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Original Article

Systematic review and meta-analysis of respiratory syncytial virus vaccines and their impact on respiratory tract infections in children under 5 years

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Respiratory syncytial virus is the main cause of respiratory tract infections in infants and children. This study systematically reviewed and conducted a meta-analysis of published data on four types of respiratory syncytial virus vaccines and their effect on respiratory tract infections. After screening of 910 studies, 16 studies involving 1189 participants aged 0 to 5 years were included in the analysis. We observed that vector-based vaccines demonstrated a significant reduction in the incidence of lower respiratory tract infections (vector based: RR: 0.47, 95% CI: 0.32–0.69; p = 0.0001), when compared to other vaccines. The study also identified that the c-DNA vaccines showed a significant increase in the incidence of upper respiratory tract infections compared to placebo groups (patients: 63.81%; placebo group: 37.25%; RR: 1.69, 95% CI: 1.17–2.46; p = 0.005). All vaccines, except c-DNA, showed reduced incidences of respiratory tract infections, with vector-based vaccines having a significant impact in reducing respiratory tract infections in infants and children.

Keywords: human respiratory syncytial virus; respiratory tract infections; vaccines; immunization; systematic review; meta-analysis.

Introduction

Respiratory syncytial virus (RSV) is the main virus that causes lung and breathing infections. It is considered as one of the most common reasons for hospitalization in infants and children worldwide.(1) RSV primarily causes upper respiratory tract infections (URTI), but it has the potential to progress to lower respiratory tract infections (LRTI), which can lead to severe complications. URTI caused by RSV typically present with symptoms such as rhinorrhea, nasal congestion, cough, sneezing, fever, and myalgia. In contrast, LRTI present with more severe symptoms including bronchitis, rhonchorous breath sounds, tachypnea, use of accessory muscles, wheezing, viral pneumonia, hypoxia, lethargy, apnea, and in some cases, acute respiratory failure.(2,3) Pediatric populations are considered to have high risk of developing severe RSV infections, particularly preterm and children suffering from chronic lung disease of prematurity, congenital heart disease, Down syndrome, immunodeficiencies, airway or neuromuscular abnormalities, or cystic fibrosis.(4)

In 2019, the global burden of RSV was estimated to cause 33 million cases of RSV-associated lower respiratory infections in young children. RSV infection remains a significant cause of early childhood mortality, with more than 100,000 deaths annually among children under 5 years of age worldwide. Notably, over 45,000 of these deaths occur in infants aged 0-6 months, representing 3.6 % of all deaths in children aged 28 days to 6 months.(5) These statistics highlight the substantial public health burden posed by RSV, underscoring the need for effective preventive strategies, including

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vaccines and therapies, to reduce RSV-related morbidity and mortality in vulnerable populations.

RSV is an enveloped, single-stranded RNA virus in the *Pneumoviridae* family.[6] It is classified into two subgroups, A and B, with subgroup A being more virulent due to variations in the G protein. The RSV genome consists of 15.2 kilobases of non-segmented RNA encoding 11 viral proteins, including nonstructural proteins (NS1, NS2), nucleoprotein (N), matrix protein (M), and the surface glycoproteins G, F, and SH. The G and F proteins play key roles in RSV binding to and entering host cells. The G protein facilitates attachment, while the F protein mediates viral entry by fusion with the host cell membrane. These interactions are critical for infection and immune modulation, making them important targets for antiviral therapies and vaccines.[7]

Globally, there remains a significant gap in the establishment of universal guidelines for the management and prevention of RSV infections in children, leading to inconsistent approaches across regions.[8] RSV treatment largely focuses on preventive strategies and supportive care, with management strategies varying based on the severity of the infection. For URTI caused by RSV, symptomatic relief is the primary approach. This includes nasal saline irrigation, antipyretics to reduce fever, and ensuring adequate hydration. In contrast, LRTI, particularly severe cases, require more intensive management, including oxygen therapy, mechanical ventilation, and intravenous fluids to address hypoxemia and respiratory distress. Antiviral therapy such as ribavirin may be used in severe RSV LRTI cases, particularly in high-risk patients, including immunocompromised individuals. However, its efficacy in routine treatment is debated, and it is not commonly used in general practice. In addition to treatment, prevention plays a critical role in reducing the impact of RSV. Monoclonal antibodies, such as Palivizumab and Nirsevimab, are used in infants to prevent hospitalization. Notably, Palivizumab is not a treatment for active infection, but serves as a prophylactic to prevent severe RSV disease in high-risk infants. On the other hand, Nirsevimab has demonstrated over 80 % efficacy in clinical trials in preventing RSV-associated LRTI and hospitalizations.[9,10,11]

In recent years, the development of RSV vaccines has garnered significant attention. Several vaccine candidates are in clinical development, utilizing a variety of approaches: live attenuated, chimeric, recombinant vector, subunit, particle-based, and nucleic acid vaccines.[12] In May 2023, the U.S. FDA approved Arexvy (RSVPreF3), marking it as the first RSV vaccine specifically aimed at preventing RSV LRTI in adults aged 60 years and older.[13] A few months later, in August 2023, Abrysvo (RSVPreF), became the first vaccine approved by the FDA for use in pregnant women to prevent RSV-related LRTI and severe LRTI in infants aged 0 to 6 months. Despite the significant progress in vaccine development, safety concerns have been raised regarding RSV vaccines, highlighting the need for continued research to ensure their safety across various populations. The objective of this study was to systematically review and perform a meta-analysis of published data evaluating the efficacy of various RSV vaccines in preventing LRTI and URTI in infants and children.

Materials and Methods

The systemic review was conducted and presented in conferred with the recommendations of the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA).[14]

Search approach

A comprehensive literature search was conducted across PubMed and Web of Science up to September 30, 2024, to identify relevant studies on RSV vaccines. Additionally, ClinicalTrials.gov was searched for registered clinical trials, and in cases where trial results were not publicly available, supplementary data were sought through Google Search and other relevant sources. The search strategy incorporated a combination of Medical Subject Headings (MeSH) and free-text terms using Boolean operators (AND, OR) to ensure a thorough and reproducible selection of studies. The following search terms were used: ("RSV vaccine" OR "Respiratory Syncytial Virus vaccine") AND ("RSV in infants" OR "Respiratory Syncytial Virus in infants") AND ("Immunization" OR "vaccination" OR "vaccine") AND "clinical Trials." Additionally,

reference lists of included studies and relevant systematic reviews were manually screened to identify further eligible articles.

Selection criteria

Studies were included and excluded based on the following criteria:

Inclusion criteria:

- vaccination of infants and children,
- administration of RSV vaccines,
- clinical trials comparing LTRI and UTRI (https://clinicaltrials.gov/), and
- studies evaluating the safety and efficacy of RSV vaccines.

Exclusion criteria:

- preclinical studies including *in vitro* experiments and animal models,
- studies on the vaccination of pregnant women or adults,
- non-randomized controlled trials,
- systematic reviews and meta-analyses,
- document types such as letters, editorials, non-English articles, non-original studies, case reports, conference abstracts, and unpublished articles were excluded during the search strategy using database filters where possible. Any remaining studies meeting these criteria were excluded during screening.

Data extraction and assessment process

The process of evaluating titles and abstracts was carried out independently by two authors to identify relevant studies meeting the inclusion criteria. Any discrepancies or disagreements between the authors were resolved through discussion, and if necessary, a third author was involved to make the final decision. The data extracted from the included studies consisted of the following key information: 1) study characteristics: first author's name, year of publication, journal of publication, study design (e.g., randomized controlled trial), sample size, intervention and comparator characteristics; 2) type of vaccine used: manufacturer/company name, PRNT (plaque reduction neutralization test) status; 3) participant characteristics: age, gender; 4) outcome measures: incidence of LRTI, incidence of respiratory tract infections (RTIs), adverse events in infants and children. The extraction aimed to capture both clinical and safety data to provide a thorough analysis of the vaccine's efficacy and safety profile.

Vaccine safety and efficacy evaluation

To evaluate the safety and efficacy of the vaccines included in the randomized clinical trials, we initially performed a narrative descriptive synthesis. The vaccines were classified into four distinct groups based on their type: 1) live attenuated vaccines: these vaccines are made from a weakened form of the RSV strain (typically RSV strain A2 or occasionally strain B). The weakened virus is used to stimulate an immune response without causing disease; 2) cDNA-derived vaccines: these vaccines utilize cDNA clones derived from RSV (most commonly RSV subgroup A, strain A2). The cDNA is used to produce viral proteins that can trigger an immune response; 3) vector-derived vaccines: these vaccines employ modified viruses (such as adenovirus or PIV3) or vectors to deliver genetic material to the cells, thereby inducing an immune response to the RSV antigen, 4) other vaccines: RSV Pre-F: a protein subunit vaccine that contains the RSV F protein, stabilized in its "prefusion" (pre-F) state. This vaccine is designed to trigger an immune response against the RSV F protein (Table 1).

The study primarily focused on children aged 0-5 years. This group represents the most vulnerable age range for RSV infections with a higher risk of severe respiratory complications. We aimed to assess safety and efficacy of vaccines using different platforms in preventing LRTI and URTI events in this group.

Data analysis

RevMan 5.4.1 software (Cochrane Collaboration, Oxford, UK) was used for the meta-analysis. For categorical and continuous variables, Risk Ratio (RR) and Standardized Mean Difference (SMD) with a 95 % confidence interval (CI) was used to measure the effect of vaccines on infections. To assess heterogeneity

across the studies, the χ^2 test was performed. The random-effects model was utilized to analyze the p-value and I^2 statistics, which helped to determine the degree of inconsistency across the studies. To assess potential publication bias, funnel plots were generated using Review Manager 5.4.1. This visual tool helped detect any asymmetry that could indicate the presence of publication bias in the included studies.

Results

Characteristics of the included studies

This systematic review initially found 910 studies from three databases: PubMed (150), Web of Science (672), and Clinicaltrials.gov (88) (Fig. 1). After excluding duplicates and irrelevant records, 16 studies were evaluated in full text for eligibility involving 1189 participants aged 0 to 5 years, with 798 in the vaccine group and 391 in the placebo group. All 16 studies were randomized, placebo-controlled, double or quadruple-blind, multicenter trials, and they were approved for the trial by relevant ethics committees (Table 1 and 2). [15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30]

Efficacy of different types of RSV vaccine in LRTI and URTI

Efficacy of different type of vaccine in LRTI

Live attenuated vaccine in LRTI

A total of six studies were included in the analysis, involving 400 children who were investigated for LRTI. Of the 400 participants, 292 were in the vaccine group and 108 in the placebo group.[15,16,17,18,19,20] Based on these results, a random-effect model was applied for the combined analysis. The incidence of LRTI in the live attenuated vaccine group was 4.45 %, compared to 6.48 % in the placebo group, showing no statistically significant difference RR: 0.59, 95 % CI: 0.19–1.84; p = 0.26 (Fig. 2A, Table 3). No significant heterogeneity was observed I^2 = 25 %, p = 0.26 (Fig. 3A, Table 3). Funnel plot analysis indicated the presence of publication bias in the included studies. These findings suggest that while there may be a trend toward reduced LRTI incidence in the vaccine group, the difference did not reach statistical significance in this meta-analysis. Further investigation with larger sample sizes and robust study designs is warranted to draw more definitive conclusions.

Vector based vaccine in LRTI

Four studies were included in this analysis, describing the incidence of LRTI in participants receiving a vector -based vaccine. A total of 406 participants were analyzed, with 251 in the vaccine group and 155 in the placebo group.[21,22,23,24] Significantly lower incidence of LRTI was observed in the vaccine group (18.33 %) when compared to the placebo group (34.83 %) RR: 0.51, 95 % CI: 0.15–1.71; p = 0.008 (Fig. 2B, Table 3). Substantial heterogeneity was observed (I2 = 75 %, P= 0.28). Funnel plot analysis showed no evidence of publication bias. These results suggest that vector-based vaccines may provide a significant protective effect against LRTI. Further studies with diverse populations and long-term follow-ups are recommended to confirm these findings and assess broader applicability.

cDNA vaccine in LRTI

Data on the effectiveness of cDNA vaccines in preventing LRTI were extracted from four studies, encompassing a total of 156 participants. Among these, 105 were in the vaccine group and 51 in the placebo group.[25,26,27,28] The analysis did not demonstrate a significant difference in the incidence of LRTI between the vaccine group and the placebo group RR: 2.35, 95 % CI: 0.28–19.58; p = 0.67 (Fig. 2C, Table 3). Moreover, there was no significant heterogeneity was observed (I^2= 0, p= 0.43). Notably, funnel plot analysis revealed evidence of publication bias, suggesting potential limitations in the available data.

RSV Pre F vaccine in LRTI

Four This RSV Pre F vaccine preventive analysis included two studies which involves 227 participants. Among them 150 were in the vaccine group and 77 in the placebo group.[29,30] This analysis showed the LRTI incidence rate in the vaccine group (0.66 %) and 2.59 % in the placebo group RR: 0.55, 95 % CI:0.06-5.18; p = 0.60. This data showed the no significance effect on the LRTI infection in vaccine group (Fig. 2D, Table 3).

Table 1. Characteristics of the included studies.

Vaccine name	Type of vaccine	Route of administration	Trial/Phase	PRNT	Company	Sample size	Endpoint
RSV-A2 strain (RSV-ts) vaccine	Live attenuated vaccines	Intranasal and by aerosol	RCT/ Phase 3	Antibody plaque formation	National Jewish Hospital and Research Center, Denver, Colorado, USA	8	LTRI/UTRI[15]
ts-1 live attenuated vaccine	Live attenuated vaccines	Intranasal	RCT/ Nine individual trials	No	Vanderbilt University School of Medicine. Nashville, Tenn. USA	34	LTRI/UTRI[16]
Live Attenuated cpts530/1009 and cpts248/955	Live attenuated vaccines	Intranasal	RCT/ Phase 1	Yes	The Johns Hopkins University, Baltimore, Maryland 21205, USA	90	LTRI/UTRI[17]
RSV cpts-248/404 and PIV3-cp45 vaccine	Live attenuated vaccines	Intranasal	RCT/ Phase 1	Yes	Saint Louis University, St. Louis, Missouri, USA	48	LTRI/UTRI[18]
rA2cp248/404DSH and rA2cp248/404/1030DSH	Live attenuated vaccines	Intranasal	RCT	Yes	NIAID and other institutes	178	LTRI/UTRI[19]
MEDI-534	Live attenuated vaccine	Intranasal	RCT/ Phase 1	No	MedImmune LLC	49	LTRI/UTRI[20]
MEDI-559, a live attenuated intranasal vaccine	RSV strain A2 based vector vaccine	Intranasal	RCT/ Phase 1/2a	Yes	MedImmune LLC	104	LTRI/UTRI[21]
Ad26.RSV.preF	Adeno vectored virus vaccine	Intramuscular	RCT/ Phase 1 and 2	No	Janssen Vaccines & Prevention B.V	36	LTRI/UTRI[22]
ChAd155-Vectored RSV Vaccine	Chimpanzee adenoviral vector	Intramuscular	RCT/ Phase 1 and 2	-	GSK	82	LTRI/UTRI[23]
Adenovector (ChAd155-RSV)	Chimpanzee adenoviral vector	Intramuscular	RCT/ Phase 1 and 2	-	GSK	192	LTRI/UTRI[24]
Recombinant live attenuated RSV 6120/ ΔNS2/1030s	cDNA derived vaccine	Intranasal	RCT/ Phase 1	Yes	NIAID	50	LTRI/UTRI[25]
Recombinant live attenuated RSV cps2	cDNA derived vaccine	Intranasal	RCT/ Phase 1	Yes	NIAID	29	LTRI/UTRI[26]
RSV LID ΔM2-2 Vaccine	cDNA derived vaccine	Intranasal	RCT/ Phase 1	Yes	NIAID	32	LTRI/UTRI[27]
LID/ΔM2-2/1030s	cDNA derived version of RSV subgroup A, strain A2	Intranasal	RCT/ Phase 1	Immuno-plaque assay	NIAID	32	LTRI/UTRI[28]
RSV ΔNS2/ Δ1313/I1314L or RSV 276	Recombinant RSV strain A2	Intranasal	RCT/ Phase 1	Yes	NIAID	21	LTRI/UTRI[29]
RSV PreF3	Recombinant RSV prefusion F protein	Intramuscular	Phase 2	Yes	GSK	206	LRTI/URTI[30]

RCT: random clinical trial. PRNT: plaque reduction neutralization test. NIAID: National Institute of Allergy and Infectious Diseases. GSK: GlaxoSmithKline. RSV: respiratory syncytial virus. Key clinical trials evaluating various types of RSV vaccines tested in infants and children for the prevention of LRTI and URTI, information on vaccine name, type, route of administration, trial phase, neutralizing antibody response (measured by PRNT), sponsoring organization, sample size, and reported clinical endpoints are summarized.

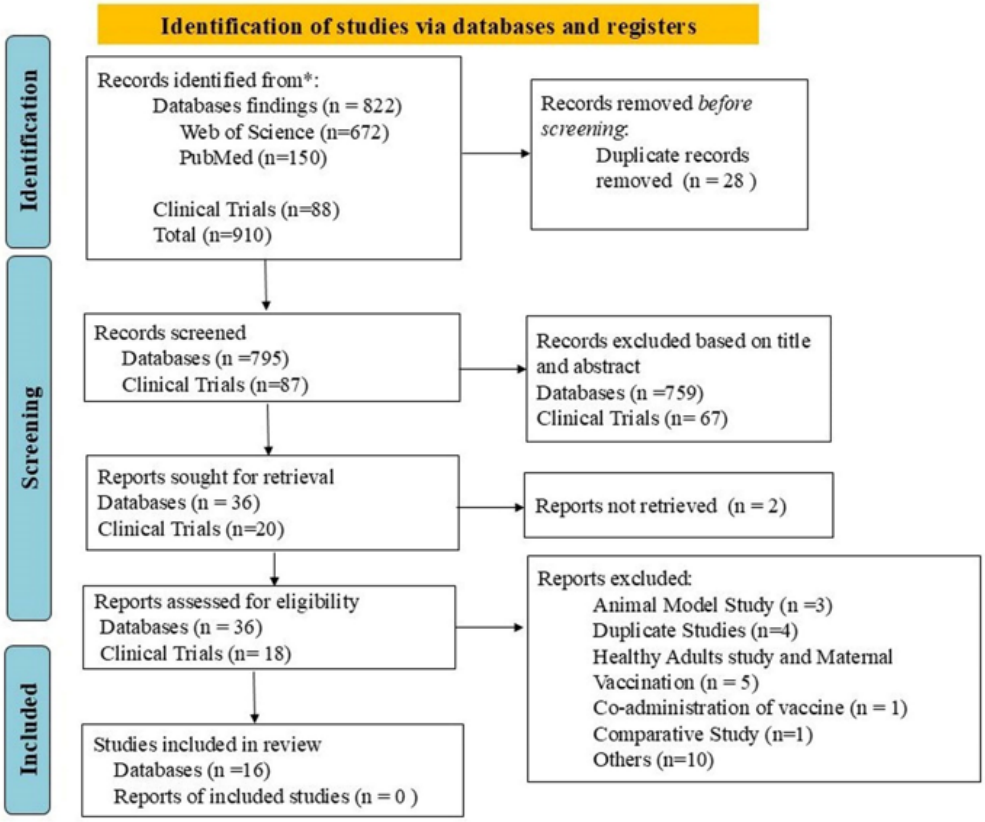

Fig. 1. Flow diagram of the study selection process.

Effect of different type of vaccine URTI

Live attenuated vaccine in URTI

Six studies were included in this evaluation. These studies provide data on URTIs in a total of 400 children.[15,16,17,18,19,20] Of the total, 292 participants were assigned to the vaccine group, while 108 were allocated to the placebo group. The analysis revealed no significant difference in the incidence of URTIs between the vaccine group (45.54 %) and the placebo group (34.25 %) RR: 1.32, 95 % CI: 0.82–2.11; p = 0.25. Moreover, no significant heterogeneity was observed I^2 = 42 %, p = 0.12 (Fig. 3A, Table 3). However, the funnel plot analysis suggested the presence of publication bias.

Vector based vaccine in URTI

The analysis included four studies on vector-based vaccines, reporting data on URTI for a total of 406 participants, with 251 in the vaccine group and 155 in the placebo group.[21,22,23,24] The analysis demonstrated a significantly lower incidence of URTI in the vaccine group (20.72 %) compared to the placebo group (42.36 %) RR: 0.53, 95 % CI: 0.34–0.82; p = 0.005. Additionally, no significant heterogeneity was observed I^2 = 32 %, p = 0.22 (Fig. 3B, Table 3). However, the funnel plot indicated the presence of publication bias.

cDNA vaccine in URTI

Data on URTI were obtained from four studies evaluating cDNA vaccines, involving a total of 156 participants, with 105 in the vaccine group and 51 in the placebo group.[25,26,27,28] The analysis showed a significantly higher incidence of URTI in the vaccine group (63.81 %) compared to the placebo group (37.25 %) RR: 1.59, 95 % CI: 0.82–3.11; p = 0.03. Notably, significant heterogeneity was observed among the studies I^2 = 64 %, p = 0.03 (Fig. 3C, Table 3).

RSV Pre F vaccine in URTI

This RSV Pre F vaccine in URTI infection data was evaluated form two studies which includes total 227 participants, 150 were in the vaccine group and 77 were in the placebo group.[29,30] The incidence of URTI

Table 2. Characterization of RSV vaccine approaches: infection targeted and demographic details.

Vaccine name	Design	Geographical area	Dose of vaccine	LRTI included	URTI included	Age
RSV-A2 strain (RSV-ts) vaccine[15]	Live attenuated	USA	Information not given	Wheezing	Information not given	0-6 years
RSV ts-1[16]	Live attenuated	USA	100 $TCID_{50}$	Pneumonia or bronchiolitis	Cough	11-19 months
cpts530/1009 and cpts248/955 live attenuated vaccines[17]	Live attenuated	USA	10^4 pfu or 10^5 pfu	Wheezing or pneumonia	Cough	< 1 year
RSV cpts-248/404 and PIV3 -cp45 vaccine[18]	Live attenuated	USA	4 x 10^5 pfu/ mL and 1 x 10^6 pfu/mL	Pneumonia	Rhinorrhea, pharyngitis, fever, cough, respiratory illness, or ear infections, nasal congestion	6–18 months
rA2cp248/404DSH and rA2cp248/404/1030DSH[19]	Live attenuated, recombinantly derived RSV vaccine candidates	USA	5 log10 pfu and 4 log10 pfu	Pneumonia	Cough, nasal congestion, laryngitis	< 6 months
MEDI-534[20]	Live attenuated	USA	10^4, 10^5, or 10^6 ($TCID_{50}$)	Wheezing or pneumonia	Cough, runny nose	1-5 years
MEDI-559, a live attenuated intranasal vaccine[21]	R strain A2 based vector vaccine	USA	10^5 ±0.5 FFU	Wheezing, bronchitis, bronchiolitis, croup, pneumonia, rales and rhonchi, apnea	Runny or stuffy nose, cough, laryngitis, epistaxis	0-2 years
Ad26.RSV.preF[22]	Adeno vectored virus vaccine	USA	5 x 10^{10} viral particles	Bronchiolitis, wheezing episodes, pneumonia	Runny nose, cough, pharyngitis	1-2 years
ChAd155-vectored RSV vaccine[23]	Chimpanzee adenoviral vector	Canada, Italy, Mexico, Panama, Spain, Taiwan and U.S.	1.5 x 10^{10} viral particles in 0.15 mL	Pneumonia, bronchiolitis	Common cold	1-2 years
Adenovector (ChAd155-RSV)[24]	Chimpanzee adenoviral vector	U.S., Spain, Poland, Italy, Canada, Mexico, Panama, Thailand	1.5 x 10^{10} viral particles in 0.15 mL	Pneumonia, bronchiolitis, wheezing,	Runny nose, mild cough, pharyngitis, fever accompanying upper respiratory symptoms	6-7 months
Recombinant live attenuated RSV 6120/ΔNS2/1030s[25]	cDNA derived vaccine	USA	$10^{5.3}$ pfu/ 0.5 mL	Bronchiolitis, wheezing, difficulty breathing	Runny nose, nasal congestion	0.5-5 years
Recombinant live attenuated RSV cps2[26]	cDNA derived vaccine	USA	10^6 to 10^7 PFU	Bronchiolitis, wheezing, difficulty breathing, pneumonia	Runny nose, nasal congestion, mild cough	0.5-2 years
RSV LID ΔM2-2 vaccine[27]	cDNA derived version of RSV subgroups A, strain A2	USA	10^5 PFU	Bronchiolitis, wheezing, respiratory distress, pneumonia	Rhinorrhea, nasal congestion, cough	0.5-2 years
LID/ΔM2-2/1030s[28]	cDNA derived version of RSV subgroups A, strain A2	USA	10^5 PFU	Bronchiolitis, wheezing, respiratory distress, pneumonia	Rhinorrhea, nasal congestion, cough	0.5-2 years
RSV ΔNS2/Δ1313/I1314L or RSV 276[29]	Recombinant RSV strain A2	USA	50 µg	Breathing difficulty	Coryza, cough	> 12 months
RSV PreF3[30]	Recombinant RSV prefusion F protein	U.S.	60/120 µg/0.5 mL	bronchiolitis, pneumonia, pyrexia, otitis media	Rhinorrhea, nasal congestion, cough	0-6 months

RSV: respiratory syncytial virus. FFU: focus forming unit. PFU: plaque forming unit. $TCID_{50}$: median tissue culture infectious dose 50.

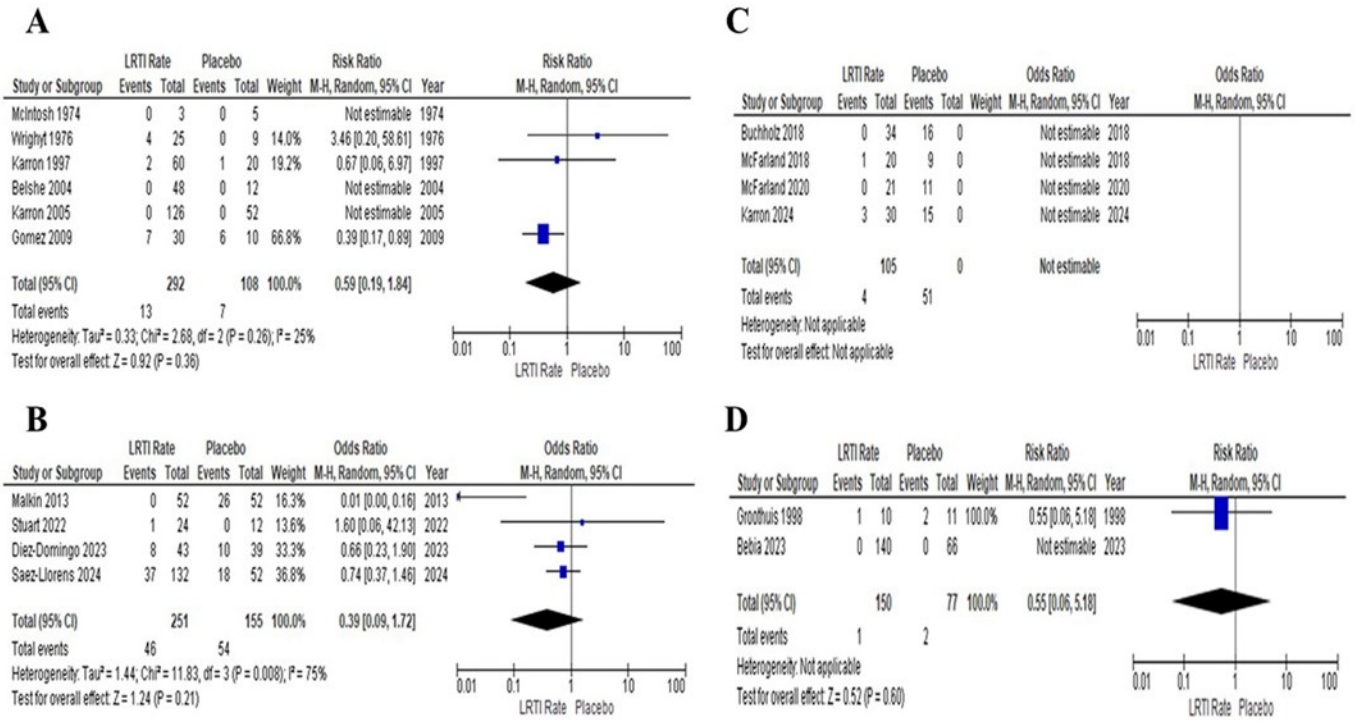

Fig. 2. Meta-analysis of the incidence of LRTI by A) Live attenuated, B) Vector-based, C) cDNA, D) Pre-F vaccines.

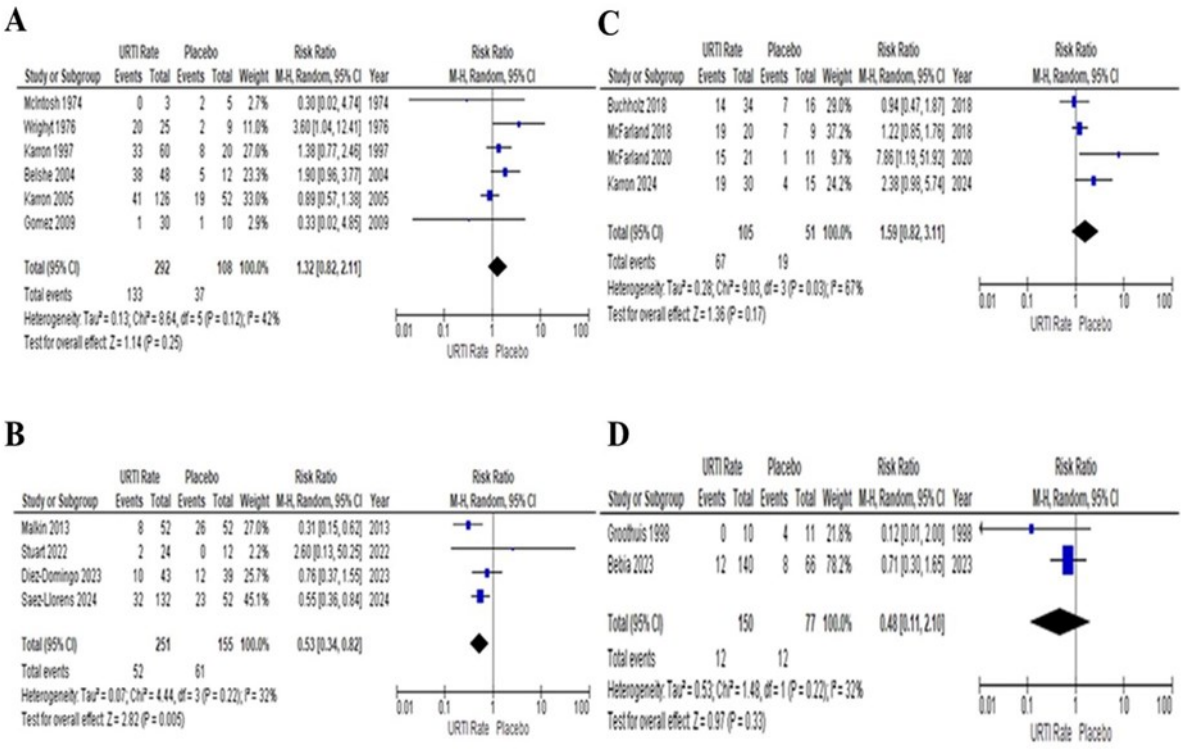

Fig. 3. Meta-analysis of the incidence of URTI by A) Live attenuated, B) Vector-based, C) cDNA, D) Pre-F vaccines.

Table 3. Meta-analysis of the incidence of LRTI and URTI by various types of vaccines.

Type of vaccine	N° of participants				RR (95% CI)	Heterogeneity					
	Vaccine	Infected N (%)	Placebo	Infected N (%)		Chi^2	df	p Value	I^2	Z value	P value
Lower respiratory tract infection											
Live attenuated vaccine	292	13 (4.45)	108	7 (6.48)	0.59 (0.19-1.84)	2.68	2	0.26	25 %	0.92	0.36
Vector based vaccine	251	46 (18.33)	155	54 (34.83)	0.51 (0.15-1.71)	11.95	3	0.008	75 %	1.09	0.28
cDNA vaccine	105	4 (3.81)	51	0 (0.0)	2.35 (0.28-19.58)	0.19	1	0.67	0 %	0.79	0.43
RSV Pre F vaccine	150	1 (0.66)	77	2 (2.59)	0.55 (0.06-5.18)	-	-	-	-	0.52	0.60
Upper respiratory tract infection											
Live attenuated vaccine	292	133 (45.54)	108	37 (34.25)	1.32 (0.82- 2.11)	8.64	5	0.12	42 %	1.14	0.25
Vector based vaccine	251	52 (20.72)	144	61 (42.36)	0.53 (0.34-0.82)	4.44	3	0.22	32%	2.82	0.005
cDNA vaccine	105	67 (63.81)	51	19 (37.25)	1.59 (0.82-3.11)	9.03	3	0.03	67%	1.36	0.17
RSV Pre F vaccine	150	12 (8)	77	12 (15.58)	0.48 (0.11- 2.10)	1.48	1	0.22	32%	0.97	0.33

RSV: respiratory syncytial virus. RR: Relative Risk. RR = 1.0 (no difference), RR < 1.0 (lower risk), and RR > 1.0 (higher risk).

infection in the vaccine group was lower (8 %) compared to the placebo group (15.58 %), RR: 0.48, 95 % CI: 0.11-2.10; p = 0.22. This study showed no significant heterogeneity I^2 = 32 %, p= 0.22, Chi^2 = 1.48, df = 1Z= 0.97, p= 0.33 (Fig. 3D, Table 3).

Discussion

RSV is a leading cause of both URTI and LRTI in infants and young children, with particularly high morbidity and mortality rates in low- and middle-income countries (LMICs).[31] The advent of vaccines to prevent RSV infection has been the subject of considerable research in recent years, driven by a greater understanding of the virus's immunological mechanisms and the use of structural immunology to design more effective antigens. A major challenge in RSV vaccine development has been to generate a robust immune response that provides long-lasting protection against RSV while minimizing immune evasion.[32] This has spurred the development of multiple vaccine platforms, including vector-based vaccines, c-DNA vaccines, and inactivated vaccines.[33] Despite significant advances, the relative efficacy of these different vaccine types in preventing both LRTI and URTI in children remains unclear, as sufficient comparative literature is limited.

In this systematic review and meta-analysis, we aimed to address this gap by evaluating the effectiveness of four major types of RSV vaccines in preventing LRTI and URTI in children aged 0-5 years. A total of 16 high-quality randomized controlled trials (RCTs) were included in this analysis, with a substantial body of evidence supporting the use of these vaccines. Our analysis was focused on two key outcomes: the prevention of LRTI and URTI, both of which are major contributors to RSV-related morbidity and mortality in children.

The findings of this study highlight several key observations. First, vector-based vaccines demonstrated

a significant reduction in the incidence of both URTI and LRTI when compared to other vaccine types. This is consistent with previous studies that have indicated the potential advantages of vector-based vaccine platforms in generating a strong and durable immune response with lower incidence of RTIs.[22,34]

The c-DNA vaccines showed a concerning trend, with a significant increase in the incidence of URTI compared to placebo groups. This observation highlights that while c-DNA vaccines hold promise in immunization strategies, their current formulations may require optimization to mitigate the potential for exacerbating respiratory conditions. These findings align with earlier studies, such as one evaluating RSV/6120/ΔNS2/1030s, a c-DNA-derived vaccine. It demonstrated immunogenicity and genetic stability in RSV-seronegative children but reported higher frequencies of respiratory infections in vaccine recipients compared to placebo groups.[28] Similarly, studies on RSVcps2 showed an incidence of upper respiratory illness in 41 % of vaccinated participants, comparable to the 44 % observed in placebo recipients, underscoring the need for comprehensive safety evaluations.[25] Our observations indicate that research on the use of the Pre-F vaccine in children remains limited. However, in adults, the RSV Pre-F vaccine has demonstrated efficacy in preventing RSV-associated LRTIs and acute respiratory illnesses, with no significant safety concerns reported.[35,36]

The current study revealed significant heterogeneity in evaluating the efficacy of c-DNA vaccines against URTI. This variability likely arises from differences in study design, including diverse vaccine formulations, dosing regimens, and trial endpoints across the included studies. For example, these vaccines use various constructs and vectors, each eliciting distinct immune responses, which complicates direct comparisons. Moreover, differences in participant characteristics, baseline health conditions, and geographic factors, contribute to the observed heterogeneity. These disparities make it challenging to draw uniform conclusions, emphasizing the need for standardized protocols and well-defined efficacy endpoints in future trials to ensure consistent and comparable evaluations.

This finding suggests that, despite the differences in vaccine platforms, the immunization strategies tested in this analysis generally offer protective benefits against RSV-related respiratory infections in young children. These results emphasize the importance of continued research into optimizing vaccine formulations and dosages to further reduce the burden of RSV disease.

Given the significant burden of RSV in LMICs, the findings of this study have several implications for vaccine strategies tailored to these regions. LMICs face unique challenges, including high RSV-related morbidity and mortality rates due to limited access to healthcare resources, higher prevalence of malnutrition, and coexisting respiratory conditions. For instance, vector-based vaccines, which demonstrated promising efficacy against URTI, could play a pivotal role if they are optimized for thermostability and simplified dosing schedules to accommodate resource-limited settings. Additionally, the concerning trend of increased URTI incidence associated with c-DNA vaccines underlines the importance of rigorous safety evaluations, especially in LMICs where healthcare systems may struggle to manage vaccine-related adverse effects.

Despite the promising findings, there are several limitations in this study that must be considered. First, the diversity of populations studied-including variations in geographical locations, ethnicity, and socio-economic status could influence the outcomes of vaccination. RSV infection rates and vaccine efficacy may differ across regions, and more research is needed to investigate how these factors impact vaccine effectiveness in diverse populations. Therefore, future studies should aim to stratify results by region, ethnicity, and other demographic factors to provide a more nuanced understanding of vaccine performance. Another significant limitation was the lack of a standardized approach in assessing the outcome markers for LRTI and URTI. In some studies, the definition of LRTI and URTI varied, potentially affecting the consistency of the results. Additionally, the follow-up duration varied across studies, which may influence the assessment of long-term efficacy. Future research should aim to establish standardized outcome measures for RSV-related infections and ensure consistent follow-up durations across studies.

This meta-analysis underscores the promise of vector-based vaccines in reducing the burden of RSV-related respiratory infections in children. However, the increased incidence of URTI observed with c-DNA vaccines raises critical safety concerns that warrant further investigation. To guide global RSV prevention strategies, future research must focus on refining vaccine formulations, standardizing efficacy measures, and conducting large-scale trials across diverse populations. Such efforts are crucial for developing a robust immunization strategy to combat RSV and improve outcomes for vulnerable pediatric populations.

Conclusions

Based on the current clinical outcomes, this meta-analysis suggests that vector-based vaccines show positive efficacy in preventing both URTI and LRTI, while cDNA vaccines demonstrate a potential increase in RTIs in children when compared to placebo. However, the effectiveness of these vaccines across multiple seasons remains unclear, and further studies are needed to evaluate the long-term efficacy and safety of these vaccines in preventing RSV-related infections in children.

Advances in molecular virology, immunology, and structural biology have significantly enhanced our understanding of the RSV infection and the molecular properties of the virus. As a result, the development of an effective RSV vaccine is expected to progress rapidly in the coming years. Vaccination is considered the most effective strategy for protecting infants and children from RSV, offering strong potential for preventing both LRTI and URTI. Therefore, RSV vaccines are increasingly recognized as a reliable and safe immunization approach for reducing the burden of RSV disease in young children. Further research focusing on optimizing vaccine formulations, evaluating safety profiles, and conducting long-term studies will be essential to confirm the findings of this meta-analysis and establish the role of RSV vaccines in global vaccination programs.

Conflict of interest

The authors declare that there is no conflict of interest.

Author's contributions

Charmi Jyotishi: conceptualization, methodology, analysis writing-original draft preparation.

Daksh Kunchala: conceptualization, methodology, analysis writing-original draft preparation.

Suresh Prajapati: making tables.

Reeshu Gupta: supervision and editing the manuscript.

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All authors have read and agreed to the published version of the manuscript.

References

1. Benítez-Guerra D, Piña-Flores C, Zamora-López M, Escalante-Padrón F, Lima-Rogel V, González-Ortiz AM, et al. Respiratory syncytial virus acute respiratory infection-associated hospitalizations in preterm Mexican infants: A cohort study. Influenza Other Respir Viruses. 2020;14(2):182-8. doi: https://10.1111/irv.12708.

2. Jain H, Schweitzer JW, Justice NA. Respiratory Syncytial Virus Infection in Children [monograph on the Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459215/. (Acces online: September 2024).

3. Wildenbeest JG, Lowe DM, Standing JF, Butler CC. Respiratory syncytial virus infections in adults: a narrative review. Lancet Respir Med. 2024;12(10):822-36. doi: https://10.1016/S2213-2600(24)00255-8.

4. Staebler S, Blake S. Respiratory Syncytial Virus Disease: Immunoprophylaxis Policy Review and Public Health Concerns in Preterm and Young Infants. Policy Polit Nurs Pract. 2021;22(1):41-50. doi: https://10.1177/1527154420965543.

5. Munro APS, Martinón-Torres F, Drysdale SB, Faust SN. The disease burden of respiratory syncytial virus in Infants. Curr Opin Infect Dis. 2023;36(5):379-84. doi: https://10.1097/QCO.0000000000000952.

6. Levy M, Chen JW, Kaiser JA, Park HS, Liu X, Yang L, et al. Intranasal respiratory syncytial virus vaccine attenuated by codon-pair deoptimization of seven open reading frames is genetically stable and elicits mucosal and systemic immunity and protection against challenge virus replication in hamsters. PLoS Pathog. 2024;20(5):e1012198. doi: https://10.1371/journal.ppat.1012198.

7. Battles MB, McLellan JS. Respiratory syncytial virus entry and how to block it. Nat Rev Microbiol. 2019;17 (4):233-45. doi: https://10.1038/s41579-019-0149-x.

8. Zhang XL, Zhang X, Hua W, Xie ZD, Liu HM, Zhang HL et al. Expert consensus on the diagnosis, treatment, and prevention of respiratory syncytial virus infections in children. World J Pediatr. 2024;20(1):11-25. doi: https://10.1007/s12519-023-00777-9.

9. Sun M, Lai H, Na F, Li S, Qiu X, Tian J, et al. Monoclonal Antibody for the Prevention of Respiratory Syncytial Virus in Infants and Children: A Systematic Review and Network Meta-analysis. JAMA Netw Open. 2023 6(2):e230023. doi: https://10.1001/jamanetworkopen.2023.0023.

10. Gatt D, Martin I, AlFouzan R, Moraes TJ. Prevention and Treatment Strategies for Respiratory Syncytial Virus (RSV). Pathogens. 2023;12(2):154. doi: https://10.3390/pathogens12020154.

11. Ananworanich J, Heaton PM. Bringing Preventive RSV Monoclonal Antibodies to Infants in Low- and Middle-Income Countries: Challenges and Opportunities. Vaccines (Basel). 2021;9(9):961. doi: https://10.3390/vaccines9090961.

12. Mazur NI, Terstappen J, Baral R, Bardají A, Beutels P, Buchholz UJ, et al. Respiratory syncytial virus prevention within reach: the vaccine and monoclonal antibody landscape. Lancet Infect Dis. 2023;23(1):e2-21. doi: https://10.1016/S1473-3099(22)00291-2.

13. Bellanti JA, Settipane RA. A trajectory of the FDA approval of the first vaccine targeting RSV: A greek tragedy with a happy ending. Allergy Asthma Proc. 2023;44(4):217-9. doi: https://10.2500/aap.2023.44.230037.

14. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. doi: https://10.1371/journal.pmed.1000097.

15. McIntosh K, Arbeter AM, Stahl MK, Orr IA, Hodes DS, Ellis EF. Attenuated respiratory syncytial virus vaccines in asthmatic children. Pediatr Res. 1974;8 (7):689-96.

16. Wright PF, Shinozaki T, Fleet W, Sell SH, Thompson J, Karzon DT. Evaluation of a live, attenuated respiratory syncytial virus vaccine in infants. J Pediatr. 1976;88(6):931-6.

17. Karron RA, Wright PF, Crowe JE Jr, Clements-Mann ML, Thompson J, Makhene M, et al. Evaluation of two live, cold-passaged, temperature-sensitive respiratory syncytial virus vaccines in chimpanzees and in human adults, infants, and children. J Infect Dis. 1997;176(6):1428-36.

18. Belshe RB, Newman FK, Anderson EL, Wright PF, Karron RA, Tollefson S, et al. Evaluation of combined live, attenuated respiratory syncytial virus and parainfluenza 3 virus vaccines in infants and young children. J Infect Dis. 2004;190(12):2096-103.

19. Karron RA, Wright PF, Belshe RB, Thumar B, Casey R, Newman F, et al. Identification of a recombinant live attenuated respiratory syncytial virus vaccine candidate that is highly attenuated in infants. J Infect Dis. 2005;191(7):1093-104.

20. Gomez M, Mufson MA, Dubovsky F, Knightly C, Zeng W, Losonsky G. Phase-I study MEDI-534, of a live, attenuated intranasal vaccine against respiratory syncytial virus and parainfluenza-3 virus in seropositive children. Pediatr Infect Dis J. 2009;28(7):655-8.

21. Malkin E, Yogev R, Abughali N, Sliman J, Wang CK, Zuo F, et al. Safety and immunogenicity of a live attenuated RSV vaccine in healthy RSV-seronegative children 5 to 24 months of age. PLoS One. 2013;8 (10):e77104. doi: https://10.1371/journal.pone.0077104.

22. Stuart ASV, Virta M, Williams K, Seppa I, Hartvickson R, Greenland M. Phase 1/2a Safety and Immunogenicity of an Adenovirus 26 Vector Respiratory Syncytial Virus (RSV) Vaccine Encoding Prefusion F in Adults 18-50 Years and RSV-Seropositive Children 12-24 Months. J Infect Dis. 2022;227(1):71-82. doi: https://10.1093/infdis/jiac407.

23. Díez-Domingo J, Sáez-Llorens X, Rodriguez-Weber MA, Epalza C, Chatterjee A, Chiu CH, et al. Safety and Immunogenicity of a ChAd155-Vectored Respiratory Syncytial Virus (RSV) Vaccine in Healthy RSV-Seropositive Children 12-23 Months of Age. J Infect Dis. 2023;227(11):1293-1302. doi: https://10.1093/infdis/jiac481.

24. Sáez-Llorens X, Norero X, Mussi-Pinhata MM, Luciani K, de la Cueva IS, Díez-Domingo J, et al. Safety and Immunogenicity of a ChAd155-Vectored Respiratory Syncytial Virus Vaccine in Infants 6-7 Months of age: A Phase 1/2 Randomized Trial. J Infect Dis. 2024;229(1):95-107. doi: https://10.1093/infdis/jiad271.

25. Buchholz UJ, Cunningham CK, Muresan P, Gnanashanmugam D, Sato P, Siberry GK, et al. Live Respiratory Syncytial Virus (RSV) Vaccine Candidate Containing Stabilized Temperature-Sensitivity Mutations Is Highly Attenuated in RSV-Seronegative Infants and Children. J Infect Dis. 2018;217(9):1338-46. doi: https://10.1093/infdis/jiy066.

26. McFarland EJ, Karron RA, Muresan P, Cunningham CK, Valentine ME, Perlowski C. Live-Attenuated Respiratory Syncytial Virus Vaccine Candidate With Deletion of RNA Synthesis Regulatory Protein M2-2 is Highly Immunogenic in Children. J Infect Dis. 2018;217 (9):1347-55. doi: https://10.1093/infdis/jiy040.

27. McFarland EJ, Karron RA, Muresan P, Cunningham CK, Libous J, Perlowski C, et al. Live Respiratory Syncytial Virus Attenuated by M2-2 Deletion and Stabilized Temperature Sensitivity Mutation 1030s Is a Promising Vaccine Candidate in Children. J Infect Dis. 2020;221(4):534-43. doi: https://10.1093/infdis/jiz603.

28. Karron RA, Luongo C, Woods S, Oliva J, Collins PL, Buchholz UJ, RSVPed Team. Evaluation of the Live-Attenuated Intranasal Respiratory Syncytial Virus (RSV) Vaccine RSV/6120/ΔNS2/1030s in RSV-Seronegative Young Children. J Infect Dis. 2024;229 (2):346-54. doi: https://10.1093/infdis/jiad281.

29. Groothuis JR, King SJ, Hogerman DA, Paradiso PR, Simoes EA. Safety and immunogenicity of a purified F protein respiratory syncytial virus (PFP-2) vaccine in seropositive children with bronchopulmonary dysplasia. J Infect Dis. 1998;177(2):467-9.

30. Bebia Z, Reyes O, Jeanfreau R, Kantele A, De Leon RG, García M, et al. Safety and Immunogenicity of an Investigational Respiratory Syncytial Virus Vaccine (RSVPreF3) in Mothers and Their Infants: A Phase 2 Randomized Trial. J Infect Dis. 2023; 228(3): 299-310. doi: https://10.1093/infdis/jiad024.

31. Driscoll AJ, Arshad SH, Bont L, Brunwasser SM, Cherian T, Englund JA, et al. Does respiratory syncytial virus lower respiratory illness in early life cause recurrent wheeze of early childhood and asthma? Critical review of the evidence and guidance for future studies from a World Health Organization-sponsored meeting. Vaccine. 2020;38(11):2435-48. doi: https://10.1016/j.vaccine.2020.01.020.

32. Graham BS. Biological challenges and technological opportunities for respiratory syncytial virus vaccine development. Immunol Rev. 2011;239(1):149-66.

33. Topalidou X, Kalergis AM, Papazisis G. Respiratory Syncytial Virus Vaccines: A Review of the Candidates and the Approved Vaccines. Pathogens. 2023;12 (10):1259. doi: https://10.3390/pathogens12101259.

34. Ma G, Xu Z, Li C, Zhou F, Hu B, Guo J, et al. Induction of neutralizing antibody responses by AAV5-based vaccine for respiratory syncytial virus in mice. Front Immunol. 2024;15:1451433. doi: https://10.3389/fimmu.2024.1451433.

35. Walsh EE, Pérez Marc G, Zareba AM, Falsey AR, Jiang Q, Patton M, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. N Engl J Med. 2023;388(16):1465-77. doi: https://10.1056/NEJMoa2213836.

36. Kotb S, Haranaka M, Folschweiller N, Nakanwagi P, Verheust C, De Schrevel N, et al. Safety and immunogenicity of a respiratory syncytial virus prefusion F protein (RSVPreF3) candidate vaccine in older Japanese adults: A phase I, randomized, observer-blind clinical trial. Respir Investig. 2023;61(2):261-9. doi: https://10.1016/j.resinv.2022.11.003.

Revisión sistemática y metaanálisis de las vacunas contra el virus respiratorio sincitial y su repercusión en las infecciones de las vías respiratorias en niños menores de 5 años

Resumen

El virus sincitial respiratorio es la principal causa de infecciones de las vías respiratorias en lactantes y niños. Este estudio revisó sistemáticamente y realizó un metanálisis de los datos publicados sobre cuatro tipos de vacunas contra el virus sincitial respiratorio y su efecto en las infecciones de las vías respiratorias. Tras revisar 910 estudios, se incluyeron en el análisis 16 estudios con 1189 participantes de 0 a 5 años. Se observó que las vacunas basadas en vectores demostraron una reducción significativa de la incidencia de infecciones de las vías respiratorias inferiores (basadas en vectores: RR: 0,47; IC del 95%: 0,32-0,69; p = 0,0001), en comparación con otras vacunas. El estudio también identificó que las vacunas c-ADN mostraron un aumento significativo en la incidencia de infecciones del tracto respiratorio superior en comparación con los grupos placebo (pacientes: 63,81%; grupo placebo: 37,25%; RR: 1,69; IC 95%: 1,17-2,46; p = 0,005). Todas las vacunas, excepto la c-ADN, mostraron una menor incidencia de infecciones de las vías respiratorias, y las vacunas basadas en vectores tuvieron un impacto significativo en la reducción de las infecciones de las vías respiratorias en lactantes y niños.

Palabras clave: virus sincitial respiratorio humano; infecciones del sistema respiratorio; vacunas; inmunización; revisión sistemática; metaanálisis.

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