PROMISE
Preparing for RSV Immunisation and Surveillance in Europe

innovative medicines initiative

101034339 – PROMISE

Preparing for RSV Immunisation and Surveillance in Europe

WP2 – Preparation for future RSV product assessment

D2.8 Identification of methodological challenges

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V1.0	30 August 2023	Final draft to be published

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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)

- **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
EU	European Union
mAb	Monoclonal antibodies
RCT	Randomised controlled trial
RSV	Respiratory syncytial virus
TND	Test-negative design

Abstract

There are several potential methodological challenges that may complicate the set up and implementation of post marketing studies on effectiveness and safety of Respiratory Syncytial Virus (RSV) preventive products (i.e., vaccines and monoclonal antibodies) or the interpretation of their results. These include bias and confounding, sample size considerations, access to these preventive products, access to health care and varying degrees of clinical testing of RSV, heterogeneity in case definitions, data availability and access to data, and challenges specific to certain target groups of RSV immunisation. While it is seldom possible to eliminate all potential challenges that threaten the feasibility or validity of an RSV impact study, many of them can be mitigated through careful choices at the study design level.

Introduction

Several methodological challenges may complicate the planning, implementation and conduct of effectiveness and safety studies of RSV preventive products (i.e., monoclonal antibodies and vaccines) or the interpretation of their results. Some of these challenges are inherent to specific study designs or target groups being studied while others are more general.

The purpose of this document is to present a brief overview of the methodological challenges related to RSV preventive product impact study designs identified in the PROMISE project.

Results

The following categories of methodological challenges were identified during the preparation of the PROMISE phase IV study protocols.

Bias and confounding

All scientific studies have the potential for bias: systematic error that can result in under- or overestimation of the outcome of interest. Types of bias include selection bias and misclassification of exposure or outcome. Another type of bias is confounding where a third factor distorts the observed relationship between exposure and outcome without being part of the causal pathway (1).

Randomised clinical trials tend to evaluate interventions under ideal conditions among highly selected populations, whereas observational studies examine effects in “real-world” settings” (2).

Observational studies are more prone to certain types of bias than randomised controlled trials (RCTs) which can minimise bias through randomisation and blinding. This does not necessarily make observational studies less desirable as they remain a rapid and cost-effective way of studying real-world effectiveness of RSV preventive products.

The effect of biases can be reduced with study design. For example, the test-negative design (TND) is thought to minimise misclassification of the outcome and minimise confounding by healthcare-seeking behaviour by, respectively, utilising accurate testing and assigning case-control status only based on a test result (3). Biases and confounding can also be adjusted for through statistical means such as multivariable models. In a cohort design, negative control outcomes may help detect residual confounding (4,5).

Sample size / statistical power

Studies should be appropriately sized to detect a relevant effect. Too small sample sizes can lead to false negative results, while too large studies are overly expensive and time-consuming to perform, at least when active subject recruitment is involved. A sample size calculation will help determine the correct study size. In a product effectiveness study, the relevant variables to consider for the power analysis are the expected or relevant immunisation effectiveness, immunisation coverage, the number of cases and the number of controls (for case-control study), duration of follow-up (for cohort study) as well as the significance level used in the statistical test.

Degree of clinical testing of RSV

In many European Union (EU) member states, systematic testing of respiratory viruses including RSV as part of the standard of care is still relatively rare especially in primary care settings. If testing is not comprehensive or testing practices differ between study sites, this negatively affects those study designs that rely on standard practice clinical testing. Moreover, testing practices can evolve over time, which is of interest if a study is to be repeated over several RSV seasons, or if testing practices change during a single RSV season depending on the phase of the season (beginning-peak-end-outside of season). This underscores the importance of collecting information on the testing practices, and tests used at the study sites and over time. Differing testing practices may be less of an issue in RCTs or TND studies where the testing procedure is part of the study design. Among older adults,

collection of more than one sample type should be considered if resources allow, because this would reduce the number of undetected infections in the control group (6,7).

Alternatively, sensitivity analyses should be performed to assess potential bias of other vaccinations (influenza or COVID-19) or prior laboratory-confirmed influenza or SARS-CoV-2 infection (e.g., a sensitivity analysis where only those who test positive for respiratory pathogens are controls). For older adults, this analysis would also hopefully reduce inclusion of RSV infected persons in the control population with false negative RSV test results due to collection of a single or limited sample types.

Access to care

If individuals in each country or study site are more or less likely to seek medical attention for symptoms compatible with RSV (because of financial or geographic barriers, or a culture of seeking care only in very severe cases), this will affect the chance that RSV infection be detected. In the TND study design, where only persons seeking care are included, this is partly dealt with, unlike in a register-based cohort study where access to care cannot be controlled for.

Data availability

Evaluation of product effectiveness and safety requires reliable information on exposure (immunisation) and outcome (such as RSV illness or an adverse event) but additional covariates should be included to control for confounding such as health-care seeking behaviour and chronic illnesses. Unavailability of these or misclassification due to poorly recorded information will reduce the reliability of study results, and low quality register data should not be used.

A specific potential concern for register-based data validity exists when diagnoses are entered into the electronic database for purposes other than patient care, e.g., in order to determine reimbursements in insurance-based health systems. Furthermore, diagnostic practices and ICD-codification may change over time. This most likely would not be a problem for a short-term study, but when planning a long-term cohort study, be it retrospective or prospective, these changes over time need to be taken into consideration in the data collection and analyses.

In the EU, data protection laws, including privacy and General Data Protection Regulation (GDPR), and their interpretation at national and local level, may limit or delay access to data. This has been discussed in detail in the deliverable D2.7 Mapping of data governance/limitations at each site with examples that have arisen in the PROMISE project in WP2.

Challenges specific to certain target groups

RSV immunisation will likely begin with risk groups such as premature infants or older adults who are at a higher risk of severe RSV infection. If a comparator group does not share the same risk factors, immunisation effectiveness may be underestimated. It should also be kept in mind that groups may differ in their rate of exposure to RSV infection.

In the target groups for RSV immunisation (pregnant women, infants / young children, older adults), the outcomes of interest would be chosen based on the typical clinical presentation of RSV in the given target group. Furthermore, conditions such as immunosuppression can act as effect modifiers or affect the study results in other ways. These concerns can be partially addressed through

stratification and sensitivity analyses.

Some concerns related to specific outcomes are described in PROMISE D2.3 (*Report on various effectiveness endpoints for clinical outcomes in RSV studies*).

Discussion

This deliverable provides a high-level overview of some aspects to consider when planning impact studies of RSV preventive products. Listing all potential methodological challenges in RSV product studies is outside the scope of this document. Nor is this document intended as a guide to performing scientific studies; the choice of the appropriate study designs and statistical tools remains with the researchers studying RSV products.

The PROMISE deliverable D2.6 (*Generic protocols for effectiveness studies of preventive products against RSV*) provides guidance for those wishing to perform TND or cohort studies of RSV product effectiveness, while D2.3 (*Report on various effectiveness endpoints for clinical outcomes in RSV studies*) lists considerations related to outcomes in studies with specific target groups. The PROMISE consortium is also working on a report on safety endpoints of RSV preventive products (D2.4) and developing different models for statistical analyses protocols (D2.9).

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