



101034339 – PROMISE

Preparing for RSV Immunisation and Surveillance in Europe

WP2 – Preparation for future RSV product assessment

D2.4 Report on identification of adverse events for safety evaluations of RSV vaccination and monoclonal antibodies

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Definitions

- **Participants** of the PROMISE Consortium are referred to herein according to the following codes:
 1. **UEDIN.** The University of Edinburgh (United Kingdom)
 2. **UMCU.** Universitair Medisch Centrum Utrecht (Netherlands)
 3. **UA.** Universiteit Antwerpen (Belgium)
 4. **Imperial.** Imperial College of Science, Technology and Medicine (United Kingdom)
 5. **UOXF.** The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom)
 6. **THL.** Terveystieteiden ja Hyvinvoinnin Laitos (Finland)
 7. **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu (Netherlands)
 8. **NIVEL.** Stichting Nederlands Instituut voor Onderzoek van de Gezondheidszorg (Netherlands)
 9. **TUCH.** Varsinais-Suomen Sairaanhoidopiirin Kuntayhtymä (Finland)
 10. **TEAMIT.** TEAM IT Research, S.L. (Spain)
 11. **ReSViNET.** Stichting Resvinet (Netherlands)
 12. **SSI.** Statens Serum Institut (Denmark)
 13. **SERGAS.** Servizo Galego de Saúde (Spain)
 14. **PENTA.** Fondazione PENTA - For the treatment and care of children with HIV and related diseases - ONLUS (Italy)
 15. **FISABIO.** Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (Spain)
 16. **MLU.** Martin-Luther-Universitaet Halle-Wittenberg (Germany)
 17. **SP.** Sanofi Pasteur, S.A. (France)
 18. **GSK.** GlaxoSmithKline plc (United Kingdom)
 19. **JANSSEN.** Janssen Pharmaceutica, N.V (Belgium)
 20. **Novavax.** Novavax, Inc. (United States)
 21. **Pfizer.** Pfizer Limited (United Kingdom)
 22. **AZ.** AstraZeneca AB (Sweden)

- **Grant Agreement.** (Including its annexes and any amendments) The agreement signed between the beneficiaries of the action and the IMI2 JU for the undertaking of the PROMISE project (Grant Agreement No. 101034339).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The PROMISE Consortium, comprising the above-mentioned participants.
- **Consortium Agreement.** The agreement concluded amongst PROMISE participants for the implementation of the Grant Agreement. The agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Abbreviations

Acronym / Abbreviation	Meaning
RSV	Respiratory syncytial virus
mAbs	Monoclonal antibodies
SAE	Serious adverse event
ECDC	European Centre for Disease Prevention and Control
AESI	Adverse event of special interest
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
EFPIA	European Federation of Pharmaceutical Industries and Associations
SPEAC	Safety Platform for Emergency Vaccines
mRNA	Messenger ribonucleic acid
RCT	Randomised Controlled Trial
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision

Abstract

This study, conducted as part of Work Package 2 (WP2) within the PROMISE Consortium, focuses on preparing for the post-licensure safety evaluation of respiratory syncytial virus (RSV) vaccines and monoclonal antibodies (mAbs). The objective is to identify adverse events of special interest (AESIs) for safety assessments in various vaccine target age groups, including infants, children, pregnant women, adults, and older adults (≥ 60 years).

The methodology involved a comprehensive literature review of clinical trial databases and expert consultations. We incorporated lists of AESIs from the Brighton Collaboration Safety Platform for Emergency Vaccines (SPEAC) as well as lists provided by the European Federation of Pharmaceutical Industries and Associations (EFPIA) partners. Background incidence rates of the identified AESI from Denmark were presented to support any rapid assessment of potential safety signals.

A total of 24 and 10 serious adverse events (SAEs) were selected as AESIs safety endpoints for RSV vaccines and mAbs, respectively, based on clinical trial data. For RSV vaccines, 8 AESIs were identified for pregnant women receiving sub-unit unadjuvanted vaccines, with 4 AESIs in infants from maternal vaccination programs. Selected AESIs included 2 for infants and children (up to 24 months), 6 for older adults (≥ 60 years), and 4 for adults. Regarding mAbs, 8 AESIs were selected in infants and children (up to 24 months) with pre-existing health conditions, following anaphylaxis with motavizumab or palivizumab. Additionally, 2 SAEs were identified in infants (up to 12 months) without pre-existing health conditions, vaccinated with nirsevimab or suptavumab. Seven additional AESIs were sourced from the SPEAC list.

The utilisation of diverse methodological approaches broadened the sources and inclusivity of potential safety endpoints. However, the study acknowledges limitations, and recommendations for AESIs for future safety evaluations should be interpreted within this context.

1. Introduction

Human respiratory syncytial virus (RSV) can cause severe disease in the very young, elderly and in high-risk groups. It is estimated that RSV was associated with 33 million cases of acute lower respiratory tract infection (ALRI), 3.6 million ALRI hospitalisations and 101,400 RSV-attributable deaths in children <5 years globally in 2019¹. In the EU, an average of 245,244 yearly hospital admissions with a respiratory infection were associated with RSV in children under the age of 5, with most cases occurring among children aged less than 1 year (75%). Infants aged less than 2 months represented the most affected group (71.6 per 1,000 children)². RSV was further associated with 1.5 million episodes in older adults aged ≥65 years residing in industrialised regions in 2015³. Additionally, it was estimated that globally in 2015, RSV was associated with 336,000 hospital admissions and 14,000 in-hospital deaths in older adults aged ≥65 years³. Its high disease burden has made RSV a priority for vaccine development for over 50 years targeted for children, pregnant women to protect infants^{4,5}, and adults aged ≥60 years⁶.

In the last 5 years substantial progress has been made in the development of immunisation products against RSV. In 2023, the European Medicines Agency as well as the Food and Drug Administration approved the first RSV vaccine suitable for protecting infants up to six months of age as well as two vaccines for older adults 60 years of age and older^{7,8}. More than 30 RSV immunisation products are in clinical development based on various approaches: recombinant vector, subunit, particle-based, live attenuated, chimeric, and nucleic acid vaccines; and monoclonal antibodies (mAbs)^{4,5,9,10}. A new monoclonal antibody product was approved for the prevention of RSV lower respiratory tract disease in newborns and infants in November 2022¹¹.

Post-licensure safety evaluation of the new RSV vaccines and mAbs is essential for the successful implementation into routine immunisation schedules. In order to identify safety outcomes of interest for post-licensure surveillance, this study aims to systematically review and synthesise evidence on the safety data from the RSV immunisation clinical trials, with a focus on serious adverse events (SAEs) registered in RSV vaccines and monoclonal antibodies clinical trial studies. Overall, the results of this study support the preparation for future RSV product assessment in line with the goals of Work Package 2 (WP2) of the PROMISE (Preparing for RSV Immunisation and Surveillance in Europe) Consortium¹².

2. Objective

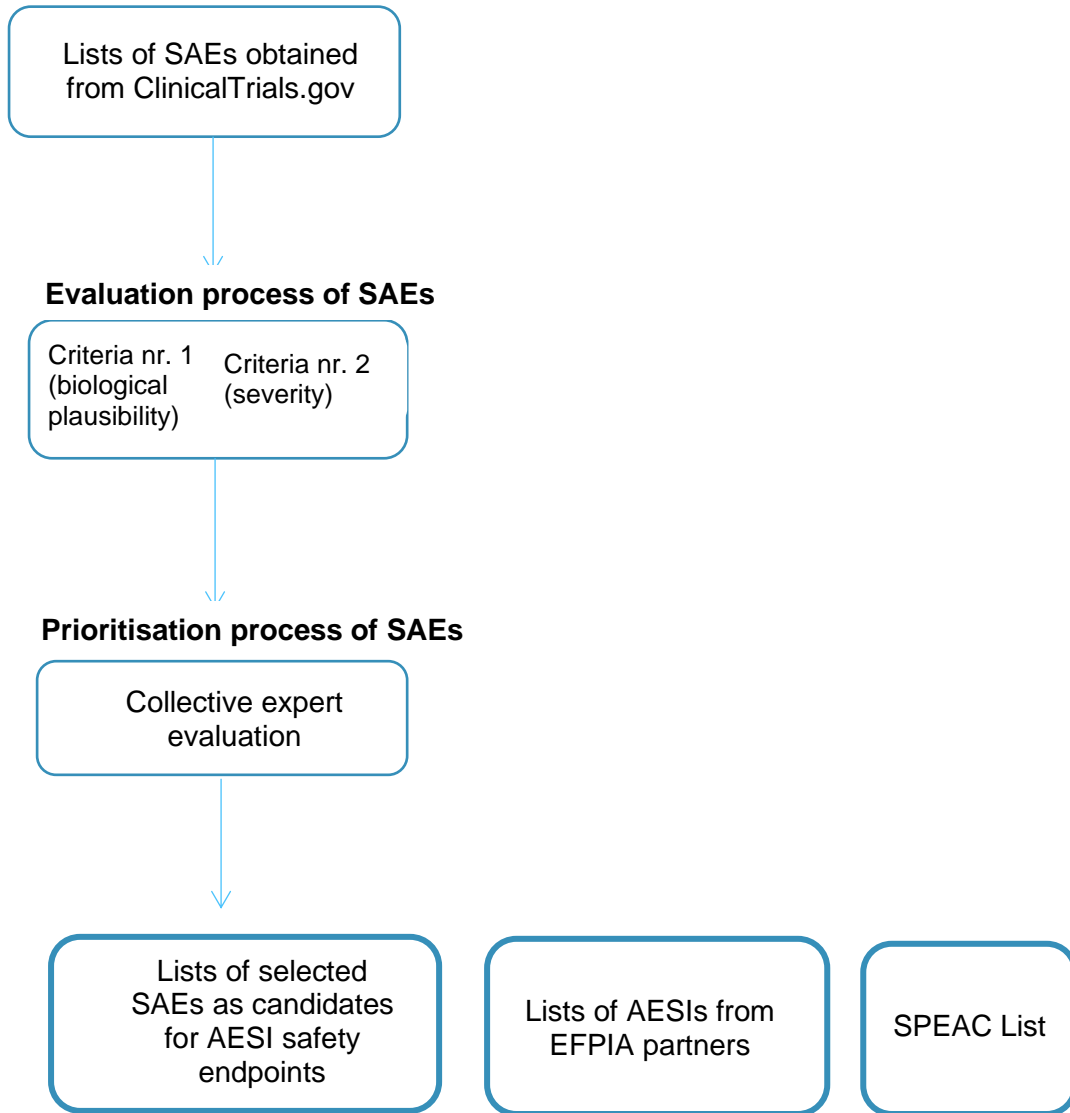
The aim of this study is to identify adverse events of special interest (AESIs) for post-licensure safety evaluations of RSV vaccination and mAbs among infants and children, pregnant women, adults and older adults ≥ 60 years of age.

3. Methods

We employed diverse methodological approaches to comprehensively identify potential AESIs for future post-licensure safety assessment. The AESIs were obtained from SAEs that were evaluated and prioritised by experts involved in this study. Based on the evaluation and prioritisation process, the SAEs were either included or excluded as AESI candidates. We consider SAEs to be clinically important in the context of post-licensure studies, for example, in the context of registry-based studies. Such studies utilise data from hospital registers, e.g., in the context of Nordic countries, which include records on health events requiring hospital contact. Due to the scarcity of real-world studies and safety evidence available for RSV vaccines and mAbs during the study period from November 2021 to November 2023, we adopted various methodologies as illustrated in Figure 1. The figure provides an overview of each methodological approach employed, and the subsequent sections elaborate on the specifics of each method.

Figure 1. Overview of the mixed approaches to identify AESIs

Clinical trial database review



3.1 Clinical trial database review

A systematic review of clinical trial results was conducted in the ClinicalTrials.gov¹³ database to identify SAEs following RSV vaccination or mAbs prophylaxis, according to specific vaccine platforms and types of mAbs, among infants and children, pregnant women, adults and older adults. The search was conducted using pre-defined search terms (see section 3.1.1). The search was limited to studies with the study results available up to 30 November 2022. The identified studies were systematically reviewed according to set eligibility criteria (Table 1) and included in the evaluation process (see Section 3.2). Overall, the study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews¹⁴.

3.1.1 Search terms

RSV vaccines

The following search terms were applied:

Terms
Synonyms
vaccine
RSV
Respiratory syncytial virus

mAbs

The following search terms were applied:

Terms
Synonyms
monoclonal antibody
Antibodies, Monoclonal
Monoclonal immunoglobulin
Monoclonal protein
antibody
Immunoglobulins
Immune Globulins
Other Ab
monoclonal
RSV
Respiratory syncytial virus

The records were subsequently crosschecked with the PATH RSV Clinical Trial Tracker (Publication date 01 August 2022) to ensure that all relevant clinical trials were identified through the search. The tracker includes clinical trials for both RSV vaccines and mAbs¹⁵.

3.1.2 Database

We utilised the ClinicalTrials.gov database¹³, a comprehensive online registry of clinical trials, to identify and extract information pertaining to adverse events reported following RSV vaccination and mAbs therapy. ClinicalTrials.gov is maintained by the National Library of Medicine¹⁶ and serves as a valuable resource for researchers, clinicians, and the public to access detailed information about ongoing and completed clinical trials.

3.1.3 Eligibility criteria

Eligible studies had to have published results in the clinical trial registers and comprised interventional clinical trials assessing the SAEs as primary or secondary outcome measures. Studies conducted on the three main target populations (i.e., pregnant women, infants and young children, and older adults ≥ 60 years) as well as adults were considered for inclusion to identify as many registered SAEs as possible. In order to include a wide variety of SAEs, we did not differentiate between phases of clinical trials and considered all trials equally valuable. mAbs clinical trials studies conducted on individuals both with and without underlying medical conditions were eligible. The PICOS framework below (Table 1) was developed to identify relevant clinical trials according to the eligibility criteria¹⁷.

Table 1: PICOS Framework

Participants	Intervention	Comparison	Outcome	Study Design
Children - children 0-24 months of age who received the vaccine - infants 0-12 months who received vaccine - infants who did not receive the vaccine but were monitored based on maternal vaccination Older adults - ≥ 60 years of age Adults - 18+ years of age Pregnant women	RSV vaccination or mAbs	Placebo, other vaccines, other mAbs, no drug	SAEs	Interventional clinical trials

Pregnant women, infants and young children, and older adults ≥60 years are the main target groups for RSV vaccines. However, all require different approaches in post-licensure safety evaluations. Similarly, vaccine platform and composition of the RSV vaccines may induce various biological mechanisms and consequently impact approaches for safety evaluations. Based on these factors, we identified safety endpoints specific to each target groups as well as vaccine platform or type of mAbs.

Rationale for the selection of the participant (target) groups:

Pregnant women, susceptible to severe infections, gain direct protection themselves, the foetus and the newborn through vaccination during pregnancy. The potential transfer of maternal antibodies and reduced transmission further amplifies the benefits of such vaccinations. However, the limited inclusion of pregnant women in clinical trials necessitates prompt post-licensure evaluations to establish evidence on maternal and foetal safety. Drawing from significant experience with maternal vaccination, particularly with Tdap and influenza vaccines, it is crucial to anticipate and address potential safety issues that may arise.

Infants and children under 5 years are chosen for this study to identify safety endpoints for post-licensure evaluations of RSV vaccines, given their vulnerability to RSV infections. This selection is driven by the need to ensure vaccine safety in this age group, considering both biologically plausible outcomes like febrile seizures and potential spurious links to vaccination.

Individuals aged 60 years and above face increased vulnerability to serious adverse events. The real-world scenario for older adults often involves multi-morbidity and polypharmacy, making it challenging to predict specific safety issues. Monitoring a general composite measure of health in this age group is crucial, encompassing health-care utilisation, morbidity burden, and mortality risk. It is essential to consider that vaccinated elderly individuals may generally be in better health than their unvaccinated peers, posing a methodological challenge in estimating vaccine effectiveness and equally relevant for safety outcomes.

3.1.4 Definition of terms

Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above, should also usually be considered serious. Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm;

blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse¹⁸.

Adverse Event of Special Interest (AESI)

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such an event may require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties may also be needed (e.g., regulators)¹⁸.

Other adverse events

An adverse event that is not an SAE, meaning that it does not result in death, is not life-threatening, does not require inpatient hospitalisation or extend a current hospital stay, does not result in an ongoing or significant incapacity or interfere substantially with normal life functions, does not cause a congenital anomaly or birth defect; does not put the participant in danger, and does not require medical or surgical intervention to prevent one of the results listed above¹⁹.

Based on the definition of SAEs and AESIs above, we used the "SAEs" compared to the "Other adverse events" recorded in the clinical trials database. This approach enabled us to identify and prioritise the most clinically important endpoints for the post-licensure safety surveillance and further research.

3.1.5 Data collection and extraction

The identified studies from the clinical trials register were recorded to data collection forms (Supplementary Tables 1 and 2), separately for vaccines and mAbs. The data collection form included information about the clinical trials, such as date of results published, ID number, study phase, number of participants enrolled, age of participants, period of follow-up and vaccine platform or type of mAbs used. The purpose of the data collection form was to have an overview of the clinical trials conducted, to track included studies and to register updates to the review with new studies if relevant. The individual SAEs from each clinical trial included in this study were extracted using R. Subsequently, the extracted lists of SAEs were checked for duplicates for vaccines and mAbs separately, and duplicates were removed.

RSV vaccines

The study records from the clinical trials register were downloaded (Clinicaltrials.gov) as xml files and divided according to the target groups and vaccine platform, irrespective of the phase of the clinical trials. The SAEs, including all-cause mortality, were extracted using the xml2²⁰ and xlsx²¹ packages in R for each clinical study. The SAEs were extracted for both the vaccine and the placebo/control groups separately. The vaccine and the placebo/control groups were differentiated accordingly.

mAbs

Similarly, the data on mAbs were extracted from the xml files according to the target groups and were further subdivided based on whether the clinical trials were conducted on healthy (prevention) or non-healthy (treatment) participants. The SAEs were extracted for both the mAbs prophylaxis and the placebo/control groups separately.

3.2 Evaluation process

In order to prioritise the clinically most important SAEs to be considered for further evaluations in post-licensure safety studies, we designed and conducted an evaluation process based on two criteria. Representatives from four European Federation of Pharmaceutical Industries and Associations (EFPIA) partner organisations and from two public health institutions were asked to evaluate the SAEs based on the following criteria:

- To the best of your knowledge, is there a likelihood of biological plausibility between vaccines/vaccine platforms in general and the SAE? (biological plausibility)
- In your opinion, how likely is this event life-threatening or likely to have a serious impact on quality of life? (severity)

For the purpose of this evaluation, the criterion of biological plausibility was based on whether the association between the vaccine, or monoclonal antibody, and the adverse event is plausible and consistent with current knowledge of the biology of the vaccine, or monoclonal antibody, and the adverse event²². The evaluation was based on a scoring scale from 1 to 5 (1-very unlikely, 2-unlikely, 3-undecided, 4-likely, 5-very likely).

The common disclaimer form outlining methodological considerations from the contributing EFPIA partners can be viewed in the Supplementary form 1. In summary, within the context of this evaluation, it is important to note that the views expressed are those of the individual safety officers who completed this assessment and do not necessarily reflect the views of EFPIA partners. The disclaimer clarifies that due to the absence of detailed case information, the evaluation considers the most severe potential outcome. Some SAEs were categorised as "3 undecided" when outcomes depended on various factors.

3.3 Prioritisation process

Once each SAE was evaluated with a score from 1 to 5 by the EFPIA and public health partners, the prioritisation process was initiated. The outcome of the SAE prioritisation process was a list of AESIs comprised of safety endpoints that we recommended for further safety evaluations. This process was conducted by an expert group comprised of safety officers, clinicians and pharmacoepidemiologists from collaborating EFPIA partners and public health institutions.

Firstly, the median score based on combined (EFPIA and public) scores was calculated for each SAE, for each of the two criteria. Secondly, all SAEs with a median score ≤ 2 (“unlikely”) in the first criteria (“biological plausibility”) were excluded and thus deprioritised for further prioritisation. Thereafter, each SAE with a median above 2 based on criteria 1 was assessed in expert group discussions. If experts reached consensus on the biological plausibility of the SAE and vaccine/mAbs, the SAE was further evaluated based on the median score of criteria 2 (“severity”). In order for the SAE to be included in the final list, the biological plausibility was established by the expert group (criteria 1 – “biological plausibility”) and the SAE was deemed to have an impact on quality of life or be life-threatening (criteria 2 – “severity”).

3.4 Lists of AESIs provided by EFPIA partners

Partners from GSK shared a suggested list of potential immune-mediated diseases (pIMDs) of interest, for possible evaluation in clinical vaccine studies²³ as well as a list of AESIs for investigation across all phases of maternal vaccine clinical trials (1-3). Partners from Sanofi made available a table of AESIs for the development program of RSV mAbs nirsevimab, and MK-11654. Moreover, AESIs considered for RSV-F maternal vaccine by Pfizer were extracted from publicly available sources. The purpose of these lists of AESIs was to complement the SAEs identified during the review of clinical trial database. The lists also served as background information for expert discussions in the prioritisation process described above.

3.5 SPEAC List of AESIs for vaccines

The list of identified AESIs was further complemented by the Brighton Collaboration Safety Platform for Emergency Vaccines (SPEAC) list of AESIs for COVID-19 vaccines²⁴. The SPEAC priority list of AESIs for COVID-19 vaccines was compiled in May 2020 and the listed AESIs were selected based on general criteria such as proven association with immunisation, vaccine platform or adjuvant, constituting theoretical concern based on immunopathogenesis or related to viral replication during wild type disease. COVID-19 vaccines were in approval or early implementation stages when this version of the SPEAC list was developed, which corresponds with the status of the RSV vaccines at the time of writing this report. We, therefore, decided to use this SPEAC list version to obtain AESIs potentially related to vaccination in general, prior to availability of any evidence from larger observational studies.

3.6 Background incidence rates

As proof-of-concept we provide background rates of the prioritised AESIs for older adults ≥ 60 years living in Denmark. A background incidence rate (BIR) of an adverse event is the incidence rate of the event one would observe in a given population in the absence of receipt of the vaccine or any other intervention^{25,26}.

A rapid response to evaluate a potential safety signal is key to maintain confidence in mass immunisation programs. The BIRs were used to calculate the number of expected cases of an event in a given population and time period in the absence of vaccine or other intervention that could be compared with the number observed following vaccination^{25,27,28}.

The BIRs in this report are comprised of primary or secondary diagnoses of inpatient or outpatient hospital contacts occurring between the years 2019-2022, and were obtained from the Danish National Patient Register²⁹. This type of register is likely to be a main source of data for post-licensure evaluations. The background rates are defined as the number of cases per 10,000 observed person-years. Outcomes with fewer than 5 observations were substituted with “<5” due to potentially identifiable personal information, and the background rates were not defined for these outcomes. Diagnoses in this register were coded using International Classification of Diseases 10th revision (ICD-10). We manually selected appropriate ICD-10 codes for each of the prioritised AESIs.

4. Results

4.1 RSV Vaccines

In total, 31 studies were included for the review of SAEs for RSV vaccines (Figure 2). Some studies cover multiple target groups e.g. both older adults and adults, or pregnant women and children. In total, 471 SAEs were identified from RSV vaccines clinical trials, after removal of duplicates. Table 2 below shows the total number of studies relevant for each target group. The children subset includes studies in children who received direct immunisation as well as those who received indirect immunisation through maternal programs.

Table 2: Numbers of clinical trials included for each target group.
Note: some clinical trials are represented in multiple target groups.

	CHILDREN	OLDER ADULTS	PREGNANT	ADULTS	TOTAL
RSV VACCINES	10	10	2	12	34

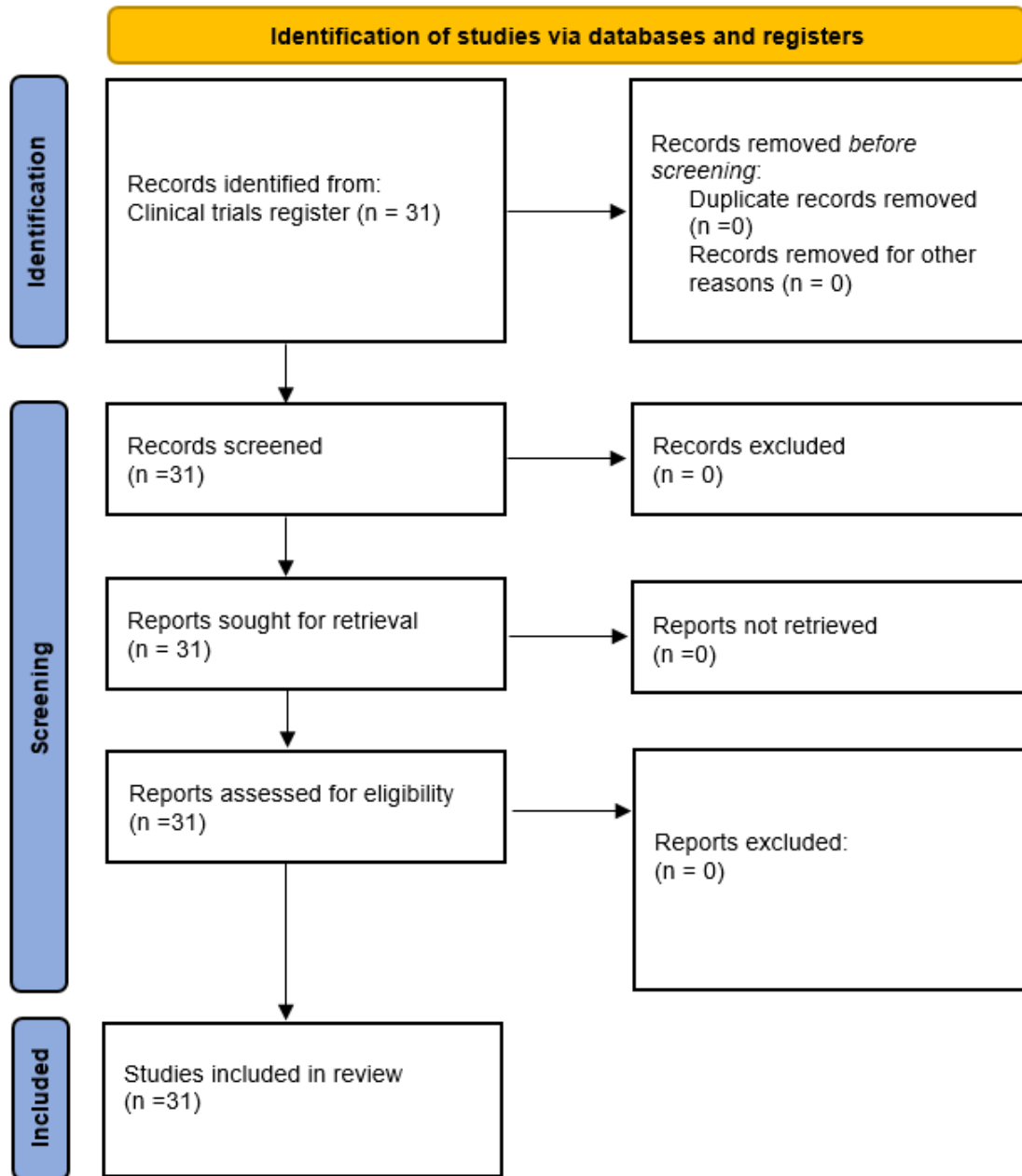


Figure 2: PRISMA Flow diagram of clinical trials records on RSV vaccines across all target groups and vaccine platforms identified and included in the review³⁰

The included clinical trials for the children target groups based on vaccine platforms are listed in the tables below. The children's group was limited to the age 0-24 months as no studies in children older than 2 years were identified. Table 3 below shows the clinical trials which were used in the review for each target group, by NCT numbers.

Table 3: Vaccine clinical trials included in the review by target group

Children and infants	Older adults	Pregnant women	Adults
NCT00493285	NCT02115815	NCT04126213	NCT02298179
NCT00686075	NCT02289820	NCT04032093	NCT02360475
NCT02794870	NCT02508194		NCT02491463
NCT02890381	NCT02873286		NCT02753413
NCT02927873	NCT03339713		NCT02956837
NCT03102034	NCT03572062		NCT03049488
NCT03227029	NCT04090658		NCT03213405
NCT03636906	NCT04657198		NCT03334695
NCT04126213	NCT03814590		NCT03529773
NCT04032093	NCT04841577		NCT03674177
10	10	2	NCT03814590
			NCT04071158
			12

4.2 Monoclonal antibodies

In total, 14 studies from clinical trials registers were included in the review of SAEs for mAbs (Figure 3). The studies were divided based on the participants' characteristics (pre-existing medical condition yes/no) and the target group. The pre-existing conditions included chronic lung disease of prematurity, hemodynamically significant congenital heart disease, and prematurity. In total, 1,062 SAEs were identified from mAbs clinical trials, after removal of duplicates.

Table 4: Numbers of clinical trials included for each target group

	CHILDREN	ADULTS	TOTAL
NO PRE-EXISTING MEDICAL CONDITION	4	2	6
WITH PRE-EXISTING MEDICAL CONDITION	8	0	8
			14

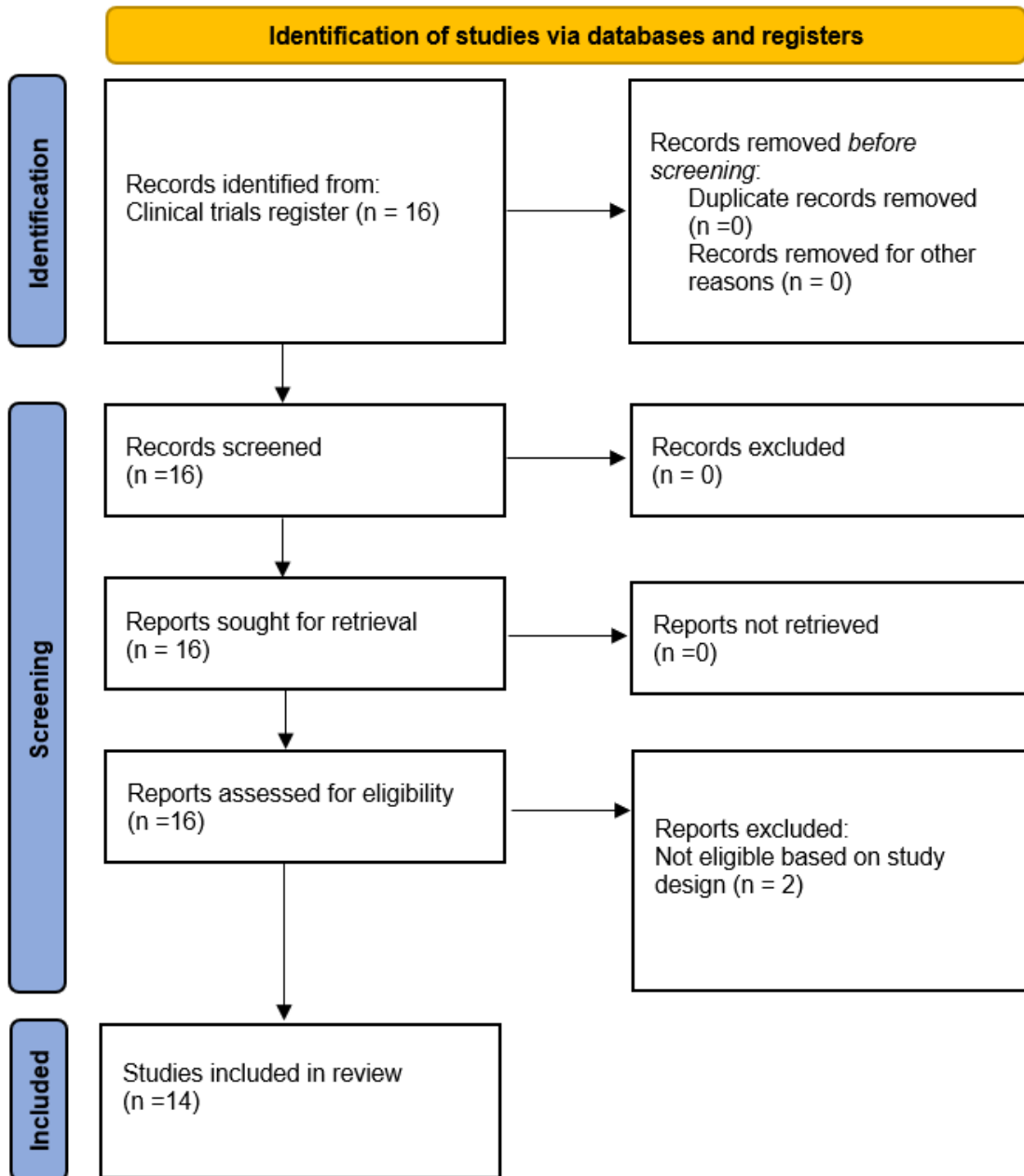


Figure 3: PRISMA Flow chart of clinical trials records for mAbs across all target groups and platform identified and included in the review ³⁰

Table 5 below shows the clinical trials which were used in the review for each target group, by NCT numbers.

Table 5: mAbs clinical trials included in the review by target group

Children and infants	Adults
NCT02290340	NCT04086472
NCT00192504	NCT02114268
NCT00421304	
NCT00435227	
NCT00129766	
NCT02878330	
NCT02325791	
NCT00316264	
NCT00113490	
NCT00121108	
NCT00538785	
NCT02968173	
12	2

4.3 Prioritised SAEs candidates

In total, 471 and 1,062 SAEs were identified from RSV vaccine and mAbs clinical trials, respectively, after removal of duplicates. Complete lists of SAEs including the evaluation scores for both the vaccines and mAbs are available upon request. Following the extraction, evaluation and prioritisation of the SAEs, lists of AESIs that are recommended for post-licensure studies of RSV vaccines and mAbs are presented in this section, according to the target groups.

4.3.1 RSV vaccines

In total, 24 SAEs were prioritised as AESI safety endpoints following RSV vaccination. The majority of events (n=8) occurred among pregnant women following vaccination with sub-unit adjuvanted and unadjuvanted vaccines. There was an agreement among the expert group to undertake the SAEs evaluation for this target group in a conservative manner as more rigorous safety monitoring is performed for maternal vaccines in pre-clinical and post-licensure settings.

Four AESIs were identified for infants monitored within maternal vaccination clinical trials of sub-unit unadjuvanted vaccines. Two AESIs were identified among infants and children 0-24 months vaccinated with live-attenuated vaccine. Six AESIs were identified among older adults ≥ 65 years and 4 AESIs among adults, following vaccination with sub-unit adjuvanted or unadjuvanted RSV vaccines. For each AESI, ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision)³¹ codes were identified to facilitate the utilisation of these safety endpoints in future post-licensure studies. The identified AESIs for each target group can be viewed in Table 6.

Table 6: Identified AESIs for RSV vaccines, by target groups

Adults

	Vaccine platform	System Organ Class	AESI	ICD-10
1	sub-unit adjuvanted	Endocrine disorders	Basedow's disease	E05.0
2	sub-unit adjuvanted	General disorders	Pyrexia	R50
3	sub-unit adjuvanted	Immune system disorders	Anaphylactic shock	T78.2 T78.0 T80.5 T88.6

4	sub-unit adjuvanted	Musculoskeletal and connective tissue disorders	Rheumatoid arthritis	M05.0 M05.1 M05.2 M05.3 M05.8 M05.9 M06.0 M06.1 M06.4 M06.8
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Older adults

	Vaccine platform	System Organ Class	AESI	ICD-10
1	sub-unit adjuvanted	Blood and lymphatic system disorders	Lymphadenopathy	R59
2	sub-unit adjuvanted	Gastrointestinal disorders	Abdominal pain	R10
3	sub-unit adjuvanted	Immune system disorders	Anaphylactic shock	T78.2 T78.0 T80.5 T88.6
4	sub-unit adjuvanted	Nervous system disorders	Acute disseminated encephalomyelitis	G04.0

5	sub-unit unadjuvanted	Cardiac disorders	Atrial fibrillation	I48.0 I48.1 I48.2
6	sub-unit unadjuvanted	Nervous system disorders	Encephalitis autoimmune	G04.9

Pregnant

	Vaccine platform	System Organ Class	AESI	ICD-10
1	sub-unit unadjuvanted	Nervous system disorders	Bell's palsy	G51.0
2	sub-unit unadjuvanted	Pregnancy, puerperium and perinatal conditions	Gestational hypertension	O13 O16
3	sub-unit unadjuvanted	Pregnancy, puerperium and perinatal conditions	Preterm premature rupture of membranes	O42 O42.0 O42.1 O42.2 O42.9
4	sub-unit adjuvanted	Pregnancy, puerperium and perinatal conditions	Pre-eclampsia	O14
5	sub-unit adjuvanted	Pregnancy, puerperium and perinatal conditions	Premature delivery	O60.1 O60.3
6	sub-unit adjuvanted	Pregnancy, puerperium and perinatal conditions	Premature labor	O60.0 O60.1 O60.2

7	sub-unit adjuvanted	Pregnancy, puerperium and perinatal conditions	Foetal hypokinesia	Q87.8
8	sub-unit adjuvanted	Pregnancy, puerperium and perinatal conditions	Oligohydramnios	O41.0 P01.2

Infants

	Vaccine platform	System Organ Class	AESI	ICD-10
1	live-attenuated	Nervous system disorders	Febrile convulsion	R56.0

Children 0-24m

	Vaccine platform	System Organ Class	AESI	ICD-10
1	live-attenuated	Respiratory, thoracic and mediastinal disorders	Wheezing	R06.2

Infants-maternal

	Vaccine platform	System Organ Class	AESI	ICD-10
1	sub-unit unadjuvanted	Blood and lymphatic system disorders	Disseminated intravascular coagulation	P60
2	sub-unit unadjuvanted	Pregnancy, puerperium and perinatal conditions	Premature baby	P07.2 P07.3

3	sub-unit unadjuvanted	Pregnancy, puerperium and perinatal conditions	Low birth weight baby	P05.0 P05.1 P07.0 P07.1
4			Lack of efficacy*	J21.0, J12.1, B97.4

*Coded as acute bronchiolitis due to respiratory syncytial virus (J21.0), respiratory syncytial virus pneumonia (J12.1), and respiratory syncytial virus as the cause of diseases classified to other chapters (B97.4) based on recommendation from the expert group.

4.3.2 Background incidence rates

The presented background rates (Table 7) for older adults are defined as the expected number of cases per 10,000 observed person-years. Outcomes with fewer than 5 observations were substituted with “<5” due to potentially identifiable personal information, and the background rates were not defined for these outcomes. The AESI with the highest background rate was abdominal pain, with the number of cases being relatively similar across calendar years, with a small increase from 23,804 cases in 2019 to 25,839 cases in 2022. The lowest background rates were observed for acute disseminated encephalomyelitis with fewer than 5 or no cases in all years.

Table 7: Background rates of SAEs for older adults ≥60 years of age living in Denmark

Serious adverse event	Year	Person-years	Number of cases	Background rate (/10,000 PY)
Lymphadenopathy	2019	1,512,553	571	3.8
	2020	1,532,400	533	3.5
	2021	1,551,982	621	4.0
	2022	1,564,254	511	3.3
Abdominal pain	2019	1,489,904	23,804	159.8
	2020	1,510,630	24,908	164.9
	2021	1,528,861	25,849	169.1
	2022	1,541,287	25,839	167.6
Anaphylactic reaction	2019	1,512,991	145	1.0
	2020	1,532,762	160	1.0
	2021	1,552,400	183	1.2
	2022	1,564,623	162	1.0
Acute disseminated encephalomyelitis	2019	1,513,159	<5	N/A
	2020	1,532,920	0	0.0
	2021	1,552,563	<5	N/A
	2022	1,564,782	0	0.0
Atrial fibrillation	2019	1,513,052	115	0.8
	2020	1,532,807	122	0.8
	2021	1,552,458	115	0.7
	2022	1,564,682	102	0.7
Encephalitis autoimmune	2019	1,492,586	18,215	122.0
	2020	1,513,318	22,089	146.0
	2021	1,531,516	22,794	148.8
	2022	1,543,659	22,927	148.5

4.3.3 Monoclonal antibodies

In total, 10 AEs were prioritised as AESI safety endpoints for mAbs for prophylactic immunisation against RSV infection. Eight AESIs were identified among infants aged 0-24 months with pre-existing health conditions following prophylaxis with motavizumab or palivizumab. Two AESIs were identified among infants up to 12 months of age with no pre-existing health conditions following prophylaxis with either nirsevimab or suptavumab. For each AESI, ICD-10 codes were identified to facilitate the utilisation of these safety endpoints in future post-licensure studies. The identified AESIs for each target group can be viewed in Table 8.

Table 8: Identified AESIs for mAbs, by target groups

Infants 0-12 months with no pre-existing conditions

	Type of mAbs	System organ class	AESI	ICD-10 (WHO)
1	nirsevimab	Nervous system disorders	Infantile spasms	G40.4
2	suptavumab	Nervous system disorders	Seizure	R56.8 P90

Infants 0-12m. with pre-existing conditions

0

Children 0-24 months with pre-existing conditions

	Type of mAbs	System organ class	AESI	ICD-10 (WHO)
1	motavizumab	Blood and lymphatic system disorders	Thrombocytopaenia	D69.3 D69.4 D69.5 D69.6 D82.0 M31.1 Q87.2
2	motavizumab	Immune system disorders	Hypersensitivity	T78.4
3	motavizumab	Skin and subcutaneous tissue disorders	Angioedema	T78.3
4	palivizumab	Nervous system disorders	Convulsion	R56.8 P90
5	palivizumab	Nervous system disorders	Convulsion neonatal	G40.3
6	palivizumab	Nervous system disorders	Febrile convulsion	R56.0
7	palivizumab	Nervous system disorders	Tonic-clonic movements	G40.3

8	palivizumab	Respiratory, thoracic and mediastinal disorders	Apnoea	R06.8 G47.3 P28.3 P28.4
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4.4 AESIs sourced from SPEAC list

The Brighton collaboration SPEAC List from 2020²⁴ suggested 7 AESIs to be relevant to vaccination in general, with no specification regarding the age or status of the vaccinees (Table 9). Their inclusion as AESIs was based on the rationales outlined below. Some of the AESIs in this list were also prioritised in section 5.3.1 RSV vaccines, further highlighting their importance. Overall, we recommend these 7 AESIs to be further explored in post-licensure studies on the safety of RSV vaccines.

Table 9: AESIs relevant to vaccination in general, adopted from Brighton Collaboration SPEAC list

Body system	AESI type	Rationale for inclusion as an AESI
Neurologic	Generalised convulsion	1,2,4
	Guillain-Barré Syndrome (GBS)	2
	Acute disseminated encephalomyelitis (ADEM)	3
Hematologic	Thrombocytopenia	1,2
Immunologic	Anaphylaxis	1,2
	Vasculitis	3,4
Other	Serious local/systemic AEFI	1,2

Rationale for inclusion as an AESI:

1. Proven association with immunisation encompassing several different vaccines.
2. Proven association with vaccine that could theoretically be true for CEPI vaccines under development.
3. Theoretical concern based on immunopathogenesis.
4. Theoretical concern related to viral replication during wild type disease.

Altogether, we recommend 38 unique adverse events across the vaccine and mAbs target groups to be investigated in future safety evaluations following RSV vaccination or mAbs prophylaxis. A summary of the 28 and 10 AESIs for vaccines and mAbs, respectively, is provided in Table 10 below.

Table 10: Summary of recommended unique 38 AESIs for RSV vaccines and mAbs

RSV vaccines			
	AESI	Target population	Source
1	Abdominal pain	Older adults	Selected as AESI safety endpoint
2	Acute disseminated encephalomyelitis	Older adults	Selected as AESI safety endpoint, SPEAC list
3	Anaphylactic shock	Adults, Older adults	Selected as AESI safety endpoint, SPEAC list
4	Atrial fibrillation	Older adults	Selected as AESI safety endpoint
5	Basedow's disease	Adults	Selected as AESI safety endpoint
6	Bell's palsy	Pregnant	Selected as AESI safety endpoint
7	Disseminated intravascular coagulation	Infants – maternal immunisation	Selected as AESI safety endpoint
8	Encephalitis autoimmune	Older adults	Selected as AESI safety endpoint
9	Febrile convulsion	Infants 0-12 months	Selected as AESI safety endpoint
10	Foetal hypokinesia	Pregnant	Selected as AESI safety endpoint
11	Generalised convulsion	Not available	SPEAC List
12	Gestational hypertension	Pregnant	Selected as AESI safety endpoint
13	Guillain-Barré Syndrome	Not available	SPEAC List
14	Lack of efficacy	Infants – maternal immunisation	Selected as AESI safety endpoint
15	Low birth weight baby	Infants – maternal immunisation	Selected as AESI safety endpoint
16	Lymphadenopathy	Older adults	Selected as AESI safety endpoint
17	Oligohydramnios	Pregnant	Selected as AESI safety endpoint
18	Pre-eclampsia	Pregnant	Selected as AESI safety endpoint
19	Premature baby	Infants – maternal immunisation	Selected as AESI safety endpoint
20	Premature delivery	Pregnant	Selected as AESI safety endpoint
21	Premature labor	Pregnant	Selected as AESI safety endpoint
22	Preterm premature rupture of membranes	Pregnant	Selected as AESI safety endpoint
23	Pyrexia	Adults	Selected as AESI safety endpoint
24	Rheumatoid arthritis	Adults	Selected as AESI safety endpoint
25	Serious local/systemic AEFI	Not available	SPEAC List
26	Thrombocytopaenia	Not available	SPEAC List
27	Vasculitis	Not available	SPEAC List
28	Wheezing	Children 0-24 months	Selected as AESI safety endpoint

Monoclonal antibodies

	AESI	Target population	Source
1	Angioedema	Children 0-24 months	Selected as AESI safety endpoint
2	Apnoea	Children 0-24 months	Selected as AESI safety endpoint
3	Convulsion	Children 0-24 months	Selected as AESI safety endpoint
4	Convulsion neonatal	Children 0-24 months	Selected as AESI safety endpoint
5	Febrile convulsion	Children 0-24 months	Selected as AESI safety endpoint
6	Hypersensitivity	Children 0-24 months	Selected as AESI safety endpoint
7	Infantile spasms	Infants 0-12 months	Selected as AESI safety endpoint

8	Seizure	Infants 0-12 months	Selected as AESI safety endpoint
9	Thrombocytopenia	Children 0-24 months	Selected as AESI safety endpoint
10	Tonic-clonic movements	Children 0-24 months	Selected as AESI safety endpoint

4.5 Lists of AESIs provided by EFPIA partners

A suggested list of potential immune-mediated diseases (pIMDs) of interest for possible evaluation in clinical vaccine studies was obtained from GSK²³. The list comprised more than 60 pIMDs across a range of systemic categories such as Endocrine disorders, Eye disorders, Gastrointestinal disorders, among others. It is important to note that this table is not intended to be exhaustive but is indicative of the type of conditions that could be included as an AESI in clinical trials. A list of AESIs assessed in all stages of clinical trials (1-3) of maternal vaccine candidates included more than 20 AESIs including pregnancy outcomes, maternal events of interest and neonatal events of interest. These lists can be viewed in Supplementary Table 3.

A list of AESIs for RSV mAbs was provided by Sanofi, which included three AESIs for the development program of nirsevimab, and two AESIs for MK-1654. The list is presented in Supplementary table 4.

Based on publicly available materials, such as clinical trials results, peer-reviewed articles, among others, a list of 30 AESIs for the RSV-F maternal vaccine by Pfizer was compiled (Supplementary table 5).

5. Discussion and Conclusions

In this report, we utilised multiple methodological approaches to identify safety endpoints for post-licensure evaluation of RSV vaccines and mAbs. Following the extraction and review of SAEs from the clinical trial database, we identified 24 and 10 AESI candidates for RSV vaccines and mAbs, respectively. Furthermore, 7 AESIs were adopted from the SPEAC lists. Altogether, we recommend 38 unique adverse events across the vaccine and mAbs target groups to be investigated in future safety evaluations following RSV vaccination or mAbs prophylaxis. These results as well as the methodology applied should, however, be interpreted in light of multiple limitations.

Our investigation relied extensively on a systematic review of published evidence regarding the safety of RSV vaccines and mAbs, specifically focusing on SAEs in the clinical trial database up to the point of SAE extraction. A notable limitation arises from the unavailability of updated information on SAEs post literature review and data extraction (November 2022) given the dynamic nature of vaccine and monoclonal antibody research, development, and post-licensure surveillance. This limitation highlights the challenge in maintaining real-time data and, thus, the lists of SAEs presented may not capture the most recent safety concerns and events in the field.

This limitation underscores the need for continuous vigilance and periodic reassessment of safety endpoints in the landscape of RSV vaccines and mAbs. To address this concern, the lists of AESI provided by EFPIA partners present the most recent publicly available evidence beyond the time of SAE extraction. Another limitation of this study stems from the nearly exclusive reliance on SAEs extracted from randomised controlled trial (RCT) results due to the developmental stage of RSV vaccines during our investigation. As these vaccines were in the approval stages, real-world evidence data, especially from post-licensure studies, were not yet available. While RCTs offer a rigorous framework, they may not capture the full spectrum of adverse events in real-world scenarios. The omission of post-licensure data in our analysis due to unavailability may limit the generalisability of our findings. It should be also noted that the causality of the identified SAEs and AESIs related to the vaccines and mAbs has not been established. While our study aimed to comprehensively identify safety endpoints, it is essential to recognise that these adverse events do not inherently imply a causal relationship with the administered interventions. Potential causal associations between the SAEs and AESIs and the interventions should be determined in further studies.

Additionally, this study's timeframe prevented the incorporation of any RCT results related to mRNA platforms, lacking potential SAEs following immunisation with mRNA-based RSV vaccines, such as

the mRNA-based RSV pre-F vaccine for older adults³². The ongoing trial, a phase 2/3 study evaluating the mRNA-Based RSV PreF Vaccine in Older Adults (aged 60 years or older)³², was published recently by Moderna in December 2023 and, therefore, was not initially included in our search. In this clinical trial, Moderna defined a list of AESIs, which included new AESIs specific to the mRNA platform, such as Myocarditis/Pericarditis (Supplementary table 6). These events were first observed in post-marketing experience in recipients of COVID mRNA vaccines and were considered a class effect of mRNA vaccines³³.

Future research should aim to include post-licensure studies to comprehensively understand the safety profile of interventions over extended periods and in diverse patient populations.

A notable limitation in our study arises from the inherent subjectivity in the collective expert evaluation and prioritisation process employed to assess the SAEs related to the RSV vaccines and monoclonal antibodies. Representatives from both private and public partner institutions were tasked with evaluating each SAE based on two criteria: the biological plausibility of the event being related to the interventions and the seriousness of the adverse event. It is crucial to acknowledge that this evaluation process lacked the support of real-world data or studies to objectively substantiate these assessments. Instead, decisions were primarily rooted in the individuals' prior experiences and expertise in the realm of vaccines. This inherent subjectivity introduces a potential source of bias in the identification of safety endpoints, as personal experiences and perspectives may vary among evaluators. Furthermore, some SAEs were difficult to score on the severity criteria as they may represent a broad spectrum of disease, e.g., abdominal pain. While efforts were made to standardise the evaluation criteria, the absence of empirical evidence on the safety of RSV vaccines and mAbs supporting the decisions made poses a challenge to the robustness of our findings.

While our collaborative effort with EFPIA partners has enriched our study in identifying safety endpoints, it is important to acknowledge a potential expertise imbalance within our collaborating network. The majority of EFPIA partners who contributed to this study have expertise within the vaccines field, creating a potential limitation in the depth of expertise available for the assessment of safety endpoints specifically related to mAbs. The distinct pharmacological profiles and safety considerations between vaccines and monoclonal antibodies underscore the importance of a diverse range of expertise. Consequently, the study may be more robust in its coverage of vaccine safety endpoints compared to monoclonal antibodies.

In light of the limitations, our study also demonstrates significant strengths, particularly in the diverse methodologies employed and the strong collaboration between public and private sectors. We employed multiple methodological approaches to comprehensively assess and identify potential AEs. The utilisation of multiple methods, including the review of clinical trials, prioritisation and evaluation of SAEs, complemented by AEs from the SPEAC list and the lists of AEs provided by GSK and Sanofi, enhanced the scope and depth of our investigation. The incorporation of various methodologies ensured incorporation of several data sources, thorough expert assessment and broader representation of potential AEs. Furthermore, the identified adverse events are supplemented with suitable ICD-10 codes to support future analysis. We also provided background rates of these adverse events following RSV vaccination among older adults based on Danish register data, which can be utilised in future studies and are suitable for various study designs, such as observed/expected analysis^{25,26,34}. It should be noted that the background rates were estimated during the years 2019-2022, covering the period of the COVID-19 pandemic. Thus, non-pharmaceutical interventions might have had an effect on these rates. The estimation of background rates is feasible for many countries since only outcome and population estimates as denominator are required²⁶. The timely availability of the background incidence rates can effectively support any future rapid signal assessments^{25,34}.

The strength of our study lies in the robust public-private partnership established between esteemed public health institutes and pharmaceutical companies. This collaborative effort integrated diverse expertise, drawing on the extensive knowledge and experience of professionals spanning epidemiology, vaccinology, pharmacovigilance, and related fields. The inclusion of pharmaceutical companies in this partnership brought forth invaluable insights into industry-specific safety considerations, providing a unique perspective that enriched the overall approach and results.

By combining the research capabilities of public health institutes with the research and development infrastructure of pharmaceutical companies, particularly in the SAE evaluation process, our study was able to undertake a more extensive and resourceful exploration of safety endpoints for RSV interventions. This collaborative spirit not only contributed to the methodological soundness of our study but also exemplifies a model for future endeavors.

Beyond the immediate implications for RSV interventions, the collaborative framework established between public health institutes and pharmaceutical companies holds broader significance. This collaborative model of the PROMISE project³⁵ showcases the potential of public-private partnerships

to address complex public health challenges and underscores the importance of leveraging the strengths of different sectors for the collective benefit of global public health. In essence, our study not only contributes valuable insights into RSV safety endpoints but also exemplifies the transformative impact of collaborative efforts at the intersection of public health and industry expertise.

6. References

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7. Supplementary materials

Supplementary Form 1: Common disclaimer form

Supplementary Table 1: Data collection form, RSV Vaccines

Supplementary Table 2: Data collection form, mAbs

Supplementary Table 3: List of AESIs provided by GSK

Supplementary Table 4: List of AESIs provided by Sanofi Pasteur, mAbs

Supplementary Table 5: Compiled list of AESIs investigated by Pfizer, RSV vaccine

Supplementary Table 6: AESIs of an mRNA-based RSV PreF vaccine in older adults (Extract of the Supplementary Table 4)

Supplementary form 1: Common disclaimer form

EFPIA COMMON DISCLAIMERS FOR THE EVALUATION OF THE SERIOUS ADVERSE EVENTS (SAEs) RSV VACCINES AND MONOCLONAL ANTIBODIES

CRITERIA NUMBER 1: To the best of your knowledge, is there a likelihood of biological plausibility between the vaccine/vaccine platform in general and the SAE?

Several criteria are relevant to establishing causality, including but not limited to temporal relationship, strength of association, consideration of alternative explanations, dose-response relationship, population-based evidence for causality, consistency of evidence, specificity, and biological plausibility. Only the last criterion was considered for the purpose of this evaluation.

For the evaluation of biological plausibility, the assessor considered whether the association between the vaccine, or monoclonal antibody, and the adverse event was plausible and compatible with current knowledge related to how the vaccine or monoclonal antibody works and the biology of the adverse event.¹

For the evaluation of the “Infants – maternal” adverse events, the biological plausibility rating could change for some events, depending on the assumption of timing of vaccine exposure during pregnancy. The most conservative approach was taken.

For trauma-related events, assumption was that there is unlikely to be any biological link to vaccination.

Assumption for temporal association of the event to drug and temporality was considered to be within the plausible time frame for the reference drug.

Safety profile as available in public domain of monoclonal antibodies or RSV vaccines (e.g., Label, Label and Package Leaflet, public assessment report available on regulatory authorities’ websites).

The views expressed are those of the individual safety officers who have completed this evaluation and do not necessarily reflect the views of EFPIA partners.

¹ Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification, 2nd ed., 2019 update. <https://www.who.int/publications/i/item/9789241516990>. Accessed January 22, 2024.

CRITERIA NUMBER 2: In your opinion, how likely is this event life-threatening or likely to have a serious impact on quality of life?

For the purpose of this evaluation, given that there was not specific case information on the adverse events to be evaluated, the most severe possible outcome was considered, where applicable. For some AEs, level "3 undecided" was chosen as the outcome of the event and may depend on different factors (as underlying comorbidities, infections etc.) that can dramatically change the outcome of the event. Similarly, impact on quality of life could be short-term or long-term and both were considered depending on the specific AE discussed.

The views expressed are those of the individual safety officers who have completed this evaluation and do not necessarily reflect the views of EFPIA partners.

Supplementary Table 1. Data collection form for RSV vaccines, clinical trials included in the review of the clinical trial database

Nr.	ID	Title	Sponsor	Year Results posted	Study design	Study status /phase	Study population	Age of participants	Period of follow up	Participants enrolled	Vaccine Type	Candidate Status (PATH22)
1	NCT02890381	Evaluating the Infectivity, Safety and Immunogenicity of a Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine (RSV LID cp ΔM2-2) in RSV-Seronegative Infants 6 to 24 Months of Age (LID)	National Institute of Allergy and Infectious Diseases (NIAID) (Medi)	2018	Interventional - randomised	Terminated/Phase 1	Child	6 Months to 24 Months	day 0-56	17	Live-Attenuated	Inactive / no longer in development
2	NCT02794870	Evaluating the Infectivity, Safety and Immunogenicity of a Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine in RSV-Seronegative Infants 6 to 24 Months of Age	National Institute of Allergy and Infectious Diseases (NIAID) (Medi)	2018	Interventional - randomised	Completed/Phase 1	Child	6 Months to 24 Months	day 0-56	33	Live-Attenuated	Active
3	NCT02360475	Safety, Reactogenicity and Immunogenicity Study of Different Formulations of GlaxoSmithKline (GSK) Biologicals' Investigational RSV Vaccine (GSK3003891A), in Healthy Women	GlaxoSmithKline	2017	Interventional - randomised	Completed/Phase 2	Adult	18 Years to 45 Years	day 0-360	507	Sub-unit Unadjuvanted Adjuvanted	Inactive / no longer in development

Nr.	ID	Title	Sponsor	Year Results posted	Study design	Study status /phase	Study population	Age of participants	Period of follow up	Participants enrolled	Vaccine Type	Candidate Status (PATH22)
4	NCT03102034	Evaluating the Infectivity, Safety, and Immunogenicity of a Single Dose of a Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine (D46/NS2/N/ΔM2-2-HindIII) in RSV-Seronegative Infants 6 to 24 Months of Age	National Institute of Allergy and Infectious Diseases (NIAID) (Sanofi)	2019	Interventional - randomised	Completed/Phase 1	Child	6 Months to 24 Months	day 0-56	32	Live-Attenuated	Active
5	NCT02956837	A Study to Rank Different Dosages of Antigen of GlaxoSmithKline (GSK) Biologicals' Investigational Respiratory Syncytial Virus (RSV) Vaccine (GSK3003891A), Based on Their Immune Response and Safety, When Administered to Healthy Adult Women	GlaxoSmithKline	2018	Interventional - randomised	Completed/Phase 2	Adult	18 Years to 45 Years	day 0-360	406	Sub-unit Unadjuvanted	Inactive / no longer in development
6	NCT04090658	A Study to Test GlaxoSmithKline's (GSK) Respiratory Syncytial Virus RSV Candidate Vaccine's Safety and Immune Response in Japanese Older Adults	GlaxoSmithKline	2022	Interventional - randomised	Completed/Phase 1	Older Adult	60 Years to 80 Years	day 1-month 14 (~426 days)	40	Sub-unit Adjuvanted	Active
7	NCT03227029	Evaluating the Infectivity, Safety, and Immunogenicity of Recombinant Live-Attenuated RSV Vaccines RSV ΔNS2/Δ1313/11314L or RSV 276 in RSV-Seronegative Infants 6 to 24 Months of Age	National Institute of Allergy and Infectious Diseases (NIAID) (Sanofi)	2021	Interventional - randomised	Completed/Phase 1	Child	6 Months to 24 Months	day 0-56	65	Live-Attenuated	Active
8	NCT03814590	A Study to Assess the Safety, Reactogenicity and Immune Response of GlaxoSmithKline (GSK) Biologicals' Investigational Respiratory Syncytial Virus (RSV) Vaccine (GSK3844766A) in Older Adults	GlaxoSmithKline	2022	Interventional - randomised	Completed/Phase 2	Adult	18 Years to 40 Years	day 1-91	1053	Sub-unit Unadjuvanted	Active

Nr.	ID	Title	Sponsor	Year Results posted	Study design	Study status /phase	Study population	Age of participants	Period of follow up	Participants enrolled	Vaccine Type	Candidate Status (PATH22)
							Older Adult	60 Years to 80 Years	day 1-month 14 (~426 days)		Sub-unit Unadjuvanted	
							Older Adult	60 Years to 80 Years	day 1-month 14 (~426 days)		Sub-unit Adjuvanted	
9	NCT02927873	A Study to Evaluate Safety, Reactogenicity and Immunogenicity of GSK Biologicals' RSV Investigational Vaccine Based on Viral Proteins Encoded by Chimpanzee-derived Adenovector (ChAd155-RSV) (GSK3389245A) in RSV-seropositive Infants	GlaxoSmithKline	2021	Interventional - randomised	Completed/Phase 2	Child	12 Months to 23 Months	day 1- 731	107	Vector-based	Inactive / no longer in development
10	NCT02753413	Safety and Reactogenicity Study of GlaxoSmithKline (GSK) Biologicals' Investigational Respiratory Syncytial Virus (RSV) Vaccine (GSK3003891A) in Healthy Women	GlaxoSmithKline	2017	Interventional - randomised	Completed/Phase 2	Adult	18 Years to 45 Years	day 0-30	102	Sub-unit Unadjuvanted	Inactive / no longer in development
11	NCT03674177	A Study to Evaluate Different Dose Levels of GlaxoSmithKline (GSK) Biologicals' Investigational Respiratory Syncytial Virus (RSV) Vaccine (GSK3888550A), Based on the Vaccine Safety and the Antibodies (Body Defences) Produced Following Vaccine Administration, When Given to Healthy Non-pregnant Women	GlaxoSmithKline	2020	Interventional - randomised	Completed/Phase 1	Adult	18 Years to 45 Years	day 1-181	502	Sub-unit Unadjuvanted	Active
12	NCT02873286	RSV-MVA-BN Vaccine Phase II Trial in ≥ 55 Year Old Adults	Bavarian Nordic	2020	Interventional - randomised	Completed/Phase 2	Older Adult	55 Years and older	day 0-week 108 (~756 days)	420	Vector-based	Active

Nr.	ID	Title	Sponsor	Year Results posted	Study design	Study status /phase	Study population	Age of participants	Period of follow up	Participants enrolled	Vaccine Type	Candidate Status (PATH22)
13	NCT04071158	A STUDY OF A RSV VACCINE WHEN GIVEN TOGETHER WITH TDAP IN HEALTHY NONPREGNANT WOMEN AGED BETWEEN 18 TO 49 YEARS	Pfizer	2021	Interventional - randomised	Completed/Phase 2	Adult	18 Years to 49 Years	day 0-35	713	Sub-unit Unadjuvanted Adjuvanted	active
14	NCT03572062	A Study to Evaluate the Safety and Immunogenicity of an Adjuvanted RSV Vaccine in Healthy Older Adults	Pfizer	2021	Interventional - randomised	Terminated/Phase 2	Older Adult	65 Years to 85 Years	day 0- months 12	317	Sub-unit Adjuvanted	Active
15	NCT04126213	Study of Safety, Reactogenicity and Immunogenicity of GlaxoSmithKline's (GSK)Respiratory Syncytial Virus (RSV)Maternal Unadjuvanted Vaccine in Healthy Pregnant Women (Aged 18 to 40 Years) and Their Infant	GlaxoSmithKline	2021	Interventional - randomised	Completed/Phase 2	Pregnant	18 Years to 40 Years	day 1- month 6 post-delivery	534	Sub-unit Unadjuvanted	Active
							Infant		day 1 (birth)- month 12 of age		Sub-unit Unadjuvanted	
16	NCT03213405	A Study to Assess Safety, Tolerability and Immunogenicity of the Live Attenuated hRSV Vaccine rBCG-N-hRSV (EVA-VRS01)	Pontificia Universidad Catolica de Chile	2020	Interventional - randomised	Completed/Phase 1	Adult	18 Years to 50 Years	day 0- 180	24	Live-Attenuated	Active
17	NCT03049488	Dose, Safety, Tolerability and Immunogenicity of a Stabilized Prefusion RSV F Subunit Protein Vaccine, VRC-RSVRGP084-00-VP (DS-Cav1), Alone or With Alum Adjuvant, in Healthy Adults	National Institute of Allergy and Infectious Diseases (NIAID)	2020	Interventional - randomised	Completed/Phase 1	Adult	18 Years to 50 Years	day 0- 308	95	Sub-unit Adjuvanted Unadjuvanted	Active
18	NCT03529773	A Study to Describe the Safety and Immunogenicity of a RSV Vaccine in Healthy Adults	Pfizer	2021	Interventional - randomised	Completed/Phase 2	Adult	18 Years to 49 Years	day 0- 798	1235	Sub-unit Adjuvanted	active

Nr.	ID	Title	Sponsor	Year Results posted	Study design	Study status /phase	Study population	Age of participants	Period of follow up	Participants enrolled	Vaccine Type	Candidate Status (PATH22)
							Adult	18 Years to 49 Years			Sub-unit Unadjuvanted	
							Older adult	50 Years to 85 Years			Sub-unit Adjuvanted	
							Older adult	50 Years to 85 Years			Sub-unit Unadjuvanted	
19	NCT02298179	A Study to Evaluate the Safety and Ability of the Vaccine to Induce Antibodies Against the Respiratory Syncytial Virus in Healthy Adults	GlaxoSmithKline	2018	Interventional - randomised	Completed/Phase 1	Adult	18 Years to 45 Years	day 1- 394	288	Sub-unit Adjuvanted Unadjuvanted	Inactive / no longer in development
20	NCT02491463	A Study to Assess the Safety, Reactogenicity and Immunogenicity of GlaxoSmithKline (GSK) Biologicals' RSV Investigational Vaccine (ChAd155-RSV) (GSK3389245A) in Healthy Adults	GlaxoSmithKline	2018	Interventional - randomised	Completed/Phase 1	Adult	18 Years to 45 Years	day 0-360	73	Vector-based	Inactive / no longer in development
21	NCT03339713	A Study to Evaluate the Safety and Immunogenicity of Seasonal Influenza Vaccine and an Adenovirus Serotype 26-Based Vaccine Encoding for the Respiratory Syncytial Virus Pre-fusion F Protein (Ad26.RSV.preF), With and Without Co-administration, in Adults Aged 60 Years and Older in Stable Health	Janssen Vaccines & Prevention B.V.	2021	Interventional - randomised	Completed/Phase 2	Older Adult	60 Years and older	day 0- 211	180	Vector-based	active

Nr.	ID	Title	Sponsor	Year Results posted	Study design	Study status /phase	Study population	Age of participants	Period of follow up	Participants enrolled	Vaccine Type	Candidate Status (PATH22)
22	NCT03334695	An Exploratory Study to Evaluate the Prophylactic Efficacy of a Single Immunization of Ad26.RSV.preF Against Respiratory Syncytial Virus Infection in a Virus Challenge Model in Healthy 18 to 50 Year-old Adults	Janssen Vaccines & Prevention B.V.	2021	Interventional - randomised	Completed/Phase 2	Adult	18 Years to 50 Years	day 0- month 6	64	Vector-based	active
23	NCT02115815	A Study to Evaluate the Safety of the Respiratory Syncytial Virus Vaccine MEDI7510 in Older Adults	MedImmune LLC	2016	Interventional - randomised	Completed/Phase 1	Older Adult	60 Years to 99 Years	day 1- 361	246	Sub-unit Adjuvanted	Inactive / no longer in development
24	NCT00686075	A Study to Evaluate the Safety, Tolerability, Immunogenicity and Vaccine-like Viral Shedding of MEDI-534, Against Respiratory Syncytial Virus (RSV) and Parainfluenza Virus Type 3 (PIV3), in Healthy 6 to <24 Month-old Children and in 2 Month-old Infants	MedImmune LLC	2014	Interventional - randomised	Completed/Phase 1	Child	2 Months to 23 Months	day 0- 365	1338	Live-Attenuated	Inactive / no longer in development
25	NCT02289820	A Study to Evaluate the Safety and Immunogenicity of MEDI7510 in Older Adults	MedImmune LLC	2018	Interventional - randomised	Completed/Phase 1	Older Adult	60 Years to 99 Years	day 1- 361	363	Sub-unit Adjuvanted	Inactive / no longer in development
26	NCT02508194	A Study to Evaluate the Efficacy of MEDI7510 in Older Adults	MedImmune LLC	2017	Interventional - randomised	Completed/Phase 2	Older Adult	60 Years to 99 Years	day 1- 365	1900	Sub-unit Adjuvanted	Inactive / no longer in development
27	NCT00493285	Safety and Tolerability Study to Evaluate MEDI-534 in Children 6 to < 24 Months of Age (CP149)	MedImmune LLC	2012	Interventional - randomised	Completed/Phase 1	Child	6 Months to 23 Months	days 0- 180	49	Live-Attenuated	Inactive / no longer in development

Nr.	ID	Title	Sponsor	Year Results posted	Study design	Study status /phase	Study population	Age of participants	Period of follow up	Participants enrolled	Vaccine Type	Candidate Status (PATH22)
28	NCT03636906	Respiratory Syncytial Virus (RSV) Investigational Vaccine in Infants Aged 6 and 7 Months Likely to be Unexposed to RSV	GlaxoSmithKline	2022	Interventional - randomised	Completed/Phase 1	Child	6 and 7 Months	Day 1-61	201	Vector-based	Inactive / no longer in development
29	NCT04657198	Extension Study to Evaluate the Safety and Immunogenicity of a Revaccination Dose of the RSVPreF3 OA Investigational Vaccine in Adults 60 Years and Older Who Participated in the RSV OA=ADJ-002 Study	GlaxoSmithKline	2022	Interventional- non-randomised	Completed/Phase 2	Older adult	60 Years and older	Day1-31	126	Sub-unit Adjuvanted	Active
30	NCT04032093	A PHASE 2B PLACEBO-CONTROLLED, RANDOMIZED STUDY OF A RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE IN PREGNANT WOMEN	Pfizer	2022	Interventional - randomised	Phase 2	Pregnant	18 Years to 49 Years	Day 1-365	1153	Sub-unit Unadjuvanted Adjuvanted	Active
31	NCT04841577	A Study on the Immune Response and Safety Elicited by a Vaccine Against Respiratory Syncytial Virus (RSV) When Given Alone and Together With a Vaccine Against Influenza in Adults Aged 60 Years and Above	GSK	2022	Interventional - randomised	Phase 3	Older Adult	60 Years and older	Day 1 - 6 months	976	Sub-unit Adjuvanted	Active
31												

Supplementary Table 2. Data collection form for mAbs, clinical trials included in the review of the clinical trial database

Nr	ID	Title	Sponsor	Results posted	Study design	Study status /phase	Target population	Age of participants	Category (healthy or pre-existing condition)	Period of follow up	Participants enrolled	Type of mAbs	Product characteristics	Notes	Candidate Status (PATH22)
1	NCT04086472	Phase 2a Respiratory Syncytial Virus (RSV) Human Challenge Study of MK-1654 in Healthy Participants (MK-1654-005)	Merck Sharp & Dohme Corp.	2021	Interventional - randomised	Completed / Phase 2	Adult	18 Years to 55 Years	Healthy	day 0-187	80	Monoclonal antibody	Clesrovimab MK-1654 (Anti-RSV mAb)		Active
2	NCT01107535	Effectiveness of Synagis (Palivizumab) Immunoprophylaxis in Preterm Infants With High Risk of Severe Respiratory Syncytial Virus (RSV) Infection (INSPIRA)	Abbott	2012	Cohort - Prospective		Child	up to 6 Months	Pre-existing condition	day 0-12 months	82	Monoclonal antibody	Palivizumab (Synagis)	Excluded due to study design	
3	NCT02290340	A Phase 1b/2a Randomized, Double-Blind, Placebo-controlled, Dose-escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants (MEDI8897 1b)	MedImmune LLC	2018	Interventional - randomised	Completed / Phase 1	Child	up to 12 Months	Healthy	day 1-361	151	Monoclonal antibody	Nirsevimab MEDI8897		Active

4	NCT00192504	Safety Study of a Monoclonal Antibody to Respiratory Syncytial Virus (RSV) in Children Hospitalized With RSV Infection	MedImmune LLC	2021	Interventional - randomised	Completed/ Phase 1	Child	up to 24 Months	Pre-existing condition	day 1-30	31	Monoclonal antibody	Motavizumab MEDI-524	unknown
5	NCT00421304	A Study to Evaluate a Single Intravenous Dose of Motavizumab for the Treatment of Children Hospitalized With Respiratory Syncytial Virus (RSV) Illness	MedImmune LLC	2021	Interventional - randomised	Completed/ Phase 2	Child	up to 12 Months	Pre-existing condition	day 1-90	118	Monoclonal antibody	Motavizumab MEDI-524	unknown
6	NCT00435227	A Study to Evaluate a Single Intramuscular Dose of Motavizumab to Treat Children With Respiratory Syncytial Virus (RSV) Illness	MedImmune LLC	2021	Interventional - randomised	Terminated/ Phase 2	Child	up to 12 Months	Pre-existing condition	day 0-90	12	Monoclonal antibody	Motavizumab MEDI-524	unknown
7	NCT00129766	Study of MEDI-524 (Motavizumab) for the Prophylaxis of Serious Respiratory Syncytial Virus (RSV) Disease in High-Risk Children	MedImmune LLC		Interventional - randomised	Completed/ Phase 3	Child	up to 24 Months	Pre-existing condition	day 0-150	6635	Monoclonal antibody	Motavizumab MEDI-524 Palivizumab (Synagis)	unknown
8	NCT02878330	A Study to Evaluate the Safety and Efficacy of MEDI8897 for the Prevention of Medically Attended RSV LRTI in Healthy Preterm Infants. (MEDI8897 Ph2b)	MedImmune LLC	2019	Interventional - randomised	Completed/ Phase 2	Child	up to 365 Days	Healthy	day 0-361	1453	Monoclonal antibody	Nirsevimab MEDI8897	Active

9	NCT02325791	Study to Evaluate the Efficacy and Safety of Suptavumab (REGN2222) for the Prevention of Medically Attended RSV (Respiratory Syncytial Virus) Infection in Preterm Infants	Regeneron Pharmaceuticals	2018	Interventional - randomised	Completed/ Phase 3	Child	up to 6 Months	Healthy	day 0-150	1177	Monoclonal antibody	Suptavumab REGN2222	Inactive / no longer in development
10	NCT00316264	Study of Motavizumab (MEDI-524) and Palivizumab Administered Sequentially in the Same Respiratory Syncytial Virus (RSV) Season	MedImmune LLC	2012	Interventional - randomised	Completed/ Phase 2	Child	up to 24 Months	Pre-existing condition	day 0-150	260	Monoclonal antibody	Motavizumab MEDI-524	unknown
11	NCT00113490	A Study to Evaluate the Safety, Tolerability, and Immunogenicity of Motavizumab (MEDI-524) After Dosing for a Second Season in Children	MedImmune LLC	2013	Interventional - randomised	Completed/ Phase 1	Child	up to 24 Months	Pre-existing condition	day 0-30	136	Monoclonal antibody	Motavizumab MEDI-524 Palivizumab (Synagis)	unknown
12	NCT00121108	MEDI-524 (Motavizumab) for the Prevention of Respiratory Syncytial Virus (RSV) Disease Among Native American Indian Infants in the Southwestern United States	MedImmune LLC	2022	Interventional - randomised	Completed/ Phase 3	Child	up to 6 Months	Healthy	day 0-150	2127	Monoclonal antibody	Motavizumab MEDI-524	unknown
13	NCT00538785	A Study to Evaluate MEDI-524 in Children With Hemodynamically	MedImmune LLC	2012	Interventional - Randomised	Completed/ Phase 2	Child	up to 24 Months	Pre-existing condition	day 0-150	1236	Monoclonal antibody	Motavizumab MEDI-524 Palivizumab (Synagis)	unknown

Significant Congenital Heart Disease

14	NCT02114268	A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI8897 in Healthy Adults	MedImmune LLC	2016	Interventional - randomised	Completed/Phase 1	Adult	18 Years to 49 Years	Healthy	day 0-391	342	Monoclonal antibody	Nirsevimab MEDI8897	Active
15	NCT02968173	A Study to Assess the Safety and Effectiveness of Palivizumab Administered to Children at High Risk of Severe Respiratory Syncytial Virus (RSV) Infection in the Russian Federation and the Republic of Belarus (Synagis Russia)	AbbVie	2018	Interventional	Completed/Phase 3	Child	up to 24 Months	Pre-existing condition	day 0-220	50	Monoclonal antibody	Palivizumab (Synagis)	unknown
16	NCT01077271	Compliance to Synagis (Palivizumab) Under Daily Pediatrician's Conditions in Premature Infants 33 - 35 wGA	Abbott	2012	Observational		Child	0-12 months	Pre-existing condition	0-90 days	124	Monoclonal antibody	Palivizumab (Synagis)	Excluded due to study design

**14
included**



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Supplementary Table 3: List of AESIs provided by GSK

Suggested list of potential immune-mediated diseases (pIMDs) of interest for possible evaluation in clinical vaccine studies.

(Note that this table is not intended to be exhaustive, but is indicative of the type of conditions that could be included as AESI in clinical trials)

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
Cranial nerve inflammatory disorders, including paralyses/paresis (e.g., Bell's palsy) Optic neuritis Multiple sclerosis	Systemic lupus erythematosus Systemic sclerosis (with limited or diffuse cutaneous involvement) Dermatomyositis Polymyositis	Psoriasis Vitiligo Erythema nodosum Autoimmune bullous skin diseases (including pemphigus, pemphigoid & dermatitis herpetiformis) Cutaneous lupus erythematosus Alopecia areata
Transverse myelitis Acute disseminated encephalomyelitis including site- specific variants: encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis, cerebellitis	Anti-synthetase syndrome Rheumatoid arthritis	Lichen planus Sweet's syndrome Morphoea
Myasthenia gravis (including Lambert-Eaton myasthenic syndrome) Immune mediated peripheral neuropathies and plexopathies, (including Guillain-Barré syndrome, Miller Fisher syndrome and other variants, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy)	Juvenile chronic arthritis (including Still's disease) Polymyalgia rheumatica Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis Psoriatic arthropathy Relapsing polychondritis Mixed connective tissue disorder	
Narcolepsy		
Liver disorders	Gastrointestinal disorders	Metabolic & endocrine disorders
Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis Autoimmune cholangitis.	Crohn's disease Ulcerative colitis Ulcerative proctitis Celiac disease	Autoimmune thyroiditis (including Hashimoto thyroiditis) Grave's or Basedow's disease Diabetes mellitus type I Addison's disease
Vasculitides	Others	
Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis & temporal arteritis Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotising vasculitis & anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis	Autoimmune haemolytic anaemia Autoimmune thrombocytopenia Antiphospholipid syndrome Pernicious anaemia Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, & mesangioproliferative glomerulonephritis) Uveitis Autoimmune myocarditis/cardiomyopathy Sarcoidosis Stevens-Johnson syndrome Sjögren's syndrome Idiopathic pulmonary fibrosis Goodpasture syndrome Raynaud's phenomenon	

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List of AESIs for RSV maternal vaccine (combination of multiple trials) *

Pregnancy Outcomes
Fetal Death / Stillbirth
Maternal Events of Interest
Maternal Death
Hypertensive Disorders of Pregnancy
Antenatal bleeding
Postpartum hemorrhage
Fetal Growth restriction
Gestational Diabetes Mellitus
Non-reassuring fetal status
Pathways to Preterm Birth
Chorioamnionitis
Standard definitions for events of interest not defined as such in GAIA (Oligohydramnios, Polyhydramnios, Intrahepatic Cholestasis of Pregnancy (ICP), Acute Fatty Liver of Pregnancy, Maternal Sepsis)
Neonatal Events of Interest
Small for Gestational Age
Low Birth Weight
Neonatal encephalopathy
Congenital Microcephaly
Congenital Anomalies
Neonatal Death
Neonatal Infections
Respiratory Distress in the Neonate
Preterm Birth
Failure to thrive
Worsening of Pre-existing conditions (for high risk pregnancies)

*Source: Clinicaltrials.gov database, including following trial, [NCT04126213](#), [NCT05045144](#), and [NCT04138056](#)

Supplementary Table 4: List of AESIS provided by Sanofi Pasteur, mAbs

AESIs	Source
Beyfortus® (nirsevimab), Anti-F mAb	Publicly available protocols for the Melody Phase 3 and Medley Phase 2/3 trials. You can find those in the additional materials, provided with the publications below.
<p>Hypersensitivity, Including Anaphylaxis Administration of polyclonal immunoglobulin preparations and mAbs has been associated with hypersensitivity (including anaphylaxis) that occurs during or after dosing. A hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both during administration of investigational product (but does not meet the definition of anaphylaxis). Anaphylaxis is a rare event, usually occurring after subsequent exposure to antigen, and it is most commonly accompanied by severe systemic skin and or mucosal reactions. It is potentially a fatal, systemic allergic reaction that is distinct from simple allergic reactions (eg, rash, pruritus) because of the simultaneous involvement of several organ systems.</p>	<p>Protocol for Melody: <i>Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. N Engl J Med 2022;386:837-46. DOI: 10.1056/NEJMoa2110275</i></p> <p>Protocol for Medley: <i>Domachowske J, Madhi SA, Simões EAF, et al. Safety of nirsevimab for RSV in infants with heart or lung disease or prematurity. N Engl J Med 2022;386:892-3. DOI: 10.1056/NEJMc2112186</i></p>
<p>Immune Complex Disease Immune complex disease can manifest in the form of a number of conditions such as vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, and arthralgias. Common examples of immune complex hypersensitivity reactions are serum sickness (systemic) and Arthus reactions (local). The clinical manifestations of serum sickness include skin rash, fever, malaise, and polyarthralgias or polyarthritis.</p>	
<p>Thrombocytopenia Thrombocytopenia is a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150,000 to 450,000 platelets per μL. General symptoms of thrombocytopenia include bleeding in the mouth and gums, bruising, nosebleeds, and petechiae (pinpoint red spots/rash). Severe bleeding is the major complication, which may occur in the brain or gastrointestinal tract.</p>	
MK-1654, Anti-F mAb	Clinicaltrials.gov database
<p>Anaphylaxis/hypersensitivity</p>	Study Title: A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Pre-Term and Full-Term Infants
<p>Rash</p>	https://clinicaltrials.gov/ct2/show/NCT04767373

Supplementary Table 5: Compiled list of AESIs investigated by Pfizer, RSV vaccine

RSV Protein-based vaccine AESIs including sources (Target indication: Maternal)

AESIs	Source
RSV-F protein vaccine, Pfizer*	Publication : <i>Simões EAF, Center KJ, Tita ATN, Swanson KA, Radley D, Houghton J, McGrory SB, Gomme E, Anderson M, Roberts JP, Scott DA, Jansen KU, Gruber WC, Dormitzer PR, Gurtman AC. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy. N Engl J Med. 2022 Apr 28;386(17):1615-1626. doi: 10.1056/NEJMoa2106062. PMID: 35476650.</i>
congenital anomalies (Major congenital anomalies (defined as structural or functional anomalies [e.g. metabolic disorders] that occur during intrauterine life and can be identified prenatally, at birth, or later in life) see page 280 of the Protocol) SOT: Congenital, familial and genetic disorders as per appendix S11: PTs: Ankyloglossia congenital; Aplasia cutis congenita; Atrial; septal defect; Birth mark; Chordee; Cleft lip; Cleft palate; Congenital naevus; Congenital; skin dimples; Cryptorchism; Dacryostenosis congenital; Hydrocele ; Hypospadias; Labial tie; Laryngomalacia ; Naevus flammeus; Patent ductus arteriosus ; Penile torsion ; Penoscrotal fusion; Spina bifida cystica ; XYY syndrome	Prefusion F Protein–Based Respiratory Syncytial Virus Immunization in Pregnancy (nejm.org)
developmental delay	The protocol, available with the full text of this article at NEJM.org: Protocol
SOT Cardiac disorders PT Mitral valve incompetence	Supplementary Appendix
SOT Gastrointestinal disorders PT Tongue cyst PT Umbilical hernia	Table S11 Adverse Events of Special Interest: Congenital Anomalies Reported Throughout the Study -Infant Participants - Safety Population (page 93)
SOT Neoplasms benign, malignant and unspecified (incl cysts and polyps) PT Haemangioma	Table S12 Listing of Special Interest Adverse Events - Infant Participants - Safety Population (page 97)
SOT Reproductive system and breast disorders PT Penile Adhesion	

*all AESIs listed are related to the Infant population

Other reference for RSV vaccine and mAb Snapshot, PATH access December 2022: [RSV Vaccine and mAb Snapshot | PATH](#)

Supplementary Table 6: AESIs of an mRNA-based RSV PreF vaccine in older adults (Extract of the supplementary Table 4)³⁶

Medical Concept	Additional Notes
Thrombocytopenia	<ul style="list-style-type: none"> • Platelet counts < 150 × 10⁹ cells per liter • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome
New onset of or worsening of neurologic diseases	Neurologic diseases include the following: <ul style="list-style-type: none"> • Guillain-Barré syndrome • Acute disseminated encephalomyelitis • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures, including but not limited to febrile seizures and/or generalized seizures/convulsions
Anaphylaxis	<ul style="list-style-type: none"> • Anaphylaxis as defined per the protocol
Myocarditis/Pericarditis	<ul style="list-style-type: none"> • Myocarditis • Pericarditis • Myopericarditis