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Preparing for RSV Immunisation and Surveillance in Europe

WP2 – WP Preparation for Future RSV Product Assessment

D2.9 Generic protocols for post-authorisation safety studies of preventive products against RSV

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Document History

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V1.0	04/06/2024	Final draft

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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**. Terveyden Ja Hyvinvoinnin Laitos (Finland)
  7. **RIVM**. Rijksinstituut voor Volksgezondheid en Milieu (Netherlands)
  8. **NIVEL**. Stichting Nedelands Instituut voor Onderzoek van de Gezondheidzorg (Netherlands)
  9. **TUCH**. Varsinais-Suomen Sairaanhoitopiirin 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 Biologicals, S.A. (Belgium)
  19. **JANSSEN**. Janssen Pharmaceutica, N.V (Belgium)
  20. **Novavax**. Novavax, Inc. (United States)
  21. **Pfizer**. Pfizer Limited (United Kingdom)
  22. **AZ**. AstraZeneca AB (Sweden)
  23. **BPE**. Bordeaux PharmacoEpi (France)
  24. **AG**. Analysis Group (USA)

- **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**
EMA	European Medicines Agency
LMIC	Low- and middle-income countries
PASS	Post-authorisation safety studies
RCT	Randomised controlled trial
RMP	Risk management plan
RSV	Respiratory syncytial virus
UMCU	University Medical Center Utrecht
VAC4EU	Vaccine Monitoring Collaboration for Europe

This list of abbreviations only covers the Abstract, Introduction, Methods, Results and Discussion sections of the deliverable document. The protocols themselves (ANNEX 1 and ANNEX 2) each provide a comprehensive index of relevant abbreviations.

Abstract

Understanding the real-world safety of respiratory syncytial virus (RSV) preventive products is crucial for public health. The University Medical Center Utrecht (UMCU) and Pfizer, in collaboration with Vaccine Monitoring Collaboration for Europe (VAC4EU) and the PROMISE Consortium, have developed two protocols for post-authorisation safety studies (PASS) to assess the safety of RSV vaccination. One protocol focuses on vaccination during pregnancy, while the other targets older adults (>60 years). These protocols are intended as generic frameworks which can be adapted to specific settings and adjusted to accommodate local data availability.

Introduction

By the time of marketing authorisation, respiratory syncytial virus (RSV) preventive products such as vaccines have undergone extensive evaluation in randomised controlled trials (RCTs). Large field studies can complement RCTs in understanding the real-world safety of these products.[1]

The methodology and purpose of observational studies differ somewhat from those of RCTs. RCTs are conducted in controlled environments and apply more stringent selection criteria, while observational studies involve real-world populations. Furthermore, RCTs are often powered to demonstrate primary efficacy endpoints but may lack the power to confidently address secondary safety endpoints, whereas observational studies frequently have larger sample sizes.[1,2]

To assist researchers in preparing their own protocols to assess the safety of RSV preventive products, the University Medical Center Utrecht (UMCU) and Pfizer, in collaboration with Vaccine Monitoring Collaboration for Europe (VAC4EU) and the PROMISE Consortium, have developed two protocols for post-authorisation safety studies (PASS) to assess the safety of RSV vaccination. These protocols are in line with the post-marketing commitment outlined in the EU risk management plan for ABRYSVO™. One protocol focuses on vaccination during pregnancy, while the other targets older adults (>60 years). These protocols are intended as generic frameworks that can be adapted to specific settings and adjusted to accommodate local data availability. The primary objective of these studies is to assess safety, with the outcomes of interest selected according to the target population and product being studied.

Methods

The methodology of the proposed studies in pregnant individuals differs from those in older adults and is described in detail in the protocols (ANNEX 1 and ANNEX 2).

Results

Two generic study protocols were developed (see ANNEX 1 and ANNEX 2).

Discussion

The development of generic protocols serves as a guiding framework, providing flexibility for researchers or study sites to adapt them to their specific circumstances. In this regard, researchers should be conscientious when using the generic protocols, ensuring that they are adjusted according to the vaccine platform, outcomes of interest, and adhere to established templates such as the one outlined in the PASS guidelines provided by the European Medicines Agency (EMA).[3]

The approval of the first RSV vaccine in 2023 marked a significant milestone as the initial approved preventive product for RSV in older adults.[4] Subsequently, a vaccine authorised for use in both older adults and pregnant individuals was also approved.[5] These generic protocols are primarily designed with this latter approved RSV vaccine in mind. However, it is important to recognise that when new products enter the market, modifications to the generic protocols may be required to accommodate these products' unique characteristics and requirements.[6] For example, the administration schedule or the timing for giving the vaccine during specific gestational weeks of pregnancy.

We want these protocols to become widely available to ensure the safety of preventive products for RSV in pregnancy and older adults. By making these protocols publicly available, we aim to support other researchers and facilitate high-quality safety research in many settings, including outside Europe and in low- and middle-income countries (LMIC).

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ANNEXES

ANNEX 1. Safety of Respiratory Syncytial Virus Preventive Products in Pregnant Individuals and Their Offspring

1.1. TITLE

A Post-Authorisation Safety Study of a Respiratory Syncytial Virus Vaccine in Pregnant Individuals and Their Offspring in a Real-World Setting: Generic Protocol for a Target Trial Emulation

1.2. LIST OF ABBREVIATIONS

Acronym / Abbreviation	Meaning
CI	Confidence interval
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GAIA	Global Alignment on Immunization safety Assessment
GBS	Guillain-Barré Syndrome
LBW	Low birth weight
LMP	Last menstrual period
LRTI	Lower respiratory tract infection
MA-LRTI	Medically attended lower respiratory tract illness
MHRA	Medicines and Healthcare Products Regulatory Agency
NITAG	National Immunisation Technical Advisory Group
PASS	Post-authorisation safety studies
RCT	Randomised controlled trial
RR	Risk ratio
RSV	Respiratory syncytial virus
SGA	Small for gestational age
SMD	Standardised Mean Difference
SPEAC	Safety Platform for Emergency Vaccines
UMCU	University Medical Center Utrecht
VAC4EU	Vaccine Monitoring Collaboration for Europe
WHO	World Health Organization

1.3. ABSTRACT

Assessing the real-world safety of preventive products against respiratory syncytial virus (RSV) holds significant public health implications. This generic protocol outlines a post-authorisation safety study (PASS) designed as a target trial emulation, specifically tailored to evaluate the safety of an RSV vaccine in pregnant individuals. Emulating target trial conditions aims to minimise confounding and bias. As we cannot truly randomise participants in a real-world observational study, the emulated trial follows a pragmatic approach. RSV-vaccinated pregnant individuals are matched (1:N ratio) with unexposed pregnant individual(s) based on gestational age (same week of gestation), calendar time (same week), maternal age (year of birth), immunocompromised status and high-risk pregnancy. These matching factors comprise key confounding factors for adverse maternal, pregnancy and birth outcomes. Key adverse outcomes of interest encompass preterm birth, time between vaccination and birth, stillbirth, hypertensive disorders of pregnancy, Guillain-Barré Syndrome (GBS), low birth weight (LBW), and small for gestational age (SGA). Additional outcomes may be added based on the risk profile of the vaccine and the Global Alignment on Immunization safety Assessment (GAIA) recommendations. Distinguishing between outcomes measured during pregnancy and those assessed at or after birth is crucial, as it affects statistical analysis and interpretation. This generic protocol is intended to guide researchers and can be adapted to specific settings and modified to account for local data availability.

Keywords: RSV, target trial emulation, safety, maternal vaccination, pregnancy, protocol

1.4. RATIONALE AND BACKGROUND

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infections (LRTIs) in young children. In 2019 alone, RSV was responsible for 33 million LRTIs globally, leading to 3.6 million hospitalisations and around 100,000 deaths.[1] Notably, about half of the global burden of RSV falls upon infants under the age of 6 months, with a significant number occurring during the neonatal period.[1] In response to the urgent need for effective prevention measures, the introduction of an RSV vaccine for maternal immunisation during pregnancy offers promise in reducing the burden of RSV-associated illness in infants.[2] The mechanism underlying maternal immunisation involves the transfer of antibodies across the placenta to protect the infant during its vulnerable neonatal period and beyond.[3]

The development of maternal RSV vaccines is progressing swiftly, with multiple candidates vaccines advancing through phases 2 and 3 of development.[4] In 2023, the first maternal RSV vaccine was approved by the European Medicines Agency (EMA), the Food and Drug Administration (FDA) and the Medicines and Healthcare Products Regulatory Agency (MHRA).[5–7] These EU, US and UK marketing authorisations in pregnant individuals are based on evidence from a global, randomised, double-blinded, placebo-controlled study (MATISSE) designed to evaluate the efficacy, safety and immunogenicity of the vaccine against medically attended lower respiratory tract illness (MA-LRTI) due to RSV in infants born to healthy individuals vaccinated during pregnancy between weeks 24 to 36 of gestation. The study enrolled a significant number of participants, with 7,358 individuals receiving either the RSV vaccine or placebo. At the time of analysis, 5,654 infants (79%) completed 6-month follow-up after birth, with follow-up ongoing for a total of 24 months.[8] However, as immunocompromised pregnant individuals and individuals with high-risk pregnancies were excluded from the trial, the safety profile of the vaccine in these populations remains unknown, highlighting the necessity for further post-authorisation safety studies (PASS).

Furthermore, whilst there was no difference in the percentage of preterm births in the vaccine versus placebo groups, in the analyses stratified by setting, there was a statistically significant difference between groups for upper-middle-income countries observed in the MATISSE trial.[9] Of note, a trial of another candidate maternal RSV vaccine was stopped early because of a higher risk of preterm birth in the vaccine group than in the placebo group.[10] As the first vaccine to be approved for the maternal indication and given this potential uncertainty about preterm birth, the regulatory agencies each approved the vaccine for use at different gestational ages.[11] The EMA decided that the vaccine can be administered beginning at 24 weeks of gestation. The FDA approved vaccination of pregnant individuals at 32 through 36 weeks of gestation and the MHRA has recommended that the vaccine may be given in the third trimester of pregnancy (weeks 28 to 36 of gestation).[12] Furthermore, Guillain-Barré Syndrome (GBS) has been reported in the clinical trial of the approved vaccine in older adults.[13] Although GBS has not been reported in clinical trials in pregnant individuals, it is highlighted as a prespecified safety event of interest.

Given the importance of addressing gaps in safety data, a protocol for a PASS to assess the safety of this RSV vaccine in pregnant individuals and their offspring in real-world settings was developed as an additional pharmacovigilance activity outlined in the EU and UK approved risk management plans and as a post-marketing requirement to the FDA.[14,15] This protocol provides a generic framework of the PASS protocol to assist researchers in the preparation of their own protocols during the post-marketing phase in the coming years.

1.5. OBJECTIVES

The primary objective of a maternal RSV immunisation study should be to estimate the occurrence of adverse maternal, pregnancy and birth outcomes in individuals who receive the vaccine during pregnancy (and their offspring), compared with a matched comparator group of pregnant individuals who do not receive the RSV vaccine during pregnancy (and their offspring). The secondary objectives may include assessing the occurrence of these adverse outcomes in immunocompromised or high-risk pregnant individuals who receive the RSV vaccine compared to those who do not, as these groups were not studied in clinical trials. Additionally, one may wish to estimate the occurrence of adverse outcomes by gestational week of vaccination to better understand effect modification by week of gestation.

1.6. RESEARCH METHODS

1.6.1. Study design

We recommend an observational retrospective comparative cohort study of pregnant individuals who receive the RSV vaccine compared to an unexposed pregnant comparator group (or an active comparator when there is one). To assess whether the RSV vaccine increases the risk of any adverse outcome in pregnancy or offspring, we propose designing the study to emulate a hypothetical pragmatic randomised trial.[16] This trial would assess the safety of administering one dose of the RSV vaccine between 24-36 weeks of gestation in pregnant individuals compared to pregnant individuals who do not receive an RSV vaccine (Figure 1.1.A). As we cannot truly randomise participants, we need to emulate this feature by carefully addressing confounding biases through various techniques such as matching and careful assessment of inclusion criteria. Time zero, designated as day 0, marks the point at which the eligibility criteria are fulfilled, and the RSV vaccine is administered to the pregnant individual. There should be sufficient data for the individual to allow for a look-back period of at least one year.

At Time zero, exposed participants should be matched to unexposed pregnant participants (1:N ratio) based on (Figure 1.1.B):

- Gestational age (same week of gestation) to account for timing of vaccination in pregnancy and the risk of preterm birth
- Calendar time (same week) because of RSV seasonality and probability of exposure
- Maternal age (year of birth) because of the association with adverse pregnancy outcomes
- Immunocompromised status because of the association with adverse maternal outcomes
- High-risk pregnancy because of the association with adverse pregnancy outcomes

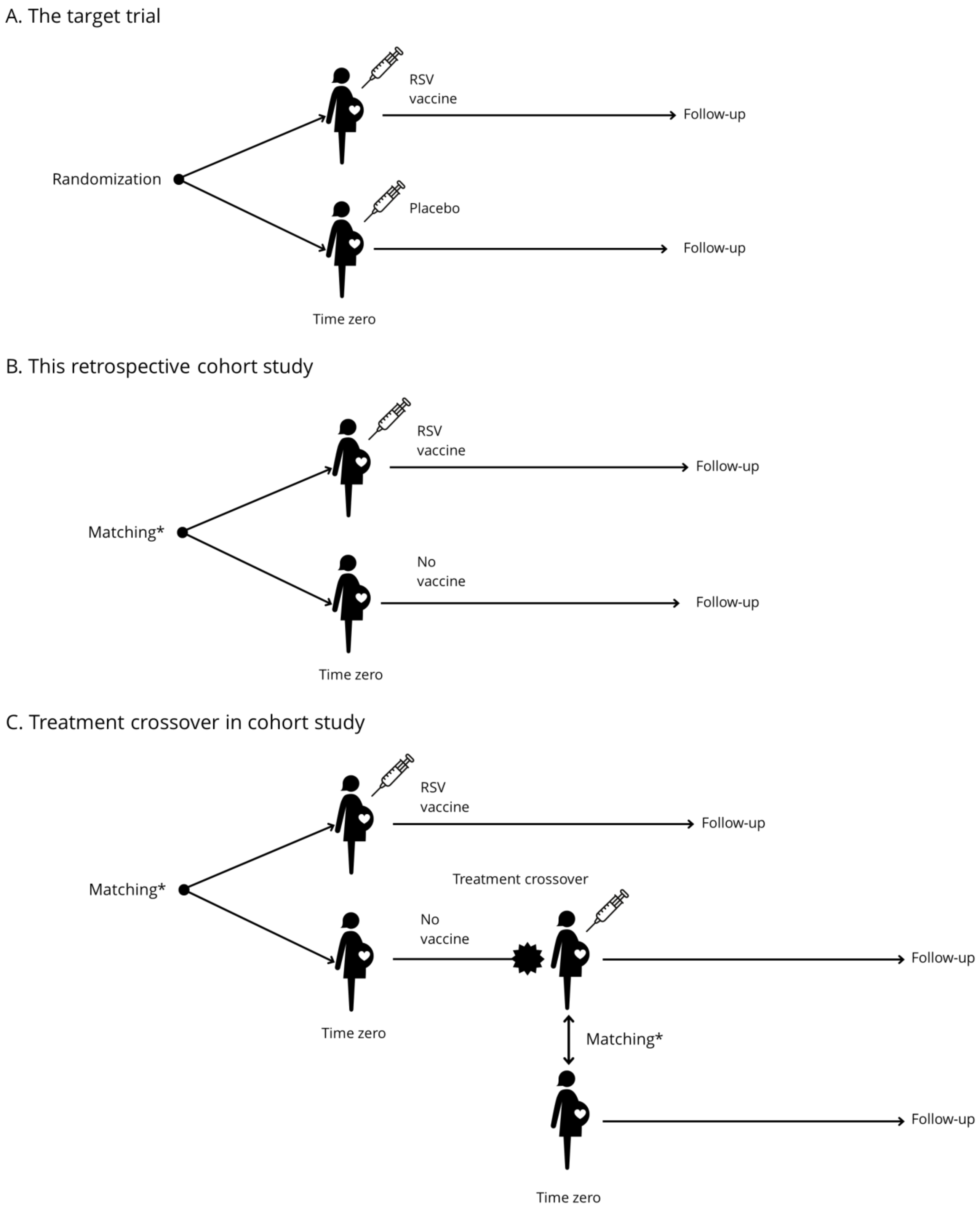

Figure 1.1. Study design

*Matching should be on gestational age (same week of gestation), calendar time (same week) and maternal age. Additional characteristics may be added.

Additional characteristics may be added that would confound the association.

A primary analytical concern is the gestational age at Time zero, which directly impacts the risk of preterm birth. Therefore, it is imperative to ensure a robust match on gestational age, and in fact, we recommend emulating a series of separate target trials for different gestational ages at vaccination i.e., 24, 25, 26, …, or 36 weeks to study effect modification.[17] Follow-up of the exposed and unexposed (or active comparator) pregnant individuals should start on day 1, and end at the earliest of N months after birth depending on the outcome being measured, maternal death, disenrollment or migration, end of data availability in the data source, treatment crossover, or occurrence of a given outcome. Treatment crossover, or protocol violation, occurs when previously unexposed pregnant individuals in the matched comparator cohort receive vaccination with an RSV vaccine during pregnancy. To uphold statistical power, unexposed pregnant individuals within the matched comparator cohort ought to be censored upon treatment violation, while exposed pregnant individuals should remain uncensored (see Section 1.6.7.2.). When unvaccinated pregnant individuals receive an RSV vaccine, they become eligible for inclusion in the vaccinated cohort (Figure 1.1.C). Follow-up of offspring to assess birth outcomes will depend on the risk window for measuring the outcome and will end at the earliest of N months of age, neonatal death, disenrollment or migration, end of data availability in the data source, or occurrence of a given outcome.

1.6.2. Study setting

To have sufficient power, the study should use real-world secondary data derived from electronic health records or claims data that can be linked on an individual level to birth registries and outcomes in offspring (mother-child linkage). The specific study setting will be defined by the availability and nature of the data source(s) utilised and will depend on the country or region covered by the data source. To assess whether data sources are fit for purpose, it will be important to ascertain the accuracy of estimating the start and end of pregnancy, the ability to detect ongoing pregnancies, the capacity to identify exposure to RSV vaccines including timing of vaccine dose, the feasibility of linking mother and child, the capability to measure outcomes and confounders of interest, and the lag time for data availability for each study component. We recommend the use of quality indicators and external benchmarks to assess whether a data source is fit for purpose.[18,19] Key aspects of this evaluation include:

- Population coverage: The data source should cover a representative sample of the population under study. This includes demographics such as age, sex, ethnicity, and geographic location.
- Data granularity: The data should be granular enough to capture individual-level information on healthcare encounters, including diagnoses, procedures, prescriptions, and outcomes.

- Longitudinal data: Longitudinal data, tracking individuals over time, is essential for understanding disease progression, treatment patterns, and outcomes.
- Data quality: High-quality data is crucial for reliable analysis. This involves accurate information recording, standardised coding systems, and measures to address missing or erroneous data.
- Data linkage: The ability to link data across different sources (e.g., primary care, hospitals, pharmacies, birth registers) enables a comprehensive view of healthcare utilisation and outcomes.
- Privacy and ethical considerations: Data sources must adhere to strict privacy regulations and ethical guidelines to protect patient confidentiality and ensure informed consent.
- Timeliness: Timely updates ensure that researchers can access the most current information, allowing for real-time or near-real-time analyses.

1.6.3. Study period

The first maternal vaccine was launched on 23 August 2023. In a hypothetical scenario focused on a study of its safety, we propose commencing data collection retrospectively from 24 August 2022. This means that we will gather data starting from the day following approval, allowing for a one-year look-back period. This period is essential for capturing prior medical history, including diseases, comorbidities, and medication use, which are critical factors to consider in the study's analysis and interpretation. Data collection will continue until the last data availability for each data access provider based on the calendar date of the last data extraction. Given the anticipated need for a significant number of participants, we expect a follow-up period of at least 5 years, with the latest data extraction planned for 2029. However, we recommend regular progress reports, with reporting triggered by the number of exposures.

1.6.4. Study population

The study population comprises all pregnant individuals who receive an RSV vaccine during pregnancy from the earliest indicated timing of gestation for which the vaccine is licensed and a matched comparator group of pregnant individuals who did not receive the RSV vaccine or received another RSV vaccine. Identification of pregnancies may vary across data sources which is very important since most data sources that link to birth registries only detect pregnancies when they end. Validated data source-specific algorithms or the ConcePTION pregnancy algorithm could be employed to determine pregnancy start and end dates of ongoing pregnancies. The ConcePTION algorithm was created to identify ongoing pregnancies using diagnosis and procedure data related to pregnancy.[20] The identification of ongoing pregnancies is important to avoid selection bias towards pregnancies that ended prematurely. In instances where pregnancy data are only available when the pregnancy has ended, a minimum of 10 months of administrative follow-up from the last menstrual period (LMP) in the data source, unless they died, is recommended for all pregnancy and birth outcomes. This period covers the gestational period plus an additional month to identify offspring outcomes at birth.[17] It is important to anticipate that individuals may have more than one pregnancy and those subsequent pregnancies could be included to increase power.

1.6.4.1. Recommended inclusion criteria

Participants are eligible if they:

- have an identified start of pregnancy date.
- are enrolled in the healthcare system for a least 12 months prior to Time zero (date of vaccination).
- are or are not vaccinated with an RSV vaccine in a specific gestational week for which the vaccine is licensed.
- have at least one day of follow-up after Time zero for maternal outcomes and at least 10 months of follow-up after the LMP for birth and pregnancy outcomes.

1.6.4.2. Recommended exclusion criteria

Participants are excluded if they:

- are exposed to an RSV vaccine prior to the current pregnancy or before or after the gestational week for which the vaccine is licensed (vaccination in a prior pregnancy is permitted).
- cannot be linked in the data source to their child (mother-child linkage).

1.6.5. Variables

1.6.5.1. Exposure

The exposure of interest is RSV vaccination during pregnancy. The vaccine data could be obtained from pharmacy dispensing records, general practice records, immunisation registers, vaccination records, medical records or other databanks. We will consider a single administration of one dose between 24-36 weeks of gestation. An individual is considered exposed from the date of vaccination until the end of pregnancy for all pregnancy and birth outcomes.

1.6.5.2. Outcomes

The proposed key outcomes of interest, along with their respective outcome-specific exposure windows, are described in Table 1.1. and encompass preterm birth, time between vaccination and birth, stillbirth, hypertensive disorders of pregnancy, Guillain-Barré Syndrome (GBS), low birth weight (LBW), and small for gestational age (SGA). The outcome time between vaccination and birth holds more statistical power than preterm birth, as preterm birth is a categorical outcome while time between vaccination and birth is continuous. Distinguishing between outcomes measured during pregnancy and those assessed at or after birth is crucial, as it affects statistical analysis and interpretation. Additional outcomes for maternal immunisation may be added based on the risk profile of the vaccine.[21] The clinical definitions for outcomes of interest should be based on either the Global Alignment on Immunization safety Assessment (GAIA), Brighton Collaboration, or the official World Health Organization (WHO) definitions.[22,23] While these definitions can be adjusted, utilising these official, globally recognised definitions will enhance harmonisation and study comparability. The outcomes should be ascertained using algorithms based on codes for diagnoses, procedures, medical products and information from each specific databank. We recommend working with each data source to understand how information can be retrieved and how outcomes and other variables are coded.

1.6.5.3. Covariates

Crucial covariates of interest include matching variables: gestational age, calendar time, maternal age, immunocompromised status and high-risk pregnancy, for which definitions are provided in Table 1.2. Similar to outcomes, covariates should be identified using diagnoses, procedures, medical products and information from each specific databank. Additionally, risk factors for each of the outcomes and exposure of interest should be included. An example is presented in Supplementary Table 1.1. Maternal vaccinations such as influenza, SARS-CoV-2, Tetanus, Diphtheria and Pertussis (Tdap) given prior to RSV vaccination should also be recorded, as well as RSV monoclonal antibodies and RSV vaccination of the offspring.

1.6.6. Study size

All individuals meeting eligibility criteria during the study observation period should be included in the study. It is currently unknown how many individuals will receive RSV vaccination during pregnancy, as the National Immunisation Technical Advisory Groups (NITAGs) need to determine whether this will be included in routine maternal immunisation programs in the country or region where the study is conducted. Minimal detectable risks can be calculated based on the assumption that every vaccinated pregnant individual could be compared with N unvaccinated pregnant individual(s) (1:N ratio). The desired alpha level is 5%, and relative risk (RR) values of 1.5, 2.0, 2.5 and 4.0 may be considered (Supplementary Table 1.2.). For pregnancy and birth outcomes, the required number of exposed individuals to achieve a power of 80% under different RR values, may assume prevalence rates in the unexposed group ranging from 0.2% to 6.0%. To detect an RR of 1.5 with 95% confidence interval (CI) for preterm birth, approximately 1200 pregnancies ending in live birth would need to be included in a data source.

Table 1.1. Outcomes of interest

Outcomes	Clinical definition	Pregnancies among which the outcome will be ascertained	Exposure risk window for outcome
Pregnancy outcomes			
Preterm birth[24]	Preterm birth is defined by the WHO as babies born alive before 37 weeks of pregnancy are completed. It is further subcategorised based on gestational age: • Extremely preterm (less than 28 weeks) • Very preterm (28 to less than 32 weeks) • Moderate to late preterm (32 to 37 weeks)	Pregnancies ending with live births	From time of vaccination to before week 37 of gestation (36 weeks and 6/7 days)
Time between vaccination and birth	Time between vaccination and birth in days.	Pregnancies ending with live and non-live births	From time of vaccination to time of birth
Stillbirth[25]	Stillbirth is defined by the WHO as the death of a foetus that has reached a birth weight of 500 gram, or if birth weight is unavailable, gestational age of 22 weeks or crown-to-heel length of 25 cm. It is further subcategorised based on gestational age: • Late foetal deaths (greater than 1000 grams or after 28 weeks) • Early foetal deaths (500–1000 grams or 22–28 weeks)	Pregnancies ending with live and non-live births	From time of vaccination to end of pregnancy
Maternal outcomes			
Hypertensives disorders of pregnancy[26,27]	Hypertensives disorders of pregnancy include: • Gestational hypertension (defined as systolic blood pressure greater than or equal to 140 mm/Hg and/or diastolic blood pressure greater than or equal to 90 mm/Hg arising de novo at ≥20 weeks' gestation in the absence of proteinuria or other findings suggestive of pre-eclampsia) • Preeclampsia de novo (defined as gestational hypertension accompanied by one or more of the following new-onset conditions at ≥20 weeks' gestation: a) Proteinuria b) Other maternal end-organ dysfunction, including neurological complications, pulmonary oedema, haematological complications, renal insufficiency, or impaired liver function c) Uteroplacental dysfunction • Preeclampsia superimposed on chronic hypertension (among persons with chronic hypertension, development of new proteinuria, another maternal organ dysfunction(s), or evidence of uteroplacental dysfunction HELLP (Haemolysis, Elevated Liver Enzyme, Low Platelet) is a serious manifestation of pre-eclampsia and should be assessed if available.	Pregnancies ending with live and non-live births	From time of vaccination to end of pregnancy
Guillain-Barré Syndrome (GBS)[28]	GBS is defined as an neurological condition in which a person's immune system attacks the peripheral nerves. It is a rare condition and the cause of it is not fully understood. Most cases follow an infection with a virus or bacteria, e.g., Campylobacter jejuni, cytomegalovirus, Epstein-Barr virus and the Zika virus. In rare instances, vaccinations may increase the risk of people getting GBS.	Pregnancies ending with live and non-live births	From time of vaccination until 42 days following vaccination
Birth outcomes			
Low birth weight (LBW)[29]	Low birth weight is defined by the WHO as a weight at birth of less than 2500 g, regardless of gestational age.	Pregnancies ending with live births	From birth until one month after birth
Small for gestational age (SGA)[30]	Small for gestational age is defined by the WHO as a birth weight below the 10th percentile for gestational age and sex. SGA can be caused by placental dysfunction, referred to as foetal growth restriction (FGR), or it can be due to a constitutionally small foetus without any pathological causes. Other possible causes include congenital malformations or infections.	Pregnancies ending with live births	From birth until one month after birth

Table 1.2. Crucial covariates of interest

Covariate	Definition
Gestational age at time of vaccination	Gestational age at time of vaccination is defined as the time between the last menstrual period (LMP) and the date of vaccination, measured in weeks.
Calendar time at time of vaccination	Calendar time at the time of vaccination is defined as the specific calendar date of the vaccination, expressed in weeks (e.g., week 48 of the year 2024 or week 12 of the year 2025).
Maternal age	Maternal age at time of vaccination is defined as the age of the pregnant person at the date of vaccination. This age is determined by subtracting the individual’s date of birth from the date of vaccination.
Immunocompromised status	Immunocompromised status is defined as meeting at least one of the following criteria at the time of vaccination or in the period prior to vaccination: • Medical conditions a) Diagnosed with symptomatic HIV/AIDS b) Diagnosed with hematologic malignancy (e.g., chronic lymphocytic leukaemia, non-Hodgkin lymphoma, multiple myeloma, acute leukaemia) c) Diagnosed with solid malignancy d) Diagnosed with rheumatologic/inflammatory conditions (e.g., Sjogren’s syndrome, SLE, psoriatic arthritis, rheumatic arthritis, arthritis spondylarthritis, polymyalgia rheumatica, demyelination multiple sclerosis, polymyalgia rheumatica, IBD, autoimmune thyroiditis) and have evidence of treatment with chemotherapy or immune modulators (see below) • Immunosuppressive treatments a) Organ transplant recipients or islet transplant recipients taking immunosuppressive therapy b) CAR-T-cell therapy or hematopoietic stem cell transplant recipients taking immunosuppressive therapy c) Rheumatologic/inflammatory conditions treated with systemic corticosteroids d) Active treatment (at time of vaccination) with various immunosuppressive agents (e.g., systemic corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, TNF blockers, and other biologic agents that are immunosuppressive or immunomodulatory). • Specific medical procedures a) Organ transplant recipients or islet transplant recipients b) CAR-T-cell therapy or hematopoietic stem cell transplant recipients
High-risk pregnancy	High-risk pregnancy is defined as pregnancies in which individuals or their offspring have a history of any of the following conditions in the current pregnancy (prior to vaccination): • Obesity • Hypertension • Pre-eclampsia/eclampsia • Multifetal pregnancy • Diabetes • Gestational diabetes • Congenital anomaly And/or any of the following conditions in previous pregnancies: • Gestational diabetes • Pre-eclampsia/eclampsia • Stillbirth or late miscarriage • Small for gestational age or foetal growth restriction • Congenital anomaly

For rare outcomes during pregnancy such as GBS, we calculated the power obtainable assuming a maximum sample size of 30,000 exposed pregnant individuals, with an incidence rate of 1/100,000 person-years in the comparator group.[31]

1.6.7. Data Analysis

Detailed methodology for summary and statistical analyses should be documented in a statistical analysis plan and be drafted prior to any analyses. Any major modifications of the prespecified analyses should be clearly reported. Changes should be annotated and amended when they are major.

1.6.7.1. Baseline characteristics

Baseline characteristics for both maternal RSV-exposed and pregnant comparator cohorts should be reported as means, standard deviations, medians and other quartiles for continuous variables, and counts and proportions for categorical variables. Any missing baseline characteristics and the duration of the look-back period should be explicitly described. To assess the comparability of matched cohorts, a standardised difference between the index and comparator cohort can be computed for each baseline characteristic. In cases where categorical variables have more than two levels, an overall standardised difference should be calculated.

1.6.7.2. Measures of effect

Primary analyses should estimate counts, proportions, and risk or rate ratios with 95% CI for events occurring and measurable during pregnancy, and counts, proportions, and prevalence ratios with 95% CI for outcomes measurable at birth. Comparison of outcomes by exposure status should be conducted using multivariable generalised linear models. These analyses should control for potential confounding by matching. Balance of covariates should be analysed using standardised mean differences (SMDs), some characteristics and risk factors for the exposure or outcomes may remain unbalanced, which should be analysed using plots of SMDs. To address this, propensity score methods can be employed and propensity scores can be adjusted or additionally matched on if necessary.[32] To obtain more power for the analysis of preterm birth, we recommend that time from vaccination to birth should be analysed using time-to-event analyses, using both the Kaplan-Meier and Cox-survival analyses, which allow for multivariate adjustment.

The primary analyses may face selective censoring due to treatment crossover in the comparator cohort, necessitating the use of inverse probability censoring weights. To maintain statistical power, unexposed pregnant individuals in the matched comparator cohort should be censored upon treatment violation, while exposed pregnant individuals should not be censored. A sensitivity analysis can be conducted to explore the effect of censoring the matched pair if treatment crossover happens in the previously unexposed pregnant individual. Another sensitivity analysis may be carried out to explore the effect of exclusion of medically indicated iatrogenic births.

For subgroup analyses, secondary analyses should be conducted among immunocompromised or high-risk pregnancies and stratified by weeks of gestation at the time of vaccination.

1.6.7.3. Meta-analysis

In case multiple data sources are utilised, we recommend employing a common analytics tool, such as an R-script, to conduct the analyses separately within each data source consistently. Subsequently, utilising the main estimates obtained from each data source, appropriate random-effects meta-analytic methods should be applied to derive a combined effect estimate.[33,34] To assess potential heterogeneity across data sources, it is advisable to visually inspect and check using forest plots, displaying the study site estimates and a pooled estimate with 95% CIs. In situations where there are zero events, we suggest pooling incidence rates, as they can be zero and still yield valid standard errors.

1.6.8. Quality control

We want to highlight that it is important to conduct quality control procedures to ensure the existence and accuracy of records. Quality control can be conducted using the INSIGHT level 1-3 data quality checks.[35] Briefly, level 1 verifies data completeness, level 2 ensures data consistency, and level 3 checks for study variables and whether data are fit for purpose.

1.6.9. Protection of human subjects

Ethical considerations are paramount in any research involving human subjects. In this generic protocol for a retrospective database study, we describe data that exist in a deidentified/pseudonymised structured format without including personal patient information, thus eliminating the need for informed consent from participants. However, in the event of conducting a new study, it is essential to adhere to ethical guidelines and obtain approval and consent to safeguard the rights and well-being of participants if needed.

There must be prospective approval from relevant Institutional Review Boards or Ethics Committees for the study protocol and amendments. Furthermore, we highly recommend conducting the study according to the guidelines for Good Pharmacoepidemiology Practice and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guide on Methodological Standards in Pharmacoepidemiology.[36,37] Additionally, the study protocol should be registered before data collection begins and adhere to transparency and scientific independence principles outlined by the ENCePP Code of Conduct.[38]

1.7. DISCUSSION

This generic protocol has been developed to assess the safety of RSV vaccines in pregnant individuals and their offspring in real-world settings utilising secondary sources of data. It presents the emulation of a target trial, assessing the safety of administering a single dose of an RSV vaccine to pregnant individuals between 24-36 weeks of gestation compared to pregnant individual who do not receive RSV vaccination during pregnancy.[8] The emulation of target trial conditions will help to reduce bias due to censoring, immortal time, competing events and confounding, improve the interpretability of estimands and highlight any remaining challenges with the data.[17] However, despite efforts to minimise bias and improve interpretability, limitations persist in target trial emulation using observational data. These may include challenges in accurately capturing all relevant confounders. Data sources that routinely collect data often provide comprehensive information on treatments and outcomes but may lack sufficient detail on clinical factors that require adjustment.[39] Fitness for purpose should be assess in feasibility studies.[18,19]

The study will use code lists or observations in birth registers to identify the covariates and outcomes of interest. An important consideration using code lists is the potential for outcome misclassification, which can introduce bias and impact the interpretation of findings. The code lists could be sourced from Vaccine Monitoring Collaboration for Europe (VAC4EU) (https://vac4eu.org/), as these have undergone thorough review by medical professionals. Only code labelled as “narrow” are included to mitigate the false-positive rate. For preterm birth, validation may be needed since preterm birth can either be spontaneous or medically indicated (iatrogenic), whereas our focus is only on spontaneous preterm birth. Codes and outcomes definitions may be scrutinised in Safety Platform for Emergency Vaccines (SPEAC) companion guides. Validation of outcomes, using Brighton or WHO definitions, may be conducted when resources are available.

In addition to outcome misclassification, it is also crucial to address exposure misclassification. Since RSV vaccination has only recently received approval for maternal immunisation, and many countries’ NITAGs have yet to decide on its inclusion in routine immunisation schedules, it can be challenging to determine whether current data sources accurately capture RSV vaccination. This challenge is reflected by the current situation in Europe, where other maternal immunisation practices vary widely across countries, and some prefer to provide monoclonal antibodies or vaccines to neonates.[2,40] Therefore, before commencing data collection, it is imperative to liaise with relevant public health organisations to understand if and how RSV vaccination will be integrated into routine immunisation programs for maternal immunisation and in which settings it is provided. Subsequently, it is essential to verify if the data source adequately captures this information and compare it with national statistics to ensure comprehensive coverage and prevent exposure misclassification in the comparator group.

It is important to note that a non-exposed comparator group may be chosen because presently there is only one approved maternal vaccine for preventing RSV infection in offspring. In the event that other RSV vaccines receive approval, it is crucial to consider their inclusion in the study design. This necessitates either incorporating all different RSV vaccines in the exposed group or excluding individuals specifically vaccinated with other RSV vaccines from the unexposed group.

Because of safety concerns, the primary outcome measure under examination is preterm birth, considering the varying recommendations by EMA, FDA and MHRA regarding the optimal gestational age for vaccination.[5–7,11,12] Notably, concerns over preterm births have led to the suspension of a phase 3 trial for another candidate RSV prefusion subunit vaccine.[10] However, a significant challenge in analysing preterm birth in observational studies lies in its direct relationship with gestational age at the time of vaccination. For instance, administering the vaccine at 35 weeks of gestation may not result in an extremely preterm birth. Therefore, we emphasise the critical importance of matching participants based on gestational age at the time of vaccination. In fact, participants will be enrolled in a sequence of weekly trials based on their gestational age at the time of vaccination. Additionally, we have added the outcome time between vaccination and birth. This outcome holds more statistical power than preterm birth, as preterm birth is a categorical outcome while time between vaccination and birth is continuous. Also, this approach allows us to examine the median time between vaccination and preterm births, which is crucial for identifying specific underlying mechanisms. For instance, it can reveal whether the preterm infants are born days, weeks, or months after vaccination. Moreover, this outcome is independent of the accuracy of gestational age assessment. Other outcomes can be chosen, and we refer to the GAIA initiative, which defined more than 20 outcomes relevant for maternal immunisation.[22]

This generic protocol is designed to offer guidance for researchers and health authorities in evaluating the safety of RSV vaccination during pregnancy. A target trial emulation approach of observational data can be selected to minimise bias and improve interpretability. We envision this protocol serving as a valuable tool, fostering alignment of research efforts and aiding in the monitoring of the safety of RSV vaccination in pregnant individuals and their offspring.

SUPPLEMENTARY INFORMATION

Supplementary Table 1.1. Risk factors for the outcomes of interest

PRETERM BIRTH[24,41]	
Risk factors	**Covariate assessment window**
Advanced maternal age (≥35 years) or early maternal age (<20 years)	At time of vaccination
Race/ethnicity: African American, Afro-Caribbean	From database entry to time of vaccination
Smoking during pregnancy, substance abuse/dependence during pregnancy	From start of pregnancy to time of vaccination
This pregnancy: nulliparity, multifetal pregnancy, ART, short uterine cervix (<25 mm in second trimester), gestational hypertension, preeclampsia, gestational diabetes, premature rupture of membrane, placenta previa, antepartum haemorrhage	From start of pregnancy to time of vaccination
Prior pregnancy history of: preterm birth, abortion, caesarean delivery	From database entry to time of vaccination
Birth space less than 2 years	From database entry to time of vaccination
Morbidities: anaemia, asthma, obesity (pre-pregnancy BMI >30 kg/m2), pre-existing diabetes, chronic hypertension, depression, thyroid disease, anomalies of the uterus (e.g., presence of a uterine septum)	Chronic comorbidities: From database entry to time of vaccination. Time-varying comorbidities: From 365 days prior to time of vaccination.
Infections: HIV, urinary tract infections, chlamydia, toxoplasmosis, trichomonas vaginalis, malaria, COVID-19	Chronic infections: From database entry to time of vaccination. Acute infections: From start pregnancy to time of vaccination.
Medicines: antidepressants, benzodiazepines, selective serotonin receptor inhibitors, antibiotics, NSAIDs	From start of pregnancy to time of vaccination
STILLBIRTH[25,42]	
Risk factors	**Covariate assessment window**
Advanced maternal age (≥35 years) or early maternal age (<20 years)	At time of vaccination
Race/ethnicity: Black, African American	From database entry to time of vaccination
Smoking, substance abuse/dependence	From start of pregnancy to time of vaccination
This pregnancy: nulliparity, multifetal pregnancy, ART, gestational hypertension, preeclampsia, gestational diabetes, FGR, congenital anomaly, premature rupture of membrane, antepartum haemorrhage, placental abruption	From start of pregnancy to time of vaccination
Prior pregnancy history of: stillbirth, pregnancy loss, miscarriage, preterm birth, SGA	From database entry to time of vaccination
Morbidities: obesity (pre-pregnancy BMI >30 kg/m^2), pre-existing diabetes, chronic hypertension, chronic kidney disease, thyroid disorders, SLE, sickle cell disease	Chronic comorbidities: From database entry to time of vaccination. Time-varying comorbidities: From 365 days prior to time of vaccination.
Infections: HIV, Escherichia coli, Klebsiella, Group B Streptococcus, Enterococcus, Mycoplasma/Ureaplasma, Haemophilus influenzae, Chlamydia	Chronic infections: From database entry to time of vaccination. Acute infections: From start pregnancy to time of vaccination.
HYPERTENSIVE DISORDERS OF PREGNANCY[26,43]	
Risk factors	**Covariate assessment window**
Advanced maternal age (≥40 years)	At time of vaccination
Race/ethnicity: African American	From database entry to time of vaccination
Smoking (protective)	From start of pregnancy to time of vaccination
This pregnancy: nulliparity, multifetal pregnancy, ART	From start of pregnancy to time of vaccination
Prior pregnancy history of: pre-eclampsia, placental abruption, stillbirth, FGR	From database entry to time of vaccination
Morbidities: obesity (pre-pregnancy BMI >30 kg/m^2), pre-existing diabetes, chronic hypertension, chronic kidney disease (inc. kidney transplanted women), SLE antiphospholipid antibody syndrome, rheumatoid arthritis, sickle cell disease, PCOS, multiple sclerosis	Chronic comorbidities: From database entry to time of vaccination. Time-varying comorbidities: From 365 days prior to time of vaccination.
Infections: urinary tract infections	Chronic infections: From database entry to time of vaccination. Acute infections: From start pregnancy to time of vaccination.

GUILLIAN-BARRÉ SYNDROME[28,44]

Risk factors	Covariate assessment window
Co-morbidities: HIV, mycoplasma pneumonia	Chronic comorbidities: From database entry to time of vaccination. Time-varying comorbidities: From 365 days prior to time of vaccination.
Infections: Campylobacter jejuni, CMV, EBV, influenza, Zika virus	Chronic infections: From database entry to time of vaccination. Acute infections: From start pregnancy to time of vaccination.

LOW BIRTH WEIGHT[29,45]

Risk factors	Covariate assessment window
Advanced maternal age (≥35 years) or early maternal age (<20 years)	At time of vaccination
Race/ethnicity: Black	From database entry to time of vaccination
Smoking, substance abuse/dependence	From start of pregnancy to time of vaccination
This pregnancy: nulliparity, multifetal pregnancy, preterm birth, gestational hypertension, preeclampsia, gestational diabetes, FGR, congenital anomaly	From start of pregnancy to time of vaccination
Prior pregnancy history of: preterm birth, low birth weight	From database entry to time of vaccination
Morbidities: anaemia, pre-existing diabetes, chronic hypertension, chronic kidney disease	Chronic comorbidities: From database entry to time of vaccination. Time-varying comorbidities: From 365 days prior to time of vaccination.
Infections: HIV, CMV, rubella, chickenpox, toxoplasmosis, chlamydia	Chronic infections: From database entry to time of vaccination. Acute infections: From start pregnancy to time of vaccination.

SMALL FOR GESTATIONAL AGE[30,45,46]

Risk factors	Covariate assessment window
Advanced maternal age (≥35 years) or early maternal age (<20 years)	At time of vaccination
Race/ethnicity: Black	From database entry to time of vaccination
Smoking, substance abuse/dependence	From start of pregnancy to time of vaccination
This pregnancy: nulliparity, multifetal pregnancy, ART, gestational hypertension, preeclampsia, gestational diabetes, FGR, congenital anomaly, placental abruption	From start of pregnancy to time of vaccination
Prior pregnancy history of: SGA	From database entry to time of vaccination
Morbidities: anaemia, pre-existing diabetes, chronic hypertension, chronic kidney disease, SLE, sickle cell disease, anomalies of the uterus (e.g., presence of a uterine septum)	Chronic comorbidities: From database entry to time of vaccination. Time-varying comorbidities: From 365 days prior to time of vaccination.
Infections: HIV, CMV, rubella, toxoplasmosis	Chronic infections: From database entry to time of vaccination. Acute infections: From start pregnancy to time of vaccination.

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; CMV, cytomegalovirus; EBV, Epstein Barr virus; FGR, foetal growth restriction; GBS, Guillain-Barré syndrome; HIV, human immunodeficiency viruses; NSAIDS, non-steroidal anti-inflammatory drugs; PCOS, polycystic ovary syndrome; SGA, small for gestational age; SLE, systemic lupus erythematosus.

Supplementary Table 1.2. Power and sample size estimates for Guillain-Barré Syndrome and pregnancy and birth outcomes

Risk Ratio (RR)	**RR=1.5**	**RR=2.0**	**RR=2.5**	**RR=4.0**
Guillain-Barré Syndrome				
Incidence rate 1/100,000 person/years, maximum number exposed 30,000, 1:1 ratio unexposed:exposed				
Power to detect	0.0341	0.0406	0.0461	0.0628
Pregnancy and birth outcomes				
Power of 80%, 1:1 ratio unexposed:exposed, rounded-up to nearest hundred				
Prevalence 0.2% (e.g., stillbirth)	38600	11300	5700	1900
Prevalence 1%	7600	2300	1200	400
Prevalence 2%	3800	1100	600	200
Prevalence 3%	2500	800	400	100
Prevalence 4%	1900	600	300	100
Prevalence 5%	1500	500	300	100
Prevalence 6% (e.g., preterm birth, low birth weight)	1200	400	200	100

Based on the Cohort Power tab of episheet by K. Rothman and O. Miettinen[31]

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ANNEX 2. Safety of Respiratory Syncytial Virus Preventive Products in Older Adults

2.1. TITLE

Safety of RSV Vaccine among Immunocompromised, or Renally or Hepatically Impaired Adults Aged 60 Years and Older: Generic Protocol for a Post-Authorisation Safety Study of Preventative Products against RSV

2.2. LIST OF ABBREVIATIONS

Acronym / Abbreviation	Meaning
ARI	Acute respiratory infection
CCI	Charlson Comorbidity Index
CI	Confidence interval
CKD	Chronic kidney disease
DVT	Deep vein thrombosis
GBS	Guillain-Barré Syndrome
IRR	Incidence Rate Ratio
IPCW	Inverse Probability Censoring Weighted
LRTD	Lower respiratory tract disease
MELD	Model for End-Stage Liver Disease
PASS	Post-authorisation safety studies
PS	Propensity score
RCT	Randomised controlled trial
RR	Risk ratio
RSV	Respiratory syncytial virus
SCRI	Self-Controlled Risk Interval Designs
SAP	Statistical Analysis Plan
VAC4EU	Vaccine Monitoring Collaboration for Europe

2.3. ABSTRACT

Respiratory syncytial virus (RSV) poses a severe threat to vulnerable populations such as immunocompromised individuals, often leading to high morbidity and mortality. This generic protocol outlines a post-authorisation safety study (PASS) for an RSV vaccine targeting immunocompromised, or renally or hepatically impaired adults aged 60 years and older in specific European countries and the UK. While the available vaccines are approved to prevent lower respiratory tract disease (LRTD) caused by RSV in this age group, its safety in these vulnerable populations remains unknown due to these populations being excluded from prior clinical trials. This study aims to estimate incidence rates and rate ratios of safety events in vaccinated compared to unvaccinated groups, applying retrospective comparative cohort and self-controlled risk interval designs (SCRI). Real-world secondary data derived from electronic health records or claims data will be utilised applying statistical analyses including weighted Poisson regression models, Inverse Probability Censoring Weighted and propensity score weighting to provide comprehensive safety insights.

Keywords: RSV, vaccination safety, older adults, vulnerable populations, immunocompromised, renal impairment, hepatic impairment, protocol

2.4. RATIONALE AND BACKGROUND

Respiratory syncytial virus (RSV) is a major cause of respiratory illness in both infants and older adults (aged 65 years and older).[1] Older adults are at higher risk of RSV illness and have a greater risk of hospitalisation and mortality with RSV compared with younger adults.[2-10] Each year in Europe, it is estimated that RSV causes more than 270,000 hospitalisations and about 20,000 deaths in individuals 60 years and older.[11] RSV illness commonly occurs in individuals with existing comorbidities, which are exacerbated due to RSV exposure.[10,12-14] According to a study across 28 EU countries, RSV infection among older adults, especially those with underlying health conditions, is a significant contributor to acute respiratory infection (ARI) related hospitalisation.[15] Older adults with compromised immune systems or pre-existing conditions such as kidney disorders, liver disorders, diabetes, heart disease, and lung disease face the highest risk of developing severe RSV infection and, therefore, are most likely to benefit from vaccination.[16,17] RSV has been recognised as a significant cause of severe illness in immunocompromised populations, including haematopoietic stem cell transplantation recipients, patients undergoing intensive chemotherapy, and lung transplant patients.[1] Immunocompromised individuals who are susceptible to severe, persistent RSV infections are known to have the highest morbidity and mortality from RSV.[12-14,18] Other older adult patient populations at high risk of both infection and severe RSV illness include those with renal or hepatic impairment.[19] This protocol describes a PASS to assess the safety of an RSV vaccine in immunocompromised, or renally or hepatically impaired adults aged 60 years and older in selected European countries and the UK, with data sources that can capture vaccine exposure in the target populations, and where outcomes and key covariates can be ascertained.

2.5. OBJECTIVES

The primary study objective is to estimate the incidence rates and rate ratios of safety events of interest in immunocompromised, or renally or hepatically impaired adults (evaluated as separate populations and, if appropriate, as a combined population) aged 60 years and older who receive the RSV vaccine compared to those who do not receive the vaccine.

2.6. RESEARCH METHODS

2.6.1. Study design

i) A comparative cohort design:

A comparative cohort design will be used to estimate incidence rates and incidence rate ratios (IRRs) of prespecified outcomes among immunocompromised, renally impaired, or hepatically impaired older adults with and without vaccine receipt. To be eligible for inclusion, unvaccinated individuals must not have a record of receipt of the RSV vaccine on the index date and in the baseline period. Still, they may later have a record of receipt of the RSV vaccine to enter the vaccinated cohort. Unvaccinated individuals will be randomly selected from patients with preventive medical care records to mitigate selection bias. The baseline period will span 12 months before the index date. Follow-up will begin on day 1 after vaccine administration or the matched index date. It will end at the earliest occurrence of the outcomes of interest, administrative follow-up cessation, end of study period, or death, with follow-up truncation at the end of defined risk windows for specific outcomes. Figures 2.1 and 2.2 depict examples of patient follow-up scenarios. In a doubly robust approach, comparative analyses will include inadequately balanced variables between the two cohorts. The unvaccinated cohort will be assigned an index date matched to a corresponding index date in the vaccinated cohort based on calendar time. Due to potential limitations in sample size, matching on additional variables will not be conducted. Instead, propensity score (PS) methods incorporating a greater number of covariates will be considered to create weight-adjusted vaccinated/unvaccinated cohorts.

The exposure cohorts for the comparative cohort design are defined as follows:

- The vaccinated cohort is defined as individuals who were administered the RSV vaccine.
- The unvaccinated cohort is individuals who did not receive the RSV vaccine or any other vaccination on the index date.

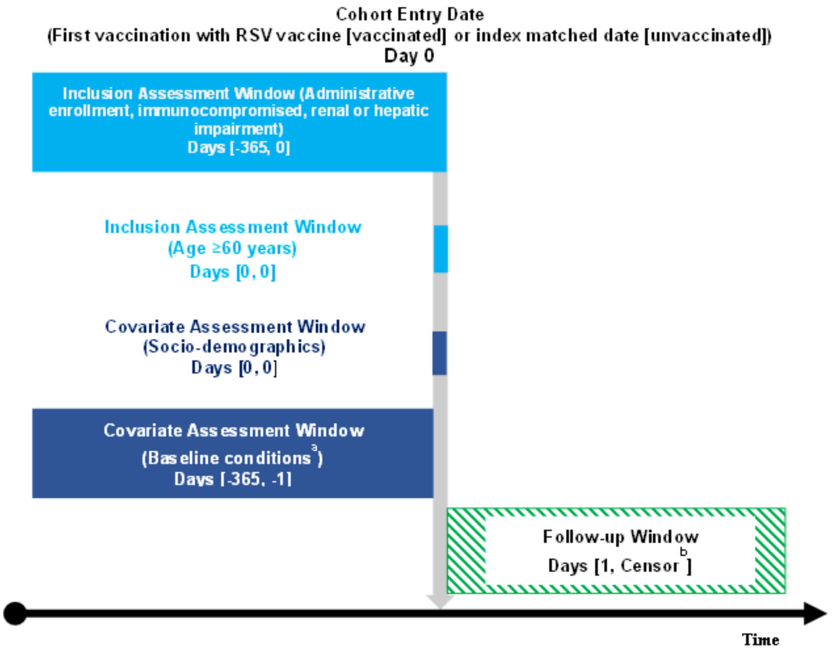

Figure 2.1. Comparative Cohort Design

a. Baseline conditions include comorbidities of interest, medications of interest, vaccination, healthcare utilisation, and/or surrogates of frailty.

b. Earliest of outcome of interest, receipt of RSV vaccine (for unvaccinated cohort), death, end of administrative enrolment, end of the study period (or risk window if applicable).

i) A self-controlled risk interval design:

An SCRI design, a simplified version of the self-controlled case series (SCCS) that uses a reduced comparison time window for the analysis, is a complementary analytic approach for a subset of study outcomes that meet the necessary study design assumptions. The assumptions for an SCRI design include that the outcome must have acute onset (up to 42 days after vaccination), short latency, and a relatively well-defined risk window. The assumptions underpinning the SCRI also require that the occurrence of the outcome does not affect the probability of exposure. Table 2.1. indicates outcomes for which an SCRI analysis is deemed valid. The SCRI design uses information from cases (i.e., vaccinated individuals who experience an outcome) to compare the incidence of an outcome in the risk interval following vaccination to the incidence in a post-vaccination control interval within the same individual.[20,21] Meanwhile, for non-acute outcomes, a retrospective cohort design will be utilised to compare the safety events between individuals who have received the RSV vaccine and those who have not yet received any RSV vaccine.

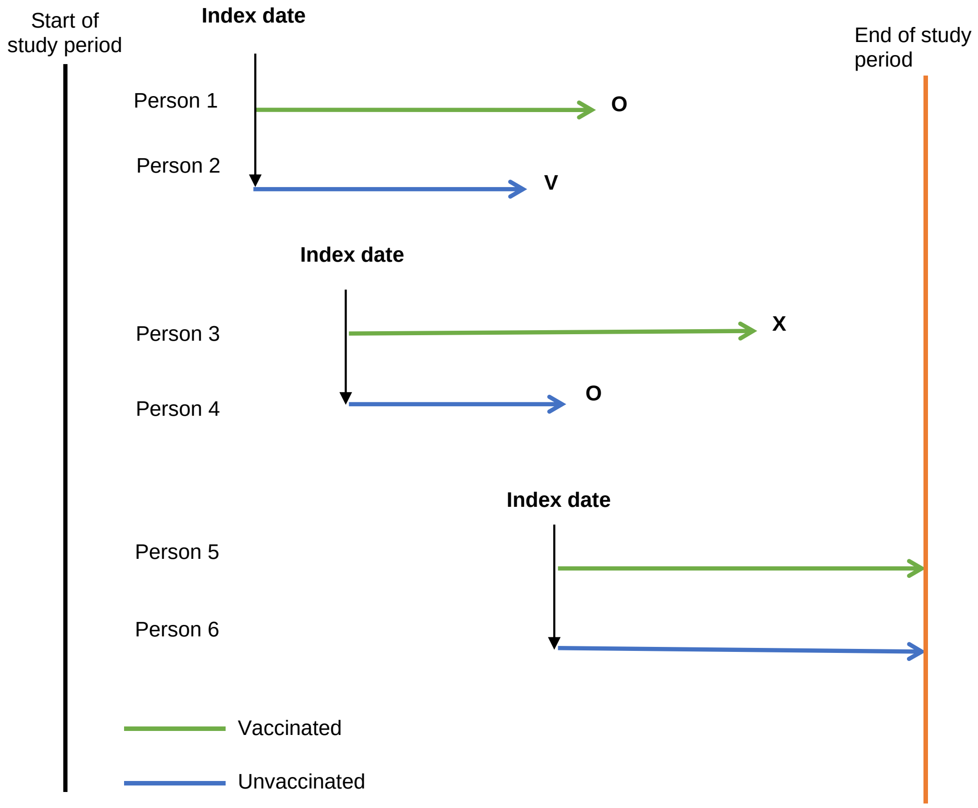

Figure 2.2. Index Matching and Follow-up Scenarios for Vaccinated and Unvaccinated in Comparative Cohort Design; O is occurrence of outcome of interest; V is vaccination with the RSV vaccine, X is censoring event prior to end of study period

Three scenarios: (a) Persons 1 and 2: during follow-up the vaccinated individual has an outcome of interest; the unvaccinated control is censored at the date of vaccination of the control (b) Persons 3 and 4: follow-up for the vaccinated person continues until follow-up is censored at the end of the risk window while the control is followed until an outcome is observed, and; (c) Persons 5 and 6: a control (Person 6) is index-matched for Person 5 at the time of vaccination and the pair are followed until the end of the study period. Neither experience is an outcome of interest.

Unlike the comparative cohort design, which may suffer from potential vaccine exposure underascertainment, misclassification, and potential residual confounding, the SCRI design is a within-person analysis that implicitly controls time-invariant confounders. Time-varying confounders still need to be controlled for, but with short, defined risk windows, the risk of time-varying confounding is limited. Risk intervals are applied starting the day after vaccination (Day 1) for a specific duration; Table 2.1. defines the risk window proposed for each outcome. A prespecified post-vaccination control interval is used for each outcome of interest. The post-vaccination control interval occurs after the risk window associated with RSV vaccine administration to avoid potential differential reporting of outcomes in the pre- and post-vaccination periods. The risk and control intervals are based on a review of the published literature, expert insights, and precedence from previous vaccine safety studies. Figure 2.3. presents the SCRI design with a 42-day risk interval and 42-day post-vaccination control interval for Guillain-Barré syndrome (GBS) as an example.

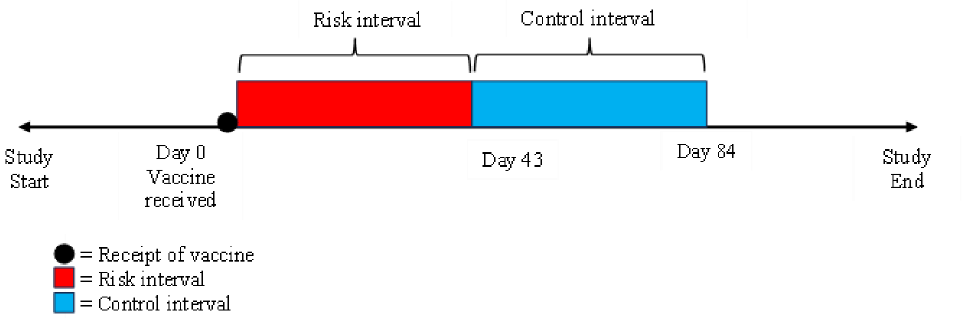

Figure 2.3. Self-controlled Risk Interval Design: example with a risk period of 42 days and a control period of 42 days

Table 2.1. List of Select Adverse Events of Special Interest

Body system/ classification	Adverse event of special interest	Estimated risk window (days)*	Analytic Approach
Autoimmune diseases	Acute disseminated encephalomyelitis	1-42^{22}	Cohort/SCRI
	Diabetes mellitus type I	1-365	Cohort
	Guillain-Barré syndrome	1-42^{22}	Cohort/SCRI
	Narcolepsy	1-365^{b}	Cohort
	Thrombocytopenia (idiopathic)	1-42^{23}	Cohort/SCRI
	Thrombosis thrombocytopenia syndrome	1-15^{22}	Cohort/SCRI
Cardiovascular system^{c}	Acute cardiovascular injury	1–28^{24}	Cohort/SCRI
	Arrhythmia	1–365	Cohort
	Coronary artery disease	1–365	Cohort
	Heart failure	1–365	Cohort
	Microangiopathy	1–365	Cohort
	Myocarditis	1–28	Cohort/SCRI
	Myocarditis and pericarditis	1–28	Cohort/SCRI
	Pericarditis	1–28	Cohort/SCRI
	Stress cardiomyopathy	1–365	Cohort
Circulatory system	Coagulation disorders: Disseminated intravascular coagulation, venous thromboembolism (pulmonary embolism, deep vein thrombosis), thrombotic microangiopathy, cerebral venous thrombosis, thrombotic thrombocytopenia syndrome, ischemic stroke, myocardial infarction, haemorrhage	1–28$^{22, d}$	Cohort/SCRI
	Single organ cutaneous vasculitis	1–28^{d}	Cohort/SCRI
	Thrombocytopenia with venous thromboembolism	1–15	Cohort/SCRI
Nerves and central nervous system	Bell’s palsy	1–42^{22}	Cohort/SCRI
	Generalised convulsion	0–42$^{22, e}$	Cohort/SCRI
	Meningoencephalitis	1–42^{22}	Cohort/SCRI
	Transverse myelitis	1–42$^{22, b}$	Cohort/SCRI
Respiratory system	Acute respiratory distress syndrome	1–365	Cohort
Skin and mucous membrane, bone and joints system	Erythema multiforme	1–42	Cohort/SCRI
Other system	Anaphylaxis	0-1$^{22, e}$	Cohort/SCRI
	Death (any causes)	0–365^{e}	Cohort

a. Day 0 is the date of vaccine administration (i.e., index date for the vaccinated cohort in the comparative cohort design and SCRI design) or matched index date (for the unvaccinated cohort in the comparative cohort design)

b. Published risk and control intervals for demyelinating diseases and cranial disorders were applied to transverse myelitis and narcolepsy/cataplexy.

c. Please note that alternative risk windows were reported in other studies.

d. Similar risk and control intervals were applied to all cardiovascular and haematological disorders characterised by damage to the blood vessels and/or arteries and clotting (i.e., coagulation disorders and single organ cutaneous vasculitis).

e. Risk intervals for most outcomes start on Day 1 post-index date, but for some outcomes, the risk interval starts on the day of vaccination due to biological plausibility of rapid onset following vaccination.

In the SCRI design, person-time within the risk window is labelled as "exposed," while person-time within the control window is labelled as "unexposed." Risk windows are tailored to the specific outcome of interest. They are defined to align with the expected time frame for an incident event following vaccine exposure, guided by biological plausibility. Since the RSV vaccines lack well-established risk windows for certain events, we determine event-specific windows based on prior studies of other vaccines (if applicable), clinical trial data (if available), and passive post-marketing surveillance activities (as they become accessible).

2.6.2 Study setting

This study uses data from secondary population-based healthcare databases reflecting electronic health records or insurance claims related to healthcare encounters. All data sources can provide high-quality data on this RSV vaccine (product types and dates), outcomes (diagnoses, procedures, and treatments), and important covariates. The extent to which this RSV vaccine is captured in data sources is not currently known. At the proposal stage for this study, members of Vaccine Monitoring Collaboration for Europe (VAC4EU) were offered the option to participate based on study requirements.

The structure and content of electronic healthcare data vary within and between European countries. This heterogeneity requires a thorough assessment of the characteristics, data content indicators, and whether data are fit for purpose. Therefore, a detailed process is essential to assess the quality of data for each of the data sources. Key aspects of this evaluation include:

- Population coverage: The data source should cover a representative sample of the population under study. This includes demographics such as age, sex, ethnicity, and geographic location.
- Data granularity: The data should be granular enough to capture individual-level information on healthcare encounters, including diagnoses, procedures, prescriptions, and outcomes.
- Longitudinal data: Longitudinal data, tracking individuals over time, is essential for understanding disease progression, treatment patterns, and outcomes.
- Data quality: High-quality data is crucial for reliable analysis. This involves accurate information recording, standardised coding systems, and measures to address missing or erroneous data.
- Data linkage: The ability to link data across different sources (e.g., primary care, hospitals, pharmacies) enables a comprehensive view of healthcare utilisation and outcomes.
- Privacy and ethical considerations: Data sources must adhere to strict privacy regulations and ethical guidelines to protect patient confidentiality and ensure informed consent.

- Timeliness: Timely updates ensure that researchers can access the most current information, allowing for real-time or near-real-time analyses.

2.6.3. Study Period

For a hypothetical scenario involving the launch of an RSV vaccine for older adults during the 2023-2024 RSV season, the study period will start on 23 August 2022 to allow at least 12 months of administrative enrolment before vaccination, with vaccination possibly starting from the date of approval in the EU. The study period, beginning on 23 August 2022, is important because it allows for a sufficient "look-back" observation period to define covariates of interest. This period is essential for capturing prior medical history, including diseases, comorbidities, and medication use, which are critical factors to consider in the study's analysis and interpretation.

Data collection extends through at least three vaccination seasons (2023, 2024, and 2025). Patient follow-up lasts up to 12 months post-vaccination, depending on the outcome; therefore, data collection will extend to the end of 2026 at a minimum. Vaccine uptake is periodically monitored to inform the length of the study period, and additional vaccination seasons (with 12-month post-vaccination follow-up) may be added based on vaccine uptake and exposure accrual. Data availability time lags will be considered for analysis and reporting purposes.

2.6.4. Study Population

2.6.4.1. Immunocompromised Population

Individuals must meet at least one of the following criteria at the index date or during the specified baseline period to be eligible for inclusion in the immunocompromised population:

- Diagnosed with a condition characterised by compromised immune function, such as primary immunodeficiency disorders or immune dysregulation disorders.[25]
- Diagnosed with HIV/AIDS.
- History of haematologic malignancy or solid malignancy with evidence of treatment.
- Diagnosed with rheumatologic or inflammatory conditions requiring treatment with chemotherapy, immune modulators, or corticosteroids.
- Recipients of solid organ or haematopoietic stem cell transplants receiving immunosuppressive therapy.
- Undergoing CAR-T-cell therapy or haematopoietic stem cell transplantation with immunosuppressive therapy.

- Under active treatment with various immunosuppressive agents, including corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, TNF blockers, or other biologic agents that modulate immune function.

2.6.4.2. Renally Impaired Population

Individuals must demonstrate evidence of moderate or severe renal impairment, which can be ascertained at the index date or within a specified baseline period using available data elements, such as:

- Diagnosed renal conditions indicating moderate or severe impairment, as identified through coded diagnoses or procedures. This may include but is not limited to conditions such as hypertensive renal disease with renal failure, chronic nephritic syndrome, chronic tubulo-interstitial nephritis, or chronic kidney disease (CKD).
- For data sources lacking laboratory results or with substantial missingness, individuals with diagnosis codes indicative of severe and moderate renal disease, as specified by relevant clinical indices, may be considered for inclusion.[26]
- In data sources where laboratory results are available, individuals may be included in the renally impaired cohort if they meet specific criteria:
    - Two separate estimated glomerular filtration rate (eGFR) test results <60 mL/min/1.73 m^2, taken at least 90 days apart (with no normal values in between), or
    - Two separate urine albumin-to-creatinine ratio (UACR) test results ≥30 mg/g, taken at least 90 days apart (with no normal values in between), indicating severe albuminuria.
- The definitions for CKD stages and stratification of renal impairment may be based on established clinical guidelines, such as the KDIGO guidelines, and adapted as necessary for the specific data source.[27,28]
- For data sources where eGFR values are unavailable, eGFR may be derived from serum creatinine levels using the CKD-EPI equation[29], with adjustments made to remove race-related coefficients and adhere to recent evidence and guideline recommendations.[30-33]

2.6.4.3. Hepatically Impaired Population

Individuals must demonstrate evidence of moderate or severe hepatic impairment, which can be ascertained at the index date and within a specified baseline period using available data elements, such as:

- Diagnosed hepatic conditions indicating moderate or severe impairment are identified through coded diagnoses or procedures.

- This may include a range of liver diseases and complications, such as oesophageal varices, alcoholic hepatic failure, toxic liver disease with hepatic necrosis, chronic hepatic failure, hepatic veno-occlusive disease, portal hypertension, or hepatorenal syndrome.
- In data sources lacking laboratory results or with substantial missingness, individuals may be considered in the target population if they have diagnosis codes corresponding to moderate or severe hepatic disease, as defined by validated clinical indices, such as the Charlson Comorbidity Index (CCI) revised by Glasheen et al.[34]
- Codes indicative of mild liver disease, as per the CCI adaptation by Ludvigsson et al.[26], may also be considered if they coexist with ascites codes, suggesting the presence of hepatic impairment.
- In data sources where laboratory results are available, severe chronic liver disease can be determined by calculating the Model for End-Stage Liver Disease (MELD) score, with a score greater than or equal to 10 indicating moderate to severe hepatic impairment.[35-37]
- As indicated by diagnosis or procedural codes, the presence of ascites or encephalopathy may also contribute to identifying individuals with hepatic impairment, with the severity assessed using scoring systems like the Child-Pugh score, if applicable.[38,39]

2.6.4.4. Recommended inclusion criteria

Patients meeting the following criteria are included in the study:

- Vaccinated Cohort: Vaccination with this RSV vaccine
- Unvaccinated Cohort: No vaccination with this RSV vaccine or other vaccines on the index date
- Each immunocompromised or renally impaired or hepatically impaired individual must meet the population-specific inclusion criteria:
    - Age 60 years and older at the index date
    - A minimum of 12 months of administrative enrolment history in one of the selected data sources to ensure adequate characterisation of medical history; this criterion may be met after the start of the study period
    - A minimum of one day of follow-up post-index date
- The following additional criteria must be met for analyses of outcomes assessed with the SCRI design. Note that the study population for each outcome-specific analysis is different.
    a. Have received this RSV vaccine
    b. Have experienced an event of interest during the risk or control interval

c. Have full accrual of data used to define the event in the risk and control intervals combined after accounting for any data lag and timing of data extraction

2.6.4.5. Recommended exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

- Have a diagnosis for the specific outcome under study during the outcome-specific clean period before the index date (to distinguish the recording of previous events from actual new events) and at any time before the index date for diabetes type 1
- Have received any RSV vaccinations during the 12-month baseline period

2.6.5. Variables

2.6.5.1. Exposure

Exposure is based on recorded prescription, dispensing, or administering this RSV vaccine. Vaccine receipt and date of vaccination are obtained from all available sources that capture vaccination, such as pharmacy dispensing records, general practice records, immunisation registers, vaccination records, medical records, or other secondary data sources. Vaccines are identified via nationally used product codes, depending on the data source. The primary exposure of interest is the receipt of this RSV vaccine.

2.6.5.2. Outcomes

Outcomes are fully and consistently defined across the data sources. Outcomes will be identified in participant data sources with algorithms based on codes for diagnoses, procedures, and treatments. Proposed algorithms and diagnostic codes for all prespecified outcomes will incorporate definitions developed by the ACCESS project 42 and will be described in more detail in the statistical analysis plan (SAP). ACCESS developed harmonised definitions and code lists for 27 outcomes for application to routine healthcare data sources across Europe[40]. These definitions were subsequently used to calculate background outcome rates to contextualise emerging COVID-19 vaccine safety data. Healthcare data covering approximately 130 million lives across 7 European countries and 22 data sources were used to generate background rates. Algorithms are tailored to the data source and consider the provenance of the medical records that have identified the outcome, e.g., primary care, access to hospital care, and access to emergency care.[41] Multiple algorithms for the same outcome may be included in the analysis to assess the potential impact of differential misclassification. Several outcomes have been validated in previous vaccine safety studies.

Outcome onset is primarily defined as the date of the healthcare encounter associated with the relevant diagnostic code. Most outcomes of interest are serious enough to warrant healthcare consultation close to symptom onset. However, for those outcomes that might include a lag between the onset of symptoms and diagnosis in a healthcare setting (e.g., deep vein thrombosis (DVT) or diabetes type 1), algorithms may incorporate additional considerations to capture onset dates closer to the symptom onset. These considerations are detailed in the SAP. Sensitivity analyses may also be incorporated to assess assumptions around outcome onset for relevant outcomes.

2.6.5.3. Covariates

The following variables are assessed at the date of vaccine administration (i.e., index date for the vaccinated cohort in the comparative cohort design and SCRI design) or matched index date (for the unvaccinated cohort in the comparative cohort design) or during the 12-month baseline period. These variables will be used to characterise the patient populations of interest and/or to control for confounding. The prespecified outcomes may have different risk factors, and outcome-specific analyses may include different covariate sets. Covariates with sufficient availability across data sources include:

- Demographics: Age categorisation (e.g., 60-64, 65-69, 70-79, 80+ years), sex, race, and/or ethnicity as relevant to each country or geographic region.
- Date of vaccination: Categorised by month or year to analyse trends in vaccine uptake.
- Comorbidities: Including but not limited to diabetes mellitus (types 1 and 2), hypertension, cardiovascular disease, cerebrovascular disease, chronic respiratory disease (e.g., asthma, chronic obstructive pulmonary disease (COPD), chronic bronchiectasis), haematological conditions, chronic kidney disease (CKD), dementia, chronic liver disease, cancer, autoimmune disorders.
- History of medical events, such as anaphylaxis, allergies, influenza, or other respiratory infections.
- Charlson Comorbidity Index: Consideration may be given to including the composite scale or individual components as relevant.
- Comedication use: Including prescriptions or dispensing of analgesics, antibiotics, antiviral medications, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), psychotropics, statins, novel oral anticoagulants, warfarin, and the number of medications used.
- Healthcare utilisation: Number of hospitalisations, emergency department visits, skilled nursing facility stays, primary care utilisation, cancer screening, and other preventive health services.

- Other vaccinations: Including seasonal influenza, COVID-19, pneumococcal (conjugate or polysaccharide), diphtheria, tetanus, and pertussis (DTP), inactivated polio vaccine (IPV), measles, mumps, and rubella (MMR), Haemophilus influenzae type b (Hib), hepatitis A (HAV), hepatitis B (HBV), varicella-zoster (VZV), herpes zoster (HZ), human papillomavirus (HPV), meningococcal (MenACWY or Meningitis B), and rotavirus vaccines.
- Additional covariates: Pending availability and completeness across data sources, socioeconomic status (e.g., social deprivation, housing, employment, income), residency in long-term care facilities, care setting of vaccine administration, personal lifestyle characteristics (e.g., smoking status, BMI), and surrogates of frailty (e.g., wheelchair use, paralysis, Parkinson's disease, etc.).[44]

2.6.6. Study Size

The study is conducted in a source population derived from participating population-based electronic healthcare data sources. Table 2.2. shows the sample size calculations for select outcomes (i.e., anaphylaxis, GBS, and arrhythmia) using the comparative cohort design, assuming a two-sided alpha level of 0.05, an equal number of individuals for the vaccinated and unvaccinated cohorts, and a power of 80% across a range of IRRs. Given a lack of published background incidence rates for outcomes among the specific populations of interest (i.e., adults aged 60 years and older who are immunocompromised or renally impaired or hepatically impaired), published incidence rates from general populations aged 60 years and older in VAC4EU databases[40] were used to estimate rates in the unvaccinated cohort. For example, to detect an IRR of 2 for arrhythmia with a power of 80% and a two-sided alpha level of 0.05, a sample size of 1,178 vaccinated individuals and 1,178 unvaccinated individuals is needed. This assumes a background rate of 2,000 arrythmia events per 100,000 person-years among the unvaccinated cohort. To detect an IRR of 3, this would decrease to 393 vaccinated and 393 unvaccinated individuals.

Table 2.2. Number of Individuals Needed to Detect Different Rate Ratios for Selected Outcomes with a Range of Background Rates

Outcome	Background rate per 100,000 person-years[a]	Background rate per person during risk interval[b]	Incidence rate ratio	Sample size	
				Vaccinated cohort	Unvaccinated cohort
Anaphylaxis	10	0.0000005	2	47,093,279	47,093,279
			3	15,697,760	15,697,760
			5	5,886,660	5,886,660
			10	2,131,795	2,131,795
	15	0.0000008	2	29,433,300	29,433,300
			3	9,811,100	9,811,100
			5	3,679,163	3,679,163

			10	1,332,372	1,332,372
Guillain-Barré syndrome	6	0.0000069	2	3,412,557	3,412,557
			3	1,137,519	1,137,519
			5	426,570	426,570
			10	154,478	154,478
	10	0.0000115	2	2,047,534	2,047,534
			3	682,512	682,512
			5	255,942	255,942
			10	92,687	92,687
Arrhythmia	2,000	0.0200000	2	1,178	1,178
			3	393	393
			5	148	148
			10	2,000	54
	5,000	0.0500000	2	471	471
			3	157	157
			5	59	59
			10	22	22

a. Background rates of outcomes among adults aged 60 years and older were approximated based on age- and sex-specific background rates published in Supplement 1, Table 1 of Willame et al (2023).[40]

b. Assuming a two-sided alpha = 0.05, power of 80%, and a ratio of 1:1 of vaccinated to unvaccinated. Examples of background IR accounting for the risk window:

- Anaphylaxis (10/100,000 person-years)/365 * risk window (risk window 2 days) = 0.0000005
- GBS (6/100,000 person-years)/365 * risk window (risk window 42 days) = 0.0000069
- Arrhythmia (2,000/100,000 person-years) = 0.02 (no risk window applied)

2.6.7. Data Analysis

Detailed methodology for summary and statistical analyses should be documented in an SAP and be drafted prior to any analyses. Any major modifications of the prespecified analyses should be clearly reported. Changes should be annotated and amended when they are major. The SAP will outline the evaluation of excess risk thresholds for each outcome, considering background incidences, significance levels (e.g., alpha = 0.01 or 0.05), and power. All analyses will be conducted using software such as R.[43] Analyses will be done separately for the three populations: immunocompromised, renally impaired, or hepatically impaired, and potentially combined if applicable. Heterogeneity will be assessed using Higgin's I^2 statistic, with a high percentage indicating combined analysis using adapted methods like a random-effects model.

2.6.7.1. Baseline characteristics

Baseline demographics and clinical characteristics for individuals vaccinated with this RSV vaccine and the unvaccinated cohort are summarised using descriptive statistics, consisting of the mean, standard deviation (SD), median, inter-quartile range, minimum, and maximum values for continuous variables and frequency distributions for categorical variables. Descriptive statistics summarise vaccine uptake characteristics, including calendar year and month of vaccination and vaccination administration care setting (e.g., outpatient clinic, pharmacy, inpatient ward if available). For the comparative cohort design analysis, standardised mean differences in the baseline characteristics will be calculated between vaccinated and unvaccinated cohorts before and after weighting. Absolute standardised mean differences <10% indicate that the baseline characteristics of vaccinated and unvaccinated cohorts are balanced.

Incidence rates per 1,000 patient-years (with 95% CIs) will be estimated by dividing the total incident events by observation time. Each population (immunocompromised, renally impaired, and hepatically impaired) in both vaccinated and unvaccinated cohorts are analysed separately. The cumulative incidence will be estimated using Kaplan-Meier and adjusted parametric incidence curves for outcomes with unknown risk windows or longer follow-up.[44] Time to outcome onset will be measured from the index date until the event or censoring, defined at death, RSV vaccination, administrative follow-up end, or data availability end, whichever is earliest. Further analyses for outcomes with a time lag between symptom onset and healthcare encounter will be detailed in the SAP.

2.6.7.2. Safety analyses

Several analyses corresponding to the comparative cohort and SCRI designs will be conducted to assess whether there is an increased risk of outcomes associated with this RSV vaccine. Analyses are conducted among all individuals meeting the study eligibility criteria. For each of the immunocompromised, renally impaired or hepatically impaired populations, respectively, the incidence rates of the prespecified outcomes following administration of this RSV vaccine will be compared against the incidence rates of the prespecified outcomes among individuals who did not receive this RSV vaccine or any other vaccine at the index date.

An Average Treatment Effect on the Treated (ATT) weighting ensures baseline comparability between the vaccinated and unvaccinated cohorts. ATT weighting creates a “pseudo-population” in which the distribution of covariates is, on average, the same in each cohort.[45] Specifically, ATT weights are calculated to estimate the average treatment effect among individuals receiving this RSV vaccine.[45] Through ATT weighting, the unvaccinated cohort is assigned weights to align the distribution of covariates with that of the vaccinated cohort, ensuring that inferences drawn from the analysis are applicable to the vaccinated population. Individuals receiving this vaccine receive an ATT weight of one. Individuals not receiving the RSV vaccine receive an ATT weight equal to the odds of receiving this vaccine conditional on their demographic and clinical characteristics as of the index date, which is calculated based on the PS. PS is defined as an individual’s probability of receiving this vaccine conditionally on observed baseline covariates, and it will be calculated using a logistic regression model. The logistic regression model includes the cohort variable (i.e., vaccinated versus unvaccinated control) as the dependent variable. The independent variables include variables deemed clinically essential and that have shown reasonable control of confounding for previous comparative vaccine studies (e.g., age, sex, place of residence, co-morbidity indices, socioeconomic status/education level), and baseline covariates that have crude standardised differences ≥10% between the two cohorts. Specifically, ATT weights are PS/(1-PS) for individuals with no record of receipt of this vaccine.

Individuals will be followed from the index date until death, end of administrative follow-up (and/or risk interval), end of the study period, or the date of this vaccine/any RSV vaccination (for unvaccinated individuals who later receive any RSV vaccine only), whichever occurs first. The degree of loss to follow-up is examined. Suppose the censoring rates differ by exposure group (i.e., indicating informative censoring) and high censoring rates are observed. In that case, inverse Probability Censoring Weighted (IPCW) will be derived from accounting for informative censoring, where the weight will be calculated for everyone as the inverse of the probability of remaining uncensored during the risk interval. The stabilised IPCW will be calculated as follows, where A=vaccination, V=covariates to adjust, and C=0 represents that the patient has remained uncensored: (Pr[C=0 | A=1])/(Pr[C=0 | A=1,V=v]) for the vaccinated cohort; (Pr[C=0 | A=0])/(Pr[C=0 | A=0,V=v]) for the unvaccinated cohort.

The final weights are calculated as the product of the ATT weight and the IPCW (ATT x IPCW) if informative censoring is observed, and the ATT weight will be used as the final weight if informative censoring is not observed. The distribution of final weights (e.g., mean, SD, minimum, and maximum values) is examined, and extreme weights are truncated or capped at the 1st and 99th percentiles. After weighting, the distribution of baseline characteristics is evaluated between the vaccinated and unvaccinated cohorts, and variables that remain inadequately balanced (standardised difference >10%) between the two cohorts are included as regression model covariates in a doubly robust approach. Weighted Poisson regression models are conducted to calculate the IRRs of outcomes among the vaccinated versus the unvaccinated cohorts. IRRs are summarised, and robust variance estimators are used to calculate the corresponding 95% CIs.

The SCRI design with post-vaccination control interval compares the incidence of prespecified outcomes occurring in the risk interval following vaccination with the incidence of prespecified safety events occurring during the post-vaccination control interval.

To account for the self-matched design, a conditional Poisson regression model will be used to estimate the relative incidence and 95% CIs. The dependent variable is the number of events occurring during the risk or control window. The independent variables in all the models are the window type (risk or control) and the person-time in each considered window, which will be handled as an offset term. The SCRI inherently adjusts for both measured and unmeasured time-constant factors such as sex and chronic health conditions, which are onset before the start of follow-up. Time-varying confounders may be included as covariates in regression models. Outcomes for which the SCRI design is complementary and the corresponding risk windows for such outcomes are described in Table 2.1.

Individuals in the SCRI design must have full accrual of data to define the outcome in the combined risk and control windows. Suppose an outcome of interest (e.g., cardiac outcome) substantially increases the mortality risk. In that case, death may prevent individuals from accruing the full follow-up period, leading to their exclusion from the SCRI study. The 30-day case fatality rate (CFR) will be calculated for each outcome to evaluate this possibility. Outcomes with a high 30-day CFR (e.g., >20%) will be considered for further adjustment in the SCRI design. Approaches may include using the Farrington adjustment as the primary analysis or extending follow-up periods to include individuals who die following an outcome of interest in the SCRI analyses.[46] The final 30-day CFR threshold and details of the adjustment method will be specified in the SAP.

For the comparative cohort and SCRI designs, an appropriate random-effects meta-analytic method is applied to the main estimates from each data source to obtain a combined effect estimate. The heterogeneity across data sources is checked, and a forest plot will be produced with the data sources and the pooled estimate.

2.6.7.3. Sensitivity Analyses

As feasible, sensitivity analyses may include, but are not necessarily limited to:

- Comparative cohort design with extended risk windows for the acute outcomes to assess potential outcome underreporting and misclassification
- SCRI with alternative risk and control windows to evaluate potential exposure misclassification
- SCRI with pre-vaccination control window. Suppose vaccination is deferred while unwell with symptoms related to outcomes. In that case, this may violate the assumption of the SCRI design that an outcome event should not alter the probability of subsequent exposure to vaccination. Defining a separate pre-vaccination window can assess these design assumptions and ensure they are not violated.

- SCRI with a washout period between risk and control windows within the subset of outcomes for which an increased risk is detected
- For outcomes with CFR >20%, SCRI analysis incorporating Farrington adjustment or extending follow-up after death for full length of risk and control window
- Use of narrow and broader definition algorithms for outcomes to assess outcome misclassification (comparative cohort and SCRI)
- Descriptive analyses assess whether there is differential receipt of other vaccines in the follow-up period between the vaccinated and unvaccinated cohort (comparative cohort design) and between the risk and control windows (SCRI design). Differential receipt of vaccines during follow-up may introduce potential time-varying confounding. If differential patterns of vaccination during follow-up are observed, the following approaches may be considered:
  - Comparative cohort analysis with censoring at receipt of another vaccine during follow-up
  - SCRI with analyses stratified by those who did and did not receive vaccinations during the risk or control window
  - For individuals receiving other vaccines close to the index date (e.g.,30 or 45 days before the index date), comparative cohort and SCRI analyses are repeated, excluding those individuals.
- Quantitative bias analysis to assess potential unmeasured confounding (comparative cohort)[47]
- A negative control outcome analysis to assess potential unmeasured confounding, selection bias, and misclassification bias (comparative cohort and SCRI)

Further details and any additional sensitivity analyses that may be conducted will be described in the SAP.

2.7. DISCUSSION

This study protocol outlines a thorough method for evaluating the safety of an RSV vaccine in adults aged 60 years and older, particularly those with specific health conditions such as immunocompromised states, renal impairment, and hepatic impairment. It will be conducted in real-world settings using secondary data sources. This section discusses key aspects of the protocol, including the background, rationale, study objectives, study design, population selection, data analysis methods, limitations, and potential implications.

RSV poses a significant health burden, particularly in older adults with underlying health conditions.[10-15] The introduction of the RSV vaccine offers a promising intervention to reduce the risk of severe

RSV illness in vulnerable populations. This is supported by evidence from previous trials which assessed the efficacy, immunogenicity, and safety of an RSV vaccine in adults aged 60 years and older.[48,49] However, given the lack of inclusion of immunocompromised, renally impaired, and hepatically impaired individuals in initial clinical trials, there is a critical need to evaluate the safety profile of the vaccine in these specific subgroups. This study protocol addresses this gap by proposing a PASS to assess the incidence rates of safety events associated with this RSV vaccine.

The study employs a multifaceted approach, combining a comparative cohort design with an SCRI design for specific outcomes to comprehensively evaluate the vaccine's safety. Rigorous criteria are outlined for population selection, including relevant groups including immunocompromised, renally impaired, and hepatically impaired individuals based on standardised diagnostic criteria. This approach enhances consistency and reliability across diverse data sources while minimising selection bias. The SCRI design compares the occurrence of an outcome in vaccinated individuals during a specified risk window after vaccination with a post-vaccination control window within the same person. Unlike other designs, SCRI inherently adjusts for time-invariant confounders and minimises the risk of time-varying confounding due to short, defined risk windows.[20,21] Detailed methodologies outlined in the SAP facilitate the analysis of safety outcomes, incorporating advanced statistical techniques like PS weighting, IPCW, and doubly robust regression modelling to mitigate potential biases and enhance validity.[45] Additionally, sensitivity analyses enable robustness testing and exploration of potential sources of bias, ensuring a comprehensive evaluation of vaccine safety.

Strengths and Limitations of the Research Methods

The strengths of this study include its utilisation of large, population-based healthcare databases from multiple countries, which provide a diverse and comprehensive dataset for analysis. Including rigorous criteria for defining target populations ensures the selection of individuals with relevant health conditions, enhancing the study's internal validity. Additionally, using standardised diagnostic criteria and coding systems across data sources improves the consistency and reliability of the data. The algorithms and diagnostic codes for predefined outcomes will adhere to definitions set by the ACCESS project.[40] Outcome onset is usually defined as the date of the healthcare encounter linked to the relevant diagnostic code. However, for conditions like type 1 diabetes, where symptom onset may precede diagnosis, adjustments will be made to capture onset dates closer to symptom onset. The study's multifaceted approach, combining a comparative cohort design with SCRI analysis, allows for a robust evaluation of vaccine safety while minimising bias and controlling for potential confounders. Furthermore, the study employs advanced statistical techniques such as PS weighting, IPCW, and sensitivity analyses to enhance the validity of findings and mitigate potential biases.

However, there are several limitations to consider. Firstly, the extent to which this RSV vaccine and product types are captured in the data sources is unknown, which may introduce bias if certain populations are underrepresented. Moreover, the observational nature of the study design limits the ability to establish causality definitively, and unmeasured confounders may influence the observed associations between vaccine exposure and adverse events.[50] There is a risk of bias toward an association with safety outcomes, as patients with severe immunocompromised conditions might be more likely to receive vaccinations due to their vulnerability to infectious diseases. Additionally, failure to appropriately account for immortal time bias, where individuals are misclassified as unexposed during a period, may affect result accuracy. Other limitations include potential exposure and outcome misclassification due to coding errors. The study design accounts for potential confounders through various analytical approaches, although residual confounding remains a concern. Sensitivity analyses and negative controls are employed to address potential biases and limitations.

The findings from this study have significant implications for public health policy and clinical practice. A comprehensive assessment of the safety profile of this RSV vaccine in vulnerable older adult populations can inform regulatory decisions, vaccine recommendations, and clinical guidelines. Furthermore, insights gained from this study can guide healthcare providers in optimising vaccination strategies and addressing safety concerns in high-risk individuals.

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