ($n=197$), RSV-related LRTI hospital admission before April 1, 2024 ($n=240$), RSV infection within the first 7 days since birth ($n=5$), inconsistent data ($n=53$), or two or more of these criteria ($n=110$) were excluded from all analyses. Additionally, the immunisation status of 2289 infants could not be determined, and thus they were excluded from the primary analysis (appendix 2 p 16). 154 173 infants were included in the primary analysis, with a median age of 6·27 months (IQR 3·20–9·17; table 1). 76 045 (49·32%) infants were female and 78 128 (50·68%) were male. There were 124 hospitalisations with secondary ICD-10 codes related to RSV.

145 087 infants were immunised by the end of the strategy roll-out (Sept 30, 2024), with 72 246 (49·79%) in the catch-up cohort and 72 841 (50·21%) in the seasonal cohort (table 1). 9086 infants were not immunised, with 6937 (76·35%) in the catch-up cohort and 2149 (23·65%) in the seasonal cohort. Cumulative immunisation coverage at the end of the 2024 RSV season on week 40 was 91·2% in the catch-up cohort and 97·1% in the seasonal cohort (figure 1). The median time to immunisation was 24 days (IQR 10–44) from the beginning of the strategy in the catch-up cohort and 1 day (0–2) from birth in the seasonal cohort, excluding infants who were not immunised by the end of the strategy roll-out (table 1). Compared with immunised infants, non-immunised infants were older, had slightly higher mean weight and gestational age at birth, were less likely to be born preterm (<37 weeks), were more likely to be born to mothers who were foreign nationals, and were more likely to live outside the Center macrozone of Chile. There was no statistically significant difference in sex distribution between immunised and non-immunised participants.

At the end of the RSV season, 957 RSV-related LRTI hospitalisations occurred among immunised infants over 72 128·31 person-years and 327 occurred among non-immunised infants over 5787·48 person-years

(table 2). Median follow-up was 137 days (IQR 87–164) for immunised infants and 11 days (2–38) for non-immunised infants. Combined effectiveness of nirsevimab (for catch-up and seasonal cohorts) against RSV-related LRTI hospitalisations was 76·41% (95% CI 72·57–79·72). Immunised infants had a lower probability

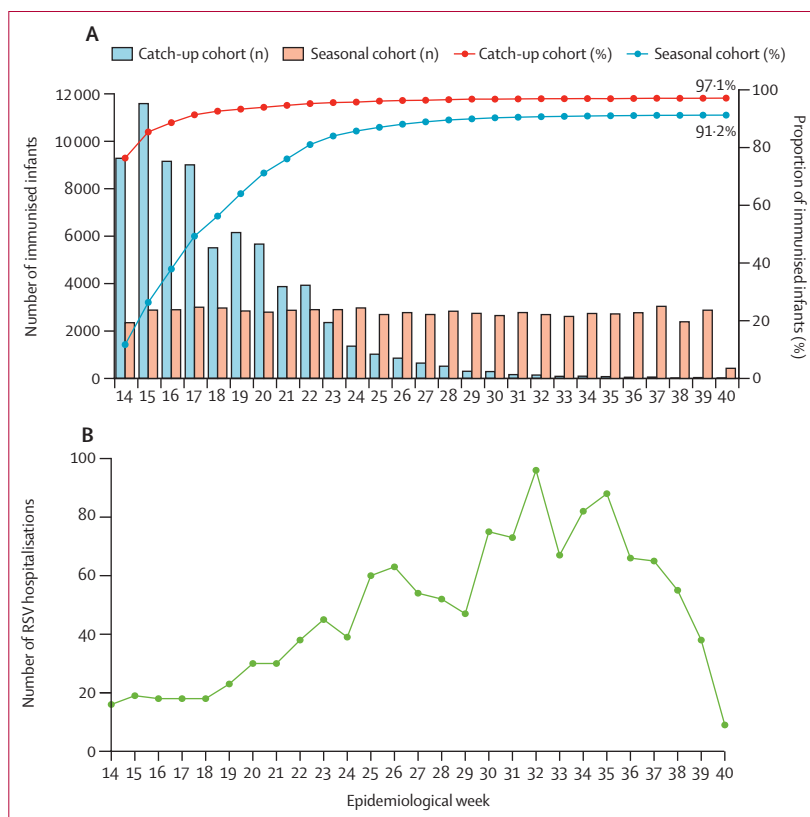


Figure 1: Nirsevimab coverage (A) and number of RSV-related LRTI hospitalisations (B) by week
The dotted lines in panel A represent the cumulative coverage for each epidemiological week in 2024. LRTI=lower respiratory tract infection. RSV=respiratory syncytial virus.

	Immunised infants (n=145 087)		Non-immunised infants (n=9086)		Effectiveness of nirsevimab (95% CI)
	Events	Person-years	Events	Person-years	
RSV-related LRTI hospitalisation	957	72 128·31	327	5787·48	76·41% (72·57–79·72)
RSV-related ICU hospitalisation	189	72 479·82	81	5789·00	84·94% (79·47–88·95)
All-cause LRTI hospitalisation*	1689	71 721·89	438	5776·54	66·50% (61·97–70·50)
All-cause hospitalisation†	6714	66 897·67	1776	5830·63	47·90% (44·35–51·21)

Effectiveness of nirsevimab was estimated using the stratified Cox proportional hazards model with time-variant covariates (including age, sex, gestational age in weeks, region, and rurality). Computation of effectiveness against RSV-related LRTI (requiring ICU or not) excluded 240 additional participants, all-cause LRTI excluded 390, and all-cause hospitalisation excluded 4194 from the seasonal cohort who had the corresponding outcome between Oct 1, 2023, and April 1, 2024. Patients with non-zero follow-up time were included. ICU=intensive care unit. LRTI=lower respiratory tract infection. RSV=respiratory syncytial virus. *Including hospitalisations with primary ICD-10 diagnosis codes J-209 to J-229 and those associated with RSV. †Including hospitalisations unrelated to RSV.

Table 2: Primary and secondary endpoints

of RSV-related LRTI hospitalisation (HR 1.31 [95% CI 1.43–1.61]; $p < 0.0001$). The Kaplan–Meier survival curves begin to separate at 75 days (figure 2A). Survival curves for the analysis of RSV-related ICU hospitalisations were similar to those of RSV-related LRTI hospitalisations (figure 2). Regarding secondary endpoints, effectiveness of nirsevimab against RSV-related ICU admissions was 84.94% (95% CI 79.47–88.95), against all-cause LRTI hospitalisations was 66.50% (61.97–70.50), and against all-cause hospitalisations was 47.90% (44.35–51.21; table 2).

In a secondary analysis, we did not associate the diagnosis code J21.9 with RSV and found that effectiveness estimates did not change substantially for

all outcomes compared with the primary analysis (appendix 2 p 17). Similarly, in a sensitivity analysis, we imputed the immunisation status of 2289 infants from the catch-up cohort whose status could not be determined. Most (94.16%) of these infants were assigned to the immunised status and 16 had RSV-related LRTI hospitalisation. Effectiveness estimates in this sensitivity analysis did not change substantially for all outcomes compared with the primary analysis (appendix 2 p 18). The negative control analysis estimated nirsevimab effectiveness against hospitalisations due to intestinal infection to be 10.1% (95% CI –20.2 to 32.7), which was not statistically significant ($p = 0.50$).

A stratified analysis showed significantly higher effectiveness of nirsevimab against RSV-related LRTI hospitalisation among females than males and against RSV-related LRTI hospitalisation and ICU admission in the catch-up cohort than in the seasonal cohort (table 3). Further analysis (appendix 2 p 19) revealed that the difference in nirsevimab effectiveness against RSV-related LRTI hospitalisation between the catch-up and seasonal cohorts persisted only when full-term infants were considered. There were no significant differences in effectiveness of nirsevimab for preterm (yes vs no), rurality (urban vs rural), or macrozone subgroups (appendix 2 p 19). However, the highest effectiveness estimates were observed for the Center macrozone, within which most of Chile's population lives. We could not reliably estimate the effectiveness of nirsevimab for the Austral macrozone due to its small population.

Conditional on being hospitalised due to an RSV-related LRTI for at least 1 day, the empirical distribution of length of stay in hospital was statistically different for immunised compared with non-immunised participants (Mann–Whitney U test $p < 0.0001$; appendix 2 p 20). The median length of stay among 880 immunised infants was 3 days (IQR 2–5) versus 4 days (2–6) among 312 non-immunised infants; the means were 4.19 days versus 5.25 days. The empirical distributions of length of RSV-related ICU admission were also statistically different for immunised compared with non-immunised participants (Mann–Whitney U test $p = 0.0062$; appendix 2 p 20). The median length of stay was 4 days (IQR 2–5) among 181 immunised infants versus 4 days (3–7) among 79 non-immunised infants; the means were 4.59 days versus 6.99 days.

The ratio of RSV-related LRTI hospitalisations among infants going through their first versus second RSV seasons was 2.88 during the 2019 RSV season, 4.11 during the 2022 RSV season, and 2.61 during the 2023 RSV season (table 4). Projecting these ratios onto the 2024 RSV season, we estimated that 3541.89–6315.39 RSV-related LRTI hospitalisations were averted among infants living their first RSV season in 2024 (mean 4632.80 [SD 1478.39]), implying a relative reduction in RSV-related LRTI hospitalisations

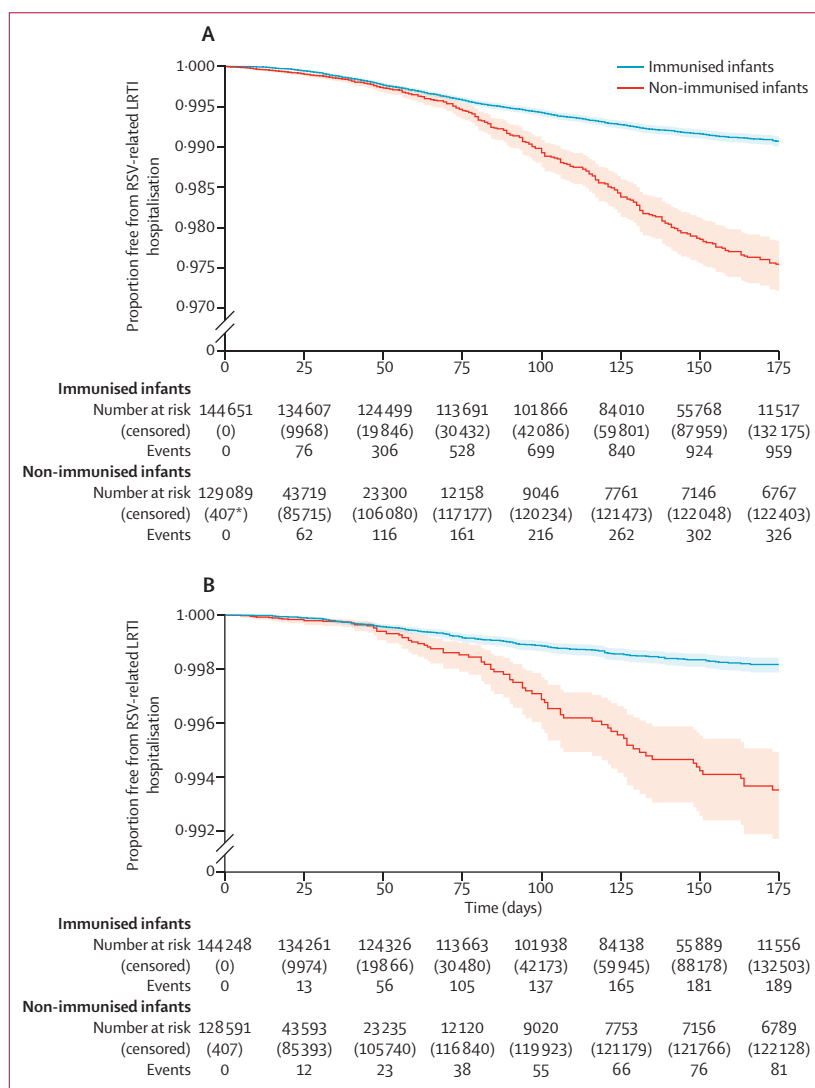


Figure 2: Kaplan–Meier curves of time to RSV-related LRTI hospitalisation (A) and intensive care unit admission (B) according to immunisation status

Shaded areas represent 95% CIs. Follow-up began on the immunisation date for immunised infants; for infants who were not immunised, follow-up began on April 1, 2024 (for infants in the catch-up cohort), or at birth (for infants in the seasonal cohort). LRTI=lower respiratory tract infection. RSV=respiratory syncytial virus. *Those censored are infants born on the last day of the campaign.

of 73.39–83.10% (mean 77.46% [5.04]). We estimated that 22.97–40.96 RSV-related LRTI hospitalisations per 1000 infants were averted (mean 30.05 [9.59]) and 24.41–43.54 infants needed to be immunised in 2024 to prevent one RSV-related LRTI hospitalisation (mean 35.37 [9.86]).

The cumulative number of RSV-related LRTI hospitalisations during the 2024 RSV season among infants who were not eligible for immunisation was similar to the number observed among the (counterfactual) non-eligible population by the end of the 2022 RSV season (appendix 2 p 21). By contrast, the cumulative number of RSV-related LRTI hospitalisations was notably lower among infants eligible for immunisation by the end of the strategy roll-out in 2024 than in infants who would have been eligible in 2022 (around 3500 fewer RSV-related LRTI hospitalisations). Cumulative numbers of RSV-related ICU admissions during 2024 among non-eligible infants were also similar to those observed by the end of the 2019 and 2022 RSV seasons. However, by the end of the 2024 RSV season, around 1000–1250 fewer severe RSV-related ICU admissions occurred among eligible infants than in infants who would have been eligible in 2019 and 2022.

During the 2024 RSV season, no infant eligible for nirsevimab died due to RSV infection compared with 13 deaths reported in 2023.³¹ There were no pronounced safety events associated with the use of nirsevimab, and none of the 18 reported adverse events (appendix 2 pp 24–27) supposedly attributable to immunisation were directly attributed to the monoclonal antibody, according to the Instituto de Salud Pública (Adiela Saldaña, Head of the Vaccine Pharmacovigilance Section, Public Health Institute of Chile [ISP], personal communication).

Discussion

Chile's national immunisation strategy during the 2024 RSV season significantly reduced RSV-related LRTI hospitalisations, especially more severe cases, compared with non-immunised infants and previous RSV seasons. Our analysis estimated the effectiveness of nirsevimab against RSV-related LRTI hospital admissions to be 76.41% (95% CI 72.57–79.72), and 84.94% (79.47–88.95) for severe RSV-related ICU admissions. Several real-life studies have been published on nirsevimab effectiveness, although our study is the largest and the first to be done in a country in the southern hemisphere. The effectiveness point estimates against RSV-related hospitalisations for the 19 studies we identified until March, 2025, ranged from 65% to 89%, and the point estimates for infants with severe RSV requiring intensive care ranged from 74% to 94%. Our estimates fall in the middle of these ranges, with the narrowest CIs reported to date. Caution in comparing estimates from different studies is required as not all studies identified outcomes in the same way or used the same measure of risk (HR vs risk ratios or odds ratios).

	RSV-related LRTI hospitalisation		RSV-related ICU admission	
	Events	Effectiveness of nirsevimab (95% CI)	Events	Effectiveness of nirsevimab (95% CI)
Sex				
Female	483	80.68% (75.51–84.76)	95	89.81% (83.29–93.79)
Male	801	73.16% (67.36–77.94)	175	80.88% (71.45–87.20)
Cohort				
Catch-up	707	80.67% (76.99–83.75)	151	87.65% (82.08–91.48)
Seasonal	577	53.19% (31.37–68.07)	119	74.13% (48.59–86.98)
Preterm				
No (≥37 weeks)	1056	77.23% (73.30–80.59)	216	85.54% (79.91–89.60)
Yes (<37 weeks)	228	68.54% (49.82–80.28)	54	79.59% (48.84–91.86)
Rurality				
Urban	1239	76.60% (72.70–79.94)	259	85.48% (80.06–89.43)
Rural	45	73.43% (37.17–88.76)	11	NA
Macrozone				
North	61	59.12% (17.56–79.73)	14	NA
Center	864	78.64% (74.28–82.27)	179	86.54% (80.31–90.80)
South	347	74.08% (65.80–80.36)	70	86.50% (76.08–92.38)
Austral	12	NA	7	NA

Effectiveness of nirsevimab was estimated using the stratified Cox proportional hazards model with time-variant covariates (including age, sex, gestational age in weeks, region, and rurality). Effectiveness estimates are displayed as NA when the width of 95% CIs was higher than 100%. Computation of effectiveness against RSV-related LRTI (requiring ICU or not) hospitalisations excluded participants from either cohort who had the corresponding outcome between Oct 1, 2023, and April 1, 2024. Patients with non-zero follow-up time were included. All-cause LRTI hospitalisation included hospitalisations with primary ICD-10 diagnosis codes J-209 to J-229 and those associated with RSV. All-cause hospitalisations included hospitalisations unrelated to RSV. ICU=intensive care unit. LRTI=lower respiratory tract infection. NA=not applicable. RSV=respiratory syncytial virus.

Table 3: Subgroup analyses of RSV-related LRTI hospitalisation and ICU admission

	2019 RSV season	2022 RSV season	2023 RSV season	Mean (SD)*
First-to-second RSV ratio†	2.88	4.11	2.61	..
Estimated number of cases in 2024‡	5325.12	7599.39	4825.89	5916.80 (1478.39)
Estimated number of cases averted in 2024§	4041.12	6315.39	3541.89	4632.80 (1478.39)
Relative reduction of cases in 2024¶	75.89%	83.10%	73.39%	77.46% (5.04)
Averted number of cases per 1000 infants in 2024	26.21	40.96	22.97	30.05 (9.59)
Number needed to immunise	38.15	24.41	43.54	35.37 (9.86)

LRTI=lower respiratory tract infection. RSV=respiratory syncytial virus. *Based on calendar years 2019, 2022, and 2023. †For a given year (t), the first-to-second RSV ratio corresponds to the number of RSV-related LRTI hospitalisations among infants born between Oct 1, year t–1, and Sept 30, year t (ie, infants in their first RSV season), over the number of RSV-related LRTI hospitalisations among infants born between Oct 1, year t–2, and Sept 30, year t–1 (ie, infants in their second RSV season). ‡Estimated number of cases among infants experiencing their first RSV season in 2024, calculated as the first-to-second RSV ratio for year t multiplied by the 1849 RSV-related LRTI hospitalisations among infants born between Oct 1, 2022, and Sept 30, 2023. §Calculated as the expected number of cases in 2024 minus the 1284 RSV-related LRTI hospitalisations observed in 2024 among infants born between Oct 1, 2023, and Sept 30, 2024. ¶Relative reduction of cases was calculated as 100 times the averted number of cases then divided by the expected number of cases. ||Number needed to immunise to prevent one RSV-related LRTI hospitalisation, calculated as the overall number of participants (n=154 173) divided by the averted number of cases.

Table 4: Impact estimates for RSV-related LRTI hospitalisations for the 2024 nirsevimab strategy based on previous years

Our stratified subgroup analysis revealed that the effectiveness of nirsevimab against RSV-related LRTI hospitalisations was significantly lower for the seasonal cohort than the catch-up cohort. Further post-hoc

subanalysis (appendix 2 p 22) revealed that such a difference in nirsevimab effectiveness persisted when only full-term (ie, not preterm) infants were considered. We conjecture that this difference in effectiveness between seasonal and catch-up cohorts was partly due to physicians adopting a more cautious approach with infants in the seasonal cohort due to their younger age and so increased vulnerability to severe RSV disease and related complications and higher risk of complications,⁴ and the fact that this was the physicians' first time administering the monoclonal antibody. This heightened vigilance could have led to a lower threshold for hospital admission, particularly when respiratory issues were present, which might also explain the lower effectiveness observed for preterm than for full-term infants in the catch-up cohort (appendix 2 p 22). However, other unmeasured factors (such as absence of breastfeeding or differences in coverage with other immunisations) might explain the lower effectiveness of nirsevimab in the seasonal than in the catch-up cohorts.

We estimated a reduction of 77·46% in RSV-related LRTI hospitalisations relative to a counterfactual non-immunisation scenario based on the average of previous years (2019–23). Empirically, the new strategy changed the dynamic of the RSV season in Chile, which typically at its peak stretched the capacity of the Chilean health-care system.³² Our study shows similar results to those reported during the 2023–24 season in high-income countries in the northern hemisphere.^{8–13}

Our study has several limitations. First, testing for RSV is not routine practice throughout Chile. Thus, we inferred RSV as a cause of hospitalisation using ICD-10 codes that were selected based on historical data from hospitals that routinely test for RSV. Presumably, misclassification of other viral infections into those ICD-10 codes might introduce subestimation bias; however, we deemed overestimation bias from considering only ICD-10 codes that explicitly mention RSV as a cause a larger problem than subestimation bias. In a secondary analysis, we considered only ICD-10 codes mentioning RSV and found that although point estimates for the primary and secondary endpoints increased, in three of four cases (the exception being RSV-related LRTI hospitalisation), CIs overlapped with those derived in the primary analysis including all ICD-10 codes (appendix 2 p 17).

Another limitation is that the immunisation status of around 2300 infants could not be determined and thus they were excluded from the primary analysis. Although these infants represented less than 2% of the study population, the absence of complete information might be a source of bias. However, evidence from a secondary analysis in which immunisation status data were imputed found similar results to the primary analysis (appendix 2 p 18).

The counterfactual scenario constructed to estimate the impact of the new strategy was based on the

circulation of RSV in recent years (2019, 2022, and 2023) and assumed that no other strategy (eg, one based on maternal vaccination) would replace nirsevimab. This analysis could have been improved by considering additional data from years before the COVID-19 pandemic and excluding data from years immediately after, by using techniques such as synthetic controls, and by extending it to other outcomes, thus enabling a more comprehensive analysis of the impact of the nirsevimab strategy in Chile. An additional limitation of our study is that the data were restricted to hospitalised infants, meaning that we did not have information on the impact of nirsevimab on less severe manifestations of RSV.

Additional covariables (such as health insurance, ethnicity, and comorbidities) might have improved the estimation of nirsevimab effectiveness; however, data on these covariates were incomplete for most of the population. Although the large sample size allowed us to estimate effectiveness in preterm infants, further stratification by gestational age was limited by sample size constraints. For example, although we provide estimates for preterm infants born before and after 32 weeks' gestation, the small number of cases in each subgroup would result in wide CIs, hypothetically reducing the precision of these estimates. Lastly, access to health care might be limited in the extreme regions of Chile and to undocumented migrants, especially in the northern part of the country, and there might be bias in that immunisation coverage might not be homogeneous across socioeconomic groups. These limitations suggest the presence of unaccounted confounders, although a negative-control analysis indicated that these effects were likely of minimal importance. Although Chile has an inclusive policy for health care and good access, data could be censored, and we did not have access to instrumental variables to uncover the potential bias.

In terms of impact, the substantial reduction in hospital bed use due to all-cause LRTI and all-cause hospitalisations following the roll-out of the strategy, which had stretched the health-care system every winter in Chile for decades, is a pronounced public health achievement. RSV remains a major cause of infant hospitalisation in the region,³³ and its seasonality, its health-care burden, and disparities in access to preventive measures warrant further study. Beyond immediate impact on hospitalisation, RSV infection has been associated with increased health-care use and respiratory morbidity in the years after infection,³⁴ further emphasising the importance of RSV prophylaxis to reduce acute and long-term consequences. In conclusion, our findings underscore the importance of introducing RSV prophylaxis into national programmes for effectively reducing the burden of RSV, especially in South American countries with a gross domestic product per capita of US\$10 000–30 000, such as Chile.

Contributors

JPT, DS, MO'R, JP, and LJB conceived the study. LJB led and coordinated the project. JP directed the Department of Statistics and Information (DEIS) team and JB worked on data consolidation and anonymisation. LJB and DS directed the Instituto Sistemas Complejos de Ingeniería (ISCI) team that performed statistical analysis. DS, MG, CT, FDS, NT, GD, and IN were responsible for data cleaning, analyses, and generating tables and figures. DS, MO'R, JPT, JP, and LJB drafted the original manuscript. All authors contributed to the methods, revised the manuscript, and approved the final version. LJB, DS, JP, and JB have accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Anonymised datasets were shared under a formal collaboration agreement between the Ministry of Health of Chile (MOH) and ISCI. Data were anonymised by DEIS officials to comply with current legislation, ensuring confidentiality, and then stored in servers at ISCI. Aggregate data are openly accessible on the DEIS website (<https://deis.minsal.cl/>) or within the repositories of Chile's National Statistics Institute (<https://www.inec.gov.cl>). Data cannot be shared directly by the authors because of data protection regulations. Data are accessible to authorised researchers after an application to the MOH.

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