Estimating effectiveness and impact of nirsevimab using sentinel surveillance data in Spain

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Sentinel ARI and SARI surveillance

- Integrated surveillance for influenza, COVID-19 and RSV since September 2020
- Sentinel system, leveraging all experience from previous influenza sentinel networks

Syndromic component

Sentinel or exhaustive

Similar distribution of age, sex, urban/rural as the surveilled region

- WHO ARI and SARI case definition as reference
- Extraction of diagnostic codes in primary care or hospitals
- Weekly ARI/SARI rates by sex and age

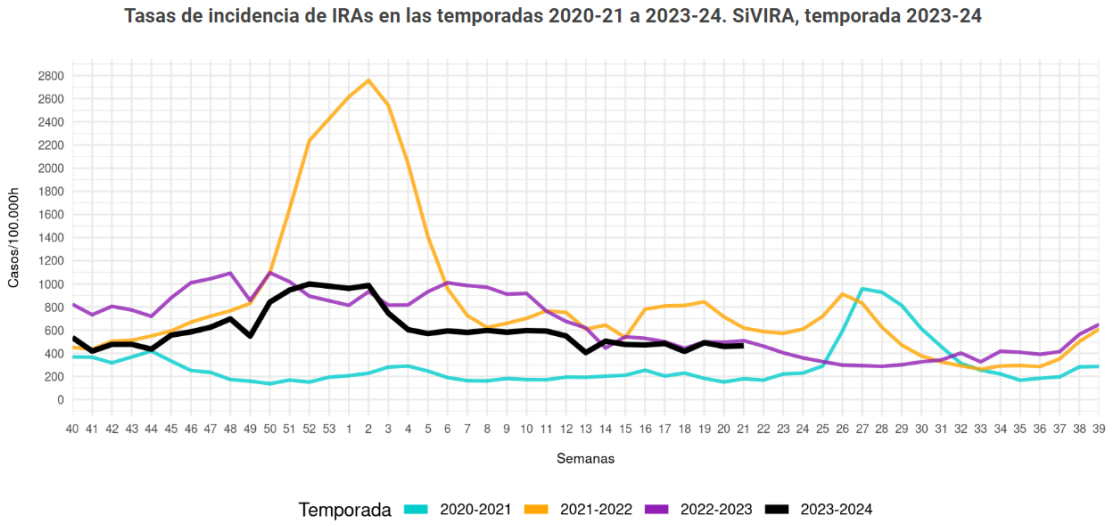
Systematic selection

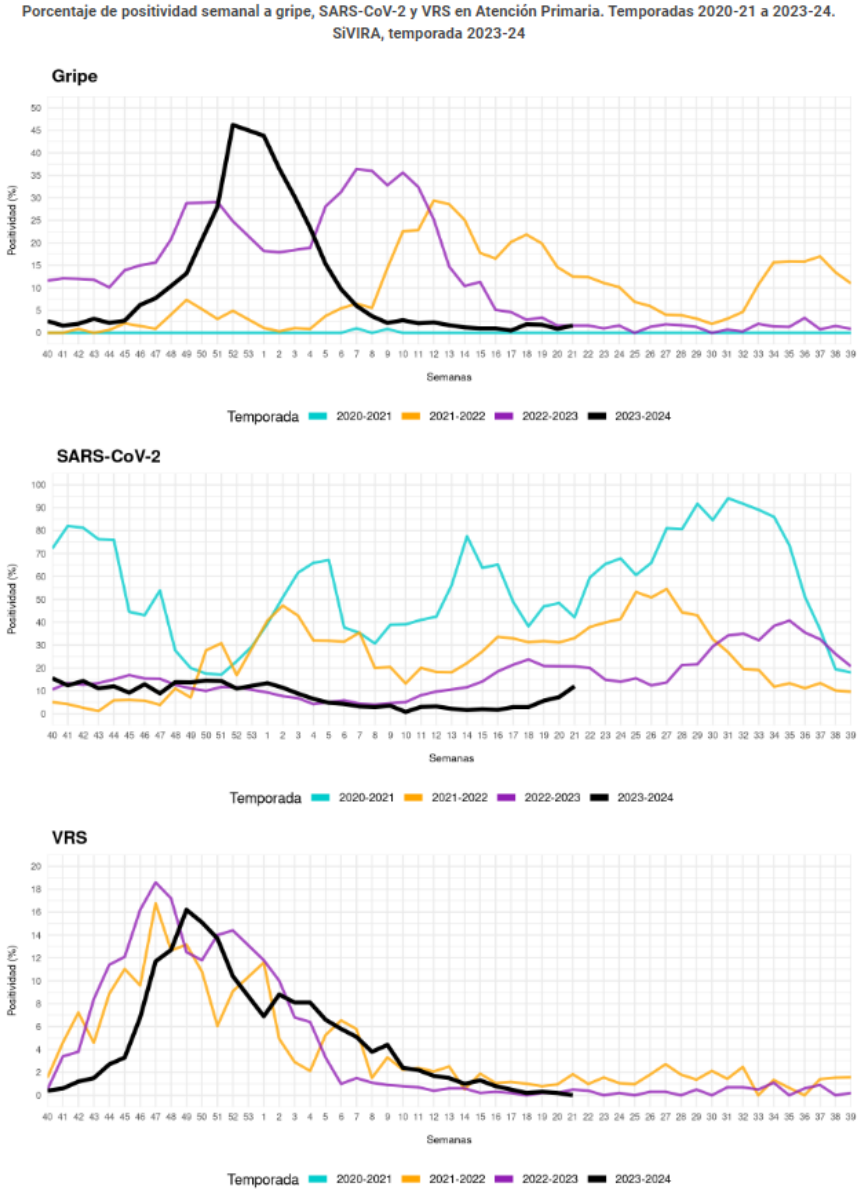
Sentinel sites

Similar distribution of age, sex, urban/rural as the surveilled region

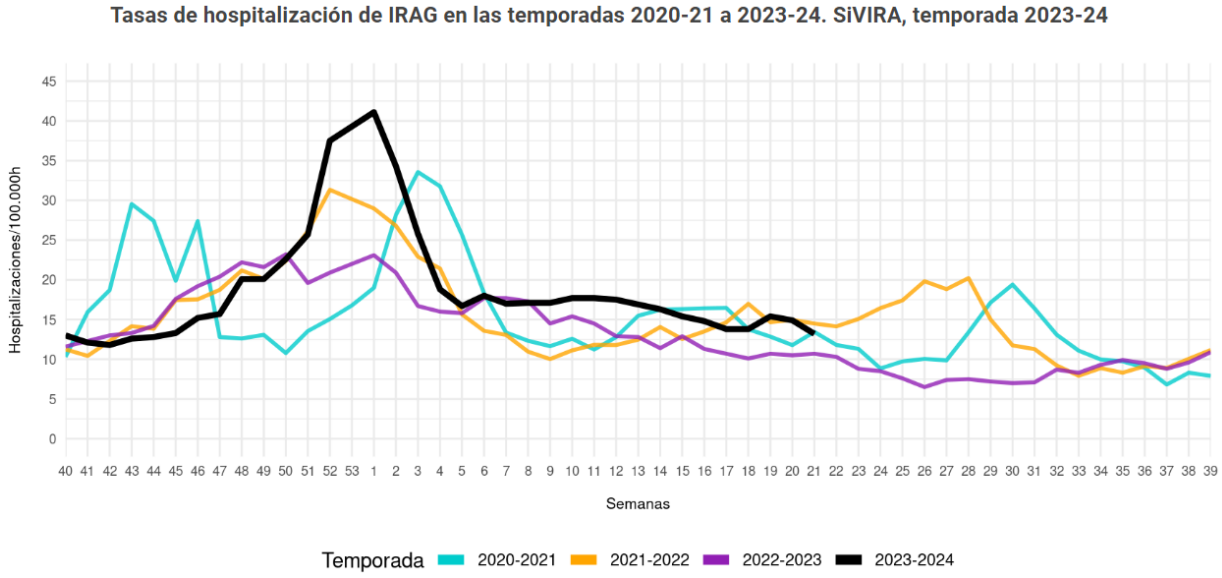
- Systematic:
  - ✓ First 2-5 weekly ARI patients in PC
  - ✓ SARI hospitalized one/two days at week
- Triple test: influenza, SARS-CoV-2 and RSV
- Clinical, virological and vaccination information, including influenza and SARS-CoV-2 sequencing

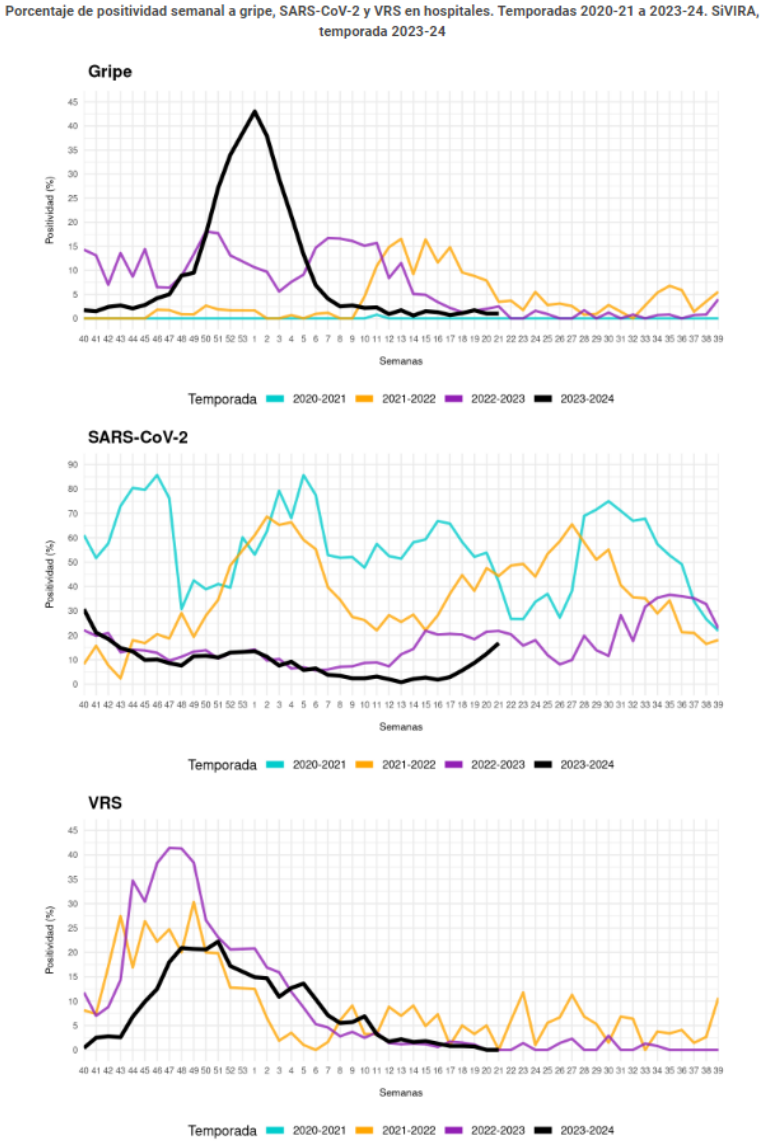
Weekly ARI rates and % positivity in Spain, 2020-21 to 2023-24



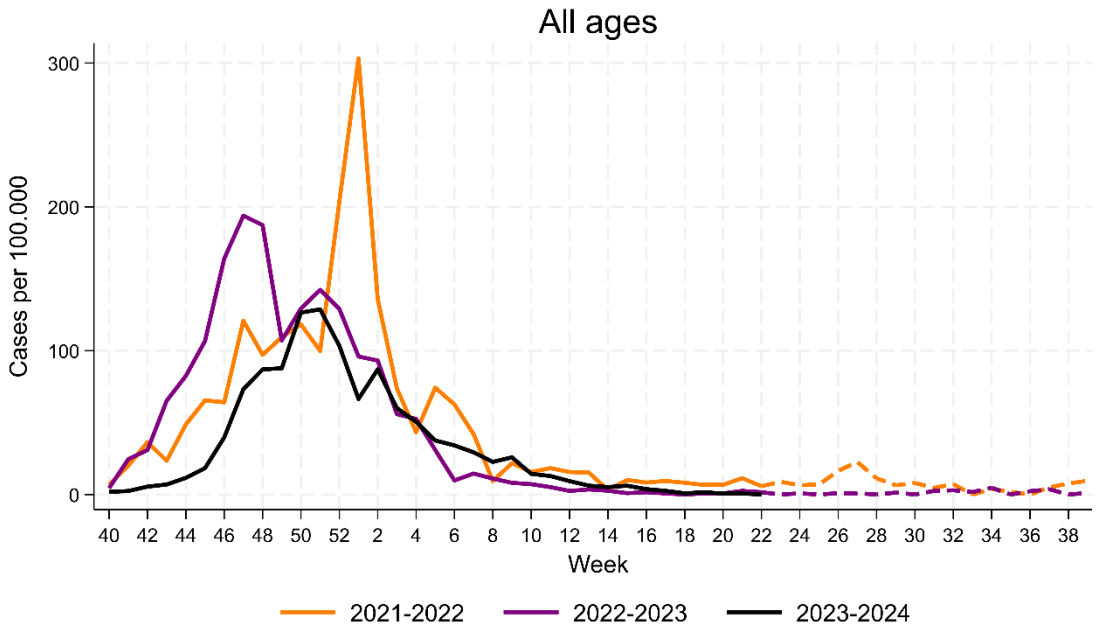


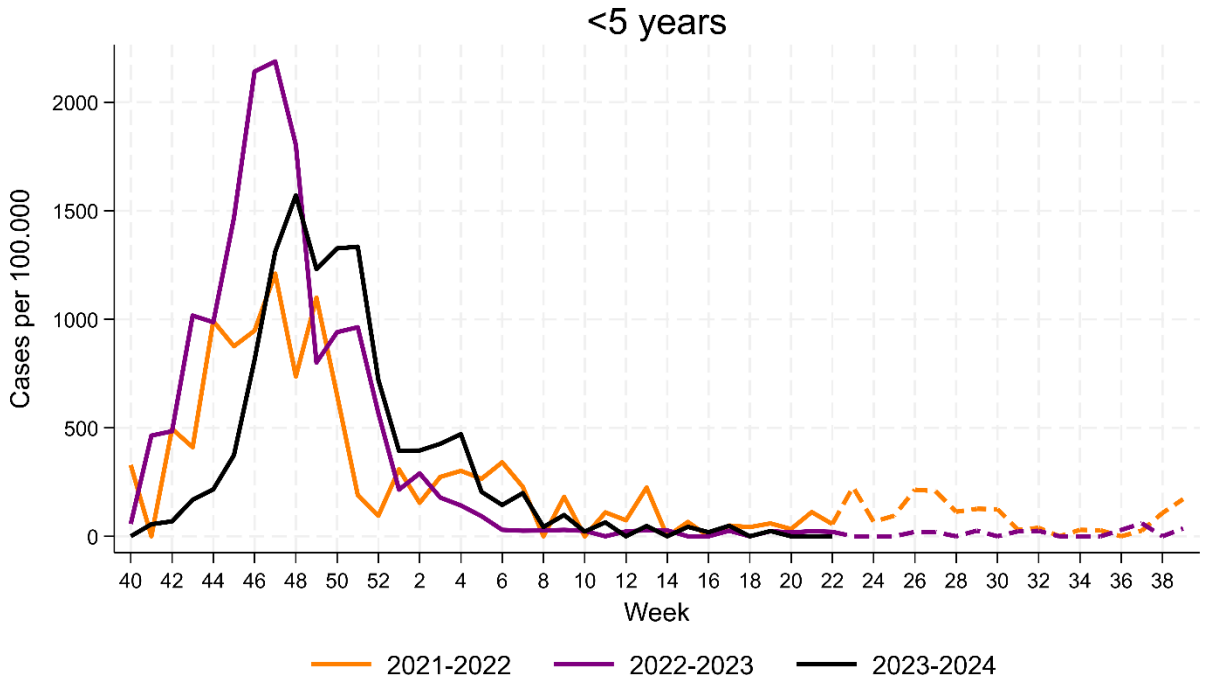
Weekly SARI rates and % positivity in Spain, 2020-21 to 2023-24



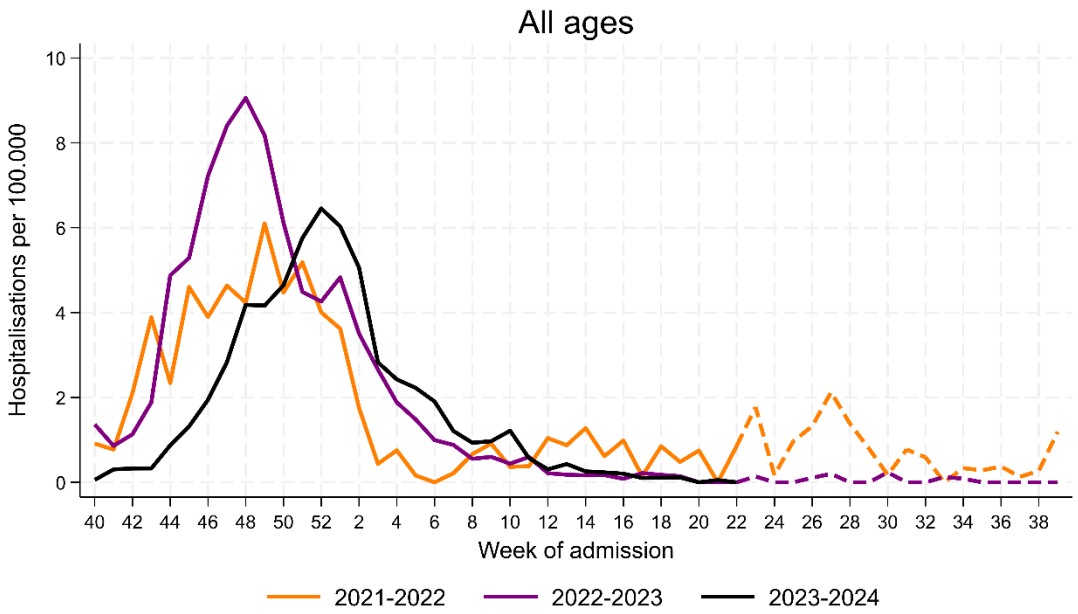


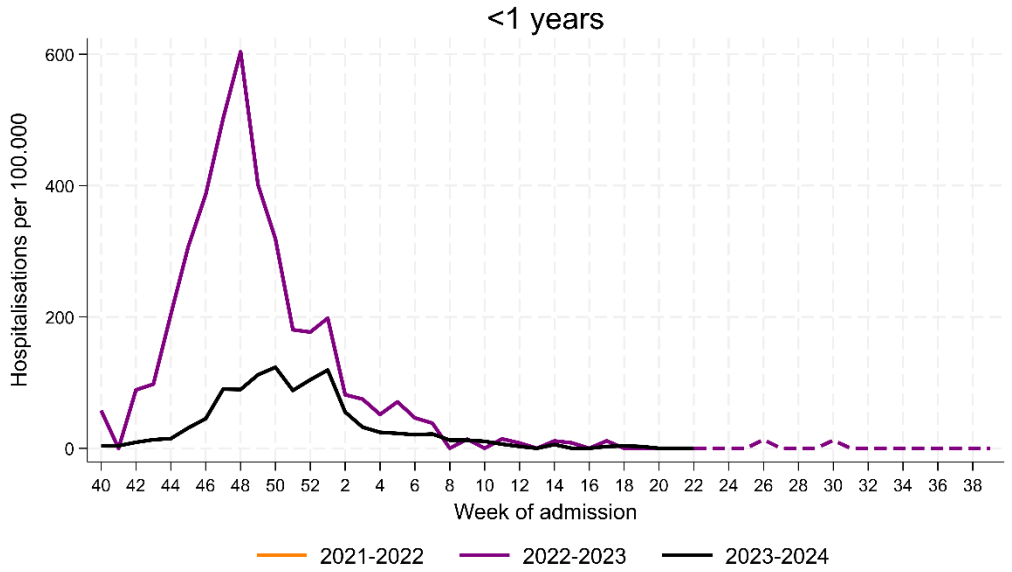
Proxy for RSV-specific rates in Primary Care

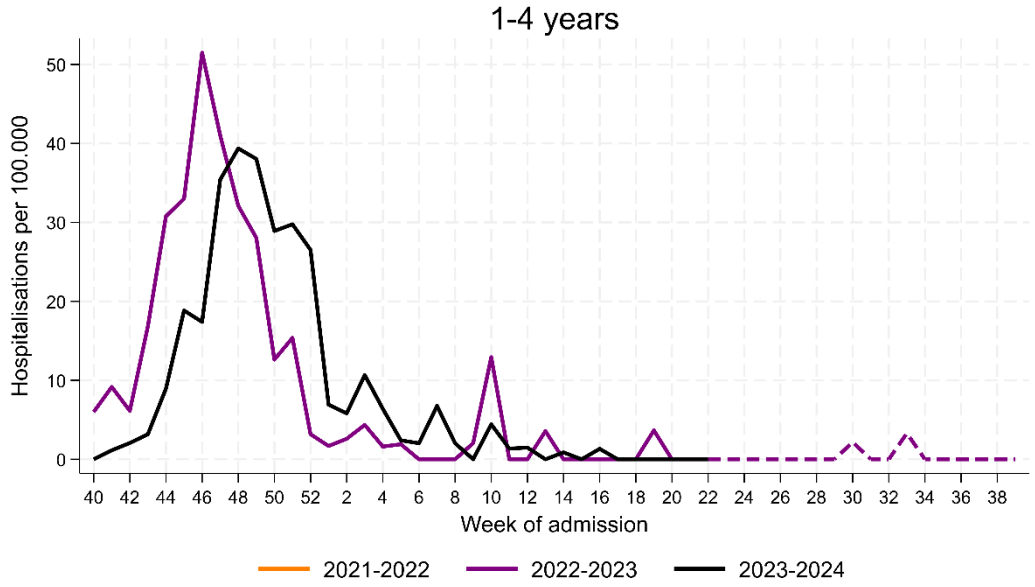




Proxy for RSV-specific hospitalisation rates







Nirsevimab systematic administration in Spain

Campaign started on 1 October 2023 (with slight differences between regions)

Recommendation:

1. Children with increased risk of severe RSV infection were previously recommended palivizumab and this season are targeted for nirsevimab instead (<24 months; premature <12 months)
2. As soon as possible after birth, normally in the first 48 hours (in the maternity or hospital), or alternatively in the first pediatric consultation, generally before 10 days of life
3. Catch-up immunization to children <6 months at the beginning of the season (born ≥1 April 2023)

Uptake >90%

Surveillance objectives

1. Monitoring the **spatio-temporal evolution** of influenza, COVID-19 and RSV epidemics
2. Epidemiological, clinical and virological **characterization**
3. Studying **risk factors** and patterns of severe disease
4. Measure **burden of disease** and impact on health systems
5. Estimate **effectiveness and impact of interventions** and preventive measures
6. **Genomic surveillance** and antiviral susceptibility

Assessment of effectiveness using surveillance data

Objective

- To estimate the reduction in the risk of hospital admission due to RSV, associated to nirsevimab administration to newborns (as soon as possible after birth)

Inconsistent results for children immunised as catch-up

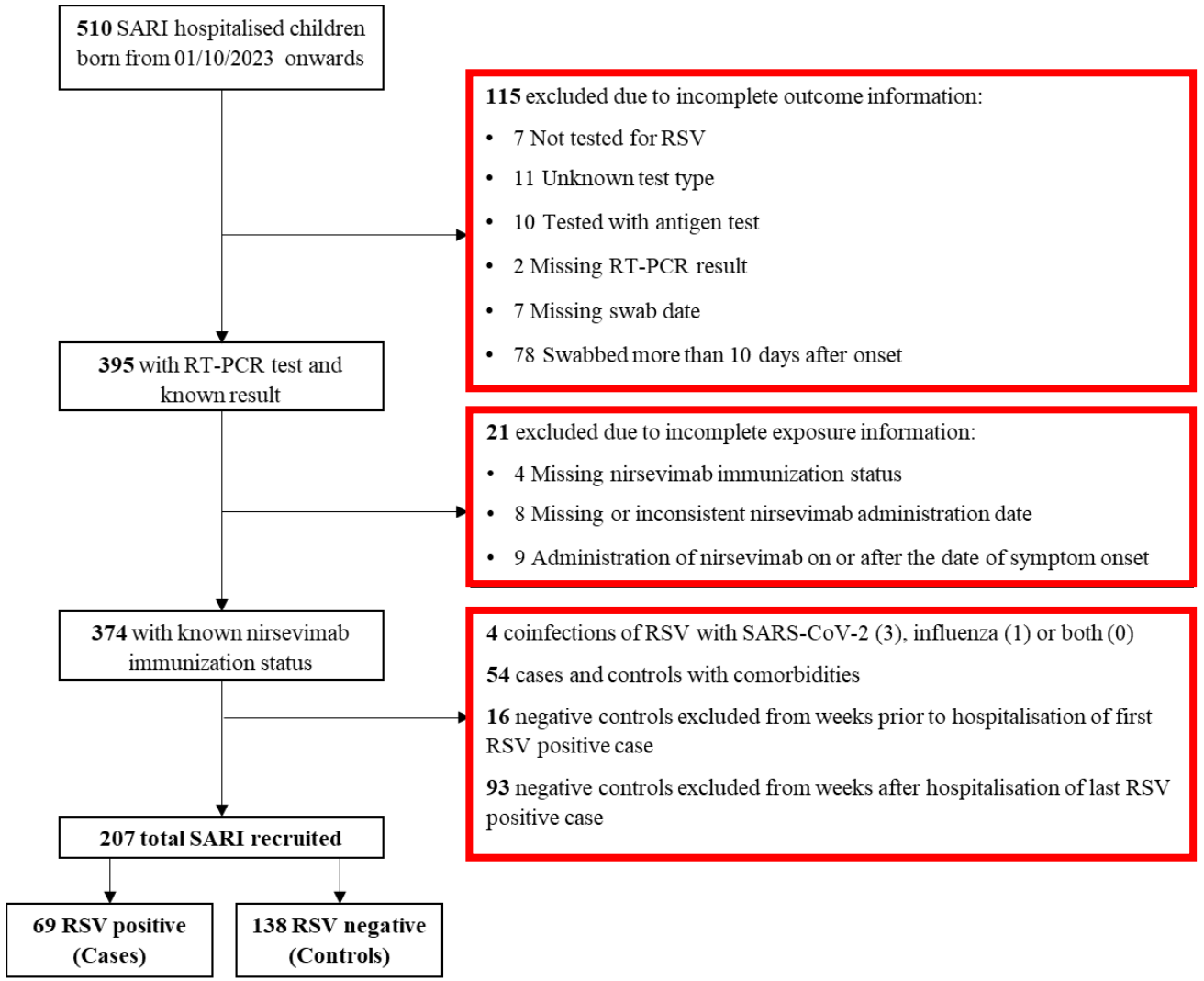
Not possible to adjust by comorbidities (low numbers with reported comorbidity), instead we restricted the study to children with no recorded comorbidities

Methods: Test-negative design

- Using SARI cases systematically selected for virological testing within surveillance system:
  - 8 regions intensified SARI surveillance to select all children < 6 months
  - Born ≥1 Oct 2023

- 99% of them were tested for RSV:
  - Positive → cases
  - Negative → controls

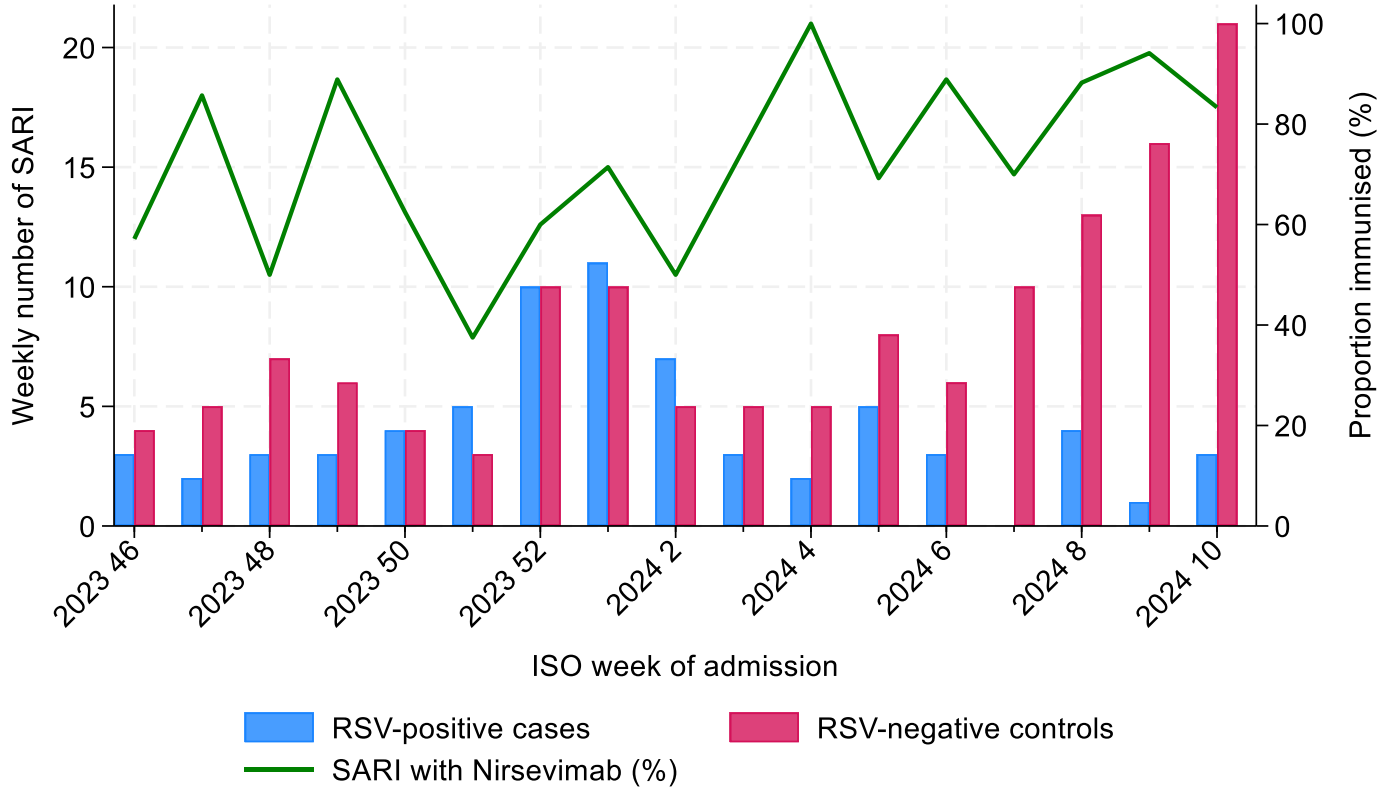
Selection of the sample



Data analysis

- Exposed = received nirsevimab up to the day before symptoms onset
- Odds of exposure compared between cases and controls
- Odds Ratio (and 95% CI) estimated using logistic regression, adjusted by:
  - ✓ sex
  - ✓ age at admission
  - ✓ epidemiological week

Results: distribution of cases and controls y date of admission



Results: characteristics of cases and controls

Variable		Born 1 Oct 2023 - 29 Feb 2024			
		Cases (N=69)		Controls (N=138)	
		N	%	N	%
Sex	Male	42	60,9	81	58,7
	Female	27	39,1	57	41,3
Age at admission	0-30 days	20	29,0	48	34,8
	31-60 days	27	39,1	49	35,5
	61-90 days	17	24,6	22	15,9
	91-120 days	4	5,8	9	6,5
	≥ 121 days	1	1,4	11	7,3
Month of birth	Oct 2023	27	39,1	23	16,7
	Nov 2023	20	29	46	33,3
	Dec 2023	16	23,2	37	26,8
	Jan 2024	3	4,3	23	16,7
	Feb 2024	3	4,3	9	6,5
Clinical course during admission*	Acute renal failure	1	1,4	0	0
	Pneumonia	2	2,9	6	4,3
	Invasive mechanical ventilation	3	4,3	2	1,4
	Admission to ICU	19	27,5	18	13
	Death	0	0	0	0
Immunised with nirsevimab	No	37	53,6	18	13,0
	Yes	32	46,4	120	87,0

Results: estimated effectiveness of nirsevimab

Analysis		Cases (immunised/total)	Controls (immunised/total)	Crude effectiveness (95% CI)	Adjusted effectiveness (95% CI)
Overall		32/69	120/138	87.03 (74.26 - 93.46)	83.78 (67.29 - 91.95)
Age at admission	**0 – 30 days**	5/20	43/48	96.12 (84.72 - 99.02)	95.72 (83.26 - 98.91)
	31 – 60 days	15/27	41/49	75.61 (28.72 - 91.65)	67.09 (2.47 - 88.90)
	61 – 90 days	8/17	20/22	91.11 (49.47 - 98.44)	73.36 (-46.41 - 95.15)
	91 – 120 days	4/4	7/9	NA	
	≥ 121 days	0/0	9/10	NA	

Nirsevimab decreased the risk of hospitalisation due to RSV by 84% (95% CI: 67-92) in children born during the respiratory season and with no recorded comorbidity. Effectiveness seemed higher children <1 month of age

Assessment of impact using surveillance data

Objective

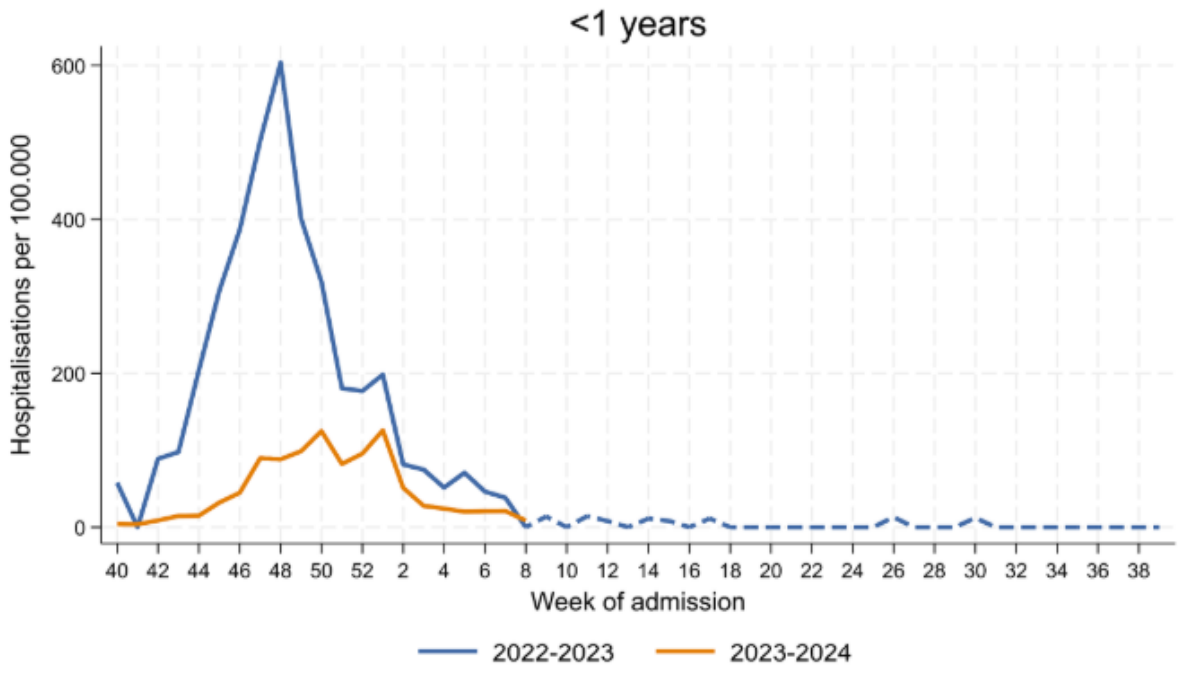
- To estimate the reduction in the number of hospital admissions due to RSV in children <1 year of age during 2023-24 respiratory season, attributable to nirsevimab

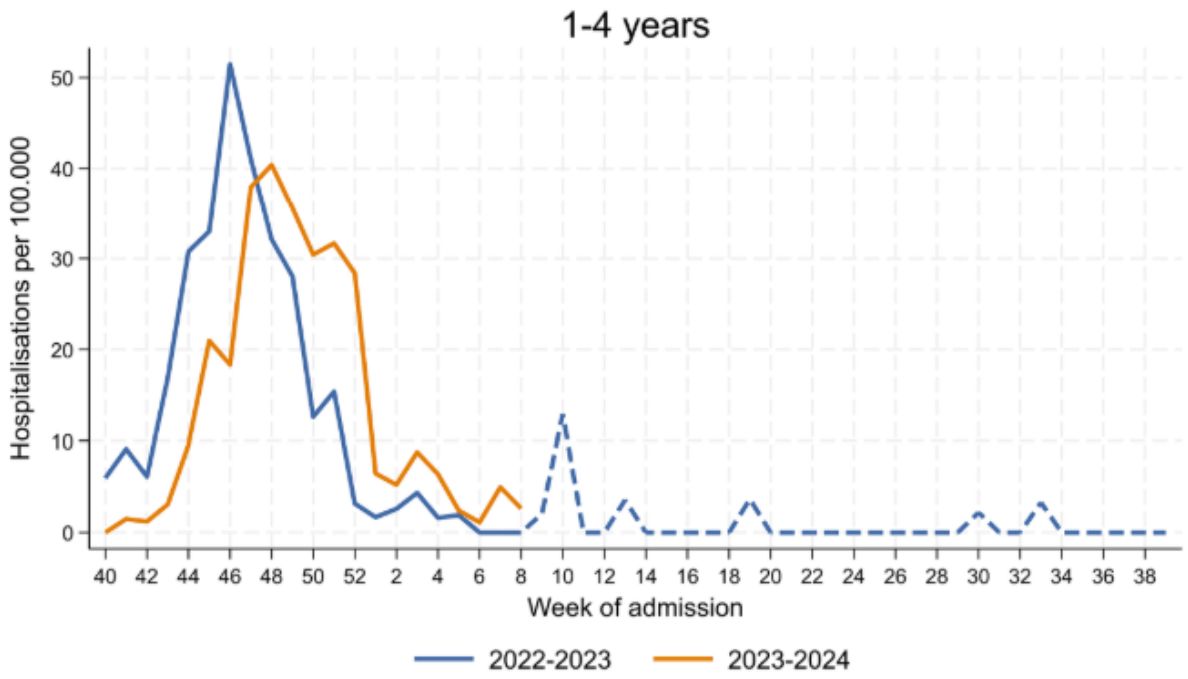
Mazagatos C, Mendioroz J, Rumayor MB, Gallardo García V, Álvarez Río V, Cebollada Gracia AD, Batalla Rebollo N, Barranco Boada MI, Pérez-Martínez O, Lameiras Azevedo AS, López González-Coviella N, Castrillejo D, Fernández Ibáñez A, Giménez Duran J, Ramírez Córcoles C, Ramos Marín V, Larrauri A, Monge S; SARI Sentinel Surveillance RSV Study Group. ***Estimated Impact of Nirsevimab on the Incidence of Respiratory Syncytial Virus Infections Requiring Hospital Admission in Children < 1 Year, Weeks 40, 2023, to 8, 2024, Spain****. Influenza Other Respir Viruses. 2024 May;18(5):e13294. doi: 10.1111/irv.13294. PMID: 38716791; PMCID: PMC11077568. https://onlinelibrary.wiley.com/doi/10.1111/irv.13294*

Methods

- *Proxy* of RSV hospitalisations
  - SARI hospitalitations rate x RSV positivity, by region, age group and sex
  - Limitation: age cutoff <1 year only available for 2022-23 and 2023-24 (only 1 season for reference)
- Extrapolated to the total number of children <1 years in Spain to estimate the total number of hospital admissions due to RSV
  - Observed in 2023-24 in <1 years (O)
  - Expected in 2023-24 in <1 years (E):
    - ✓ directly taken from the previous season 2022-23, or
    - ✓ corrected by th background change in RSV incidence beween current and past season in groups not targeted for nirsevimab – either total population or children 1-4 years of age (scaling factor)
- Relative Risk = O/E ; Absolute Impact = E - O

Results: *proxy* RSV hospitalisation rate





Results

TABLE 1 | Estimated number of respiratory syncytial virus (RSV) hospitalisations in Spain, by age group.

	Observed (O), weeks 40, 2022, to 8, 2023	Observed (O), weeks 40, 2023, to 8, 2024	Scaling factor (2023/24 vs. 2022/23)	Model	Expected (E) in <1 year, 2023/24[a]	Incidence ratio (O/E) in <1 year	Averted hospitalisations (E − O) in <1 year
<1 year	13,120	3357	NA	Crude	13,120	0.26	9763
1–4 years	4494	4357	0.97	A	12,721	0.26	9364
1–110 years	19,688	19,856	1.01	B	13,233	0.25	9875

Note: Number of cases between weeks 40 to 8 are estimated for seasons 2022/23 and 2023/24[a] and referred to as observed (O). Expected cases (E) in < 1-year-olds in 2023/24 are directly obtained from the observed cases in 2022/23 in < 1-year-olds in the 'crude' analysis or by applying to these the scaling factor from 1- to 4-year-olds (Model A) or from 1- to 110-year-olds (Model B). Incidence ratios and number of averted RSV hospitalisations are then computed.
Abbreviation: NA, not applicable.
[a]The RSV *proxy* hospitalisation rates are applied to the population size by age group and autonomous community; data are aggregated across autonomous communities for the totals by age groups shown in the table. Numbers are not reproducible by hand-calculation due to the inclusion of multiple decimal positions.

There were 74% less RSV hospitalisations than expected in children <1 years of age during season 2023-24, which could be attributable to nisevimab. This would translate into close to 10,000 RSV hospitalisations averted

Conclusions

- Surveillance data could be timely used to evaluate the introduction of a new population-level preventive intervention, such as nirsevimab
- Advantages include readily available data, easy to use methods, and high representativeness
- Limitations were insufficient sample size, particularly with high uptake, possible bias due to using hospital controls and limitted data quality
- Nirsevimab administration in newborns without recorded comorbidities was associated to an 84% reduction in the risk of RSV hospital admission, even higher in children <1 month of age
- The number of hospital admissions in children <1 year of age was 74% lower than expected during the season, which translated into close to 10,000 hospital admissions averted

Acknowledgements

- All the participants in SiVIRA in Spain, within the ARI surveillance in Primary Care and SARI surveillance in hospitals
- ECDC support through initiatives “ECDC SARI Network“, “ECDC COVID-VE” and “Vaccine Effectiveness, Burden and Impact Studies (VEBIS) of COVID-19 and Influenza”
- Influenza & ORV surveillance Units at National Centre of Epidemiology and National Centre of Microbiology (Carlos III Health Institute)

Many thanks for you attention!