



101034339 – PROMISE

Preparing for RSV Immunisation and Surveillance in Europe

WP3 –Clinical validation studies

D3.5 Midterm recruitment report for Study 2 (PROMISE case-control validation study)

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Definitions

- **Participants** of the PROMISE Consortium are referred to herein according to the following acronyms:
 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.** Terveysten Ja Hyvinvoinnin Laitos (Finland)
 7. **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu (Netherlands)
 8. **NIVEL.** Stichting Nedelands Instituut voor Onderzoek van de Gezondheidszorg (Netherlands)
 9. **TUCH.** Varsinais-Suomen Sairaanhoidopiirin Kuntayhtymä (Finland)
 10. **TEAMIT.** TEAM IT Research, S.L. (Spain)
 11. **ReSViNET.** Stichting Resvinet (Netherlands)
 12. **SSI.** Statens Serum Institut (Denmark)
 13. **SERGAS.** Servizo Galego de Saúde (Spain)
 14. **PENTA.** Fondazione PENTA - For the treatment and care of children with HIV and related diseases - ONLUS (Italy)
 15. **FISABIO.** Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (Spain)
 16. **MLU.** Martin-Luther-Universitaet Halle-Wittenberg (Germany)
 17. **SP.** Sanofi Pasteur, S.A. (France)
 18. **GSK.** GlaxoSmithKline 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
UMC Utrecht	University Medical Center Utrecht
WP	Work Package
IRB	Institutional Review Board
RESCEU	REspiratory Syncytial virus Consortium EUrope

Publishable summary

The PROMISE case-control validation study (study 2) is a prospective monocenter study conducted at UMC Utrecht. The objectives of this study are to validate biomarkers for severity of respiratory syncytial virus (RSV) disease in infants found in the RESCEU infant studies and to validate a new severity score developed by WP1. The aim is to collect biological samples and clinical information from 160 previously healthy infants (<1 year of age) sub-divided into the following groups:

- Hospitalized, ventilated infants with RSV infection (N=40)
- Hospitalized, non-ventilated infants with RSV infection (N=40)
- Medically attended, non-hospitalized infants with RSV infection (N=40)
- Healthy infants without respiratory tract infection (N=40)

The study started in November 2021. Until March 2023, 99 infants have been recruited with an even distribution across the 4 subgroups. Recruitment has been challenging due to the changed RSV epidemiology during the COVID-19 pandemic. During the 2022-2023 season, another recruiting (general) hospital has been added and the number of participating general practitioner (GP) practices has been extended, which resulted in an increase in recruitment rates during the 2022-2023 season, but the intended recruitment rate of 40 infants per subgroup has not been reached.

Proposed mitigation strategies included extension of recruitment to the 2023-2024 RSV season and to recalculate the sample size based on results from a recent analysis of the RESCEU case-control study. Additional sample size calculation simulations were performed under several scenarios and indicated that a sample size of at least 20 infants per group is expected to be sufficiently informative for the validation of the most important pre-identified biomarkers. Based on this, the intention is to not extend the study for another season, which is to be confirmed at the PROMISE General Assembly Meeting in May 2023.

1. Introduction

The **infant case-control validation study (Study 2)**. In this validation study we aim to collect samples to validate the biomarkers pre-identified from the RESCEU infant case-control study as part of the Work Package (WP) 4 activities. WP4 is the Biomarker identification validation WP that will analyse samples collected in the case-control biomarker validation study conducted by WP3, which is the clinical validation studies WP. This study maintains a similar design to the RESCEU infant case-control study (protocol RESCEU infant case-control study described in Jefferies et al, JID 2020, doi: 10.1093/infdis/jiaa239).

We will also validate a new severity score which has been developed by WP1. WP1 (RSV epidemiology and impact of COVID-19) has written a report incorporating all evidence from literature reviews and utilized data from RESCEU clinical studies and proposed a novel simplified severity score for RSV bronchiolitis in children (see D1.1).

2. Methods

The case-control validation study is being conducted at UMC Utrecht (monocenter) and will provide biological samples for the PROMISE biobank (for analysis in WP3 and WP4) with the aim to validate biomarkers of severe RSV disease and of sequelae in infants after RSV infection identified in the RESCEU case-control study. This study will also be used to validate a new severity score, which has been developed by WP1.

The aim is to prospectively collect biological samples and clinical information from 160 previously healthy infants (<1 year of age) sub-divided into the following 4 groups:

- Hospitalized, ventilated infants with RSV infection (N=40)
- Hospitalized, non-ventilated infants with RSV infection (N=40)
- Medically attended, non-hospitalized infants with RSV infection (N=40)
- Healthy infants without respiratory tract infection (N=40)

Blood, stool, buccal, urine and nasopharyngeal samples (and bronchial samples if ventilated) will be obtained from all infants at presentation and also from RSV-positive infants in convalescence 6-8 weeks later. Clinical symptoms will be collected from medical charts and parents are asked to fill out a questionnaire at the time of inclusion in the study and a symptom diary for 14 days (only if RSV-positive). Families will be followed up with yearly questionnaires until the end of the study to document the long-term sequelae of RSV infection in the first year of life (see D3.1 for study protocol).

The protocol for the PROMISE infant case-control study has been developed in collaboration with WP4. The study design is similar to the RESCEU infant case-control study and includes the establishment of a biobank for collected samples (see D3.1). Institutional Review Board (IRB) approval was obtained in September 2021 (see D3.3).

The intended period to conduct the study is from January 2022 (M3, First patient in) until October 2024 (M24, Last patient visit for primary outcome).

3. Results

The first patient was recruited in November 2021. Until March 2023, 99/160 participants have been recruited (Table 1). Due to the COVID-19 pandemic RSV seasonality has changed considerably with a peak in the summer of 2021, followed by a lower-than-normal RSV infection rate during the 2021-2022 winter season, which continued during the spring and summer of 2022 and diminished in August-September 2022. Since the beginning of October 2022, RSV infections were rising again with a peak in December 2022, followed by a steep decline since January 2023 (Figure 1).

Recruitment has been challenging, partly due to the unpredictable RSV season, but also due to the effects of the ongoing COVID-19 pandemic during the first half of 2022 (shortages of personnel at participating GP practices, fewer physical visits to GP practices, high workload because of COVID-19 infections). Recruitment has been lower than expected for hospitalized, non-ventilated infants and medically attended, non-hospitalized infants during the first year. To increase recruitment in these subgroups during the 2022-2023 season, another recruiting (general) hospital was added and the number of participating GP practices was extended, which resulted in an increase in recruitment rates in these groups, but the intended recruitment rate of 40 infants per subgroup has not been reached. Proposed mitigation strategies were discussed with WP3 and WP4 members during combined meetings and with all WP leads during the SC-meeting and included the extension of recruitment to the 2023-2024 RSV season and to recalculate the sample size based on results from a recent analysis of the RESCEU case-control study.

Table 1: Number of included infants in the PROMISE case-control study per group.

	Hospitalized, ventilated infants	Hospitalized, non-ventilated infants	Medically attended, non-hospitalized infants	Healthy infants
Number of inclusions	21	24	27	27
% total (n=40)	52.5 %	60%	67.5%	67.5 %

In February 2023 sample size calculations were reviewed based on the actual recruitment rate while nearing the end of the 2022-2023 season (Figure 1) and results from the blood transcriptomics biomarker study from RESCEU, which have become available recently. These calculations showed that the current sample size of at least 20 infants per group is expected to be sufficiently informative for the validation of the most important pre-identified biomarkers.

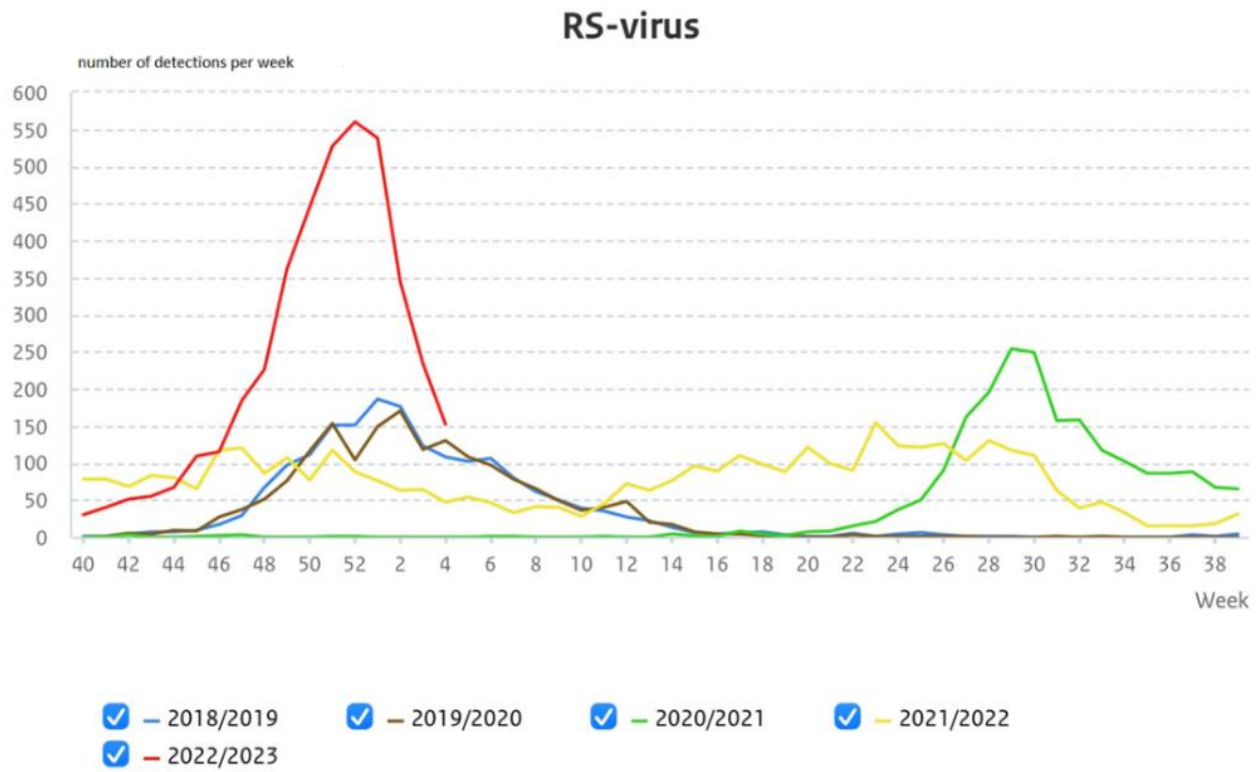


Figure 1. RSV seasonality during the last 5 years in the Netherlands. The high number of detections in the 2022-2023 season is partly due to increased RSV testing.

4. Conclusion and next steps

Until March 2023, 99 of 160 infants have been recruited for study 2, the infant case-control validation study. Included infants are evenly distributed across the 4 groups (RSV hospitalized, ventilated; RSV hospitalized, non-ventilated; RSV medically attended, non-hospitalized; and healthy controls), with at least 20 infants per group. Recruitment was challenging because of changes in RSV epidemiology during the COVID-19 pandemic. To correct for low recruitment in the hospitalized, non-ventilated and medically attended, non-hospitalized groups during the first year, another recruiting (general) hospital was added and the number of participating GP practices has been extended, which resulted in an increase in recruitment rates in these groups during the 2022-2023 season, but the intended recruitment rate of 40 infants per subgroup was not reached.

Proposed mitigation strategies included the extension of recruitment to the 2023-2024 RSV season and to recalculate sample size based on results from recent analysis of the RESCEU case-control study. Additional sample size calculation simulations were performed under several scenarios and indicated that a sample size of at least 20 infants per group is expected to be sufficiently informative for the validation of the most pre-identified biomarkers. Based on this, the intention is to not extend the study for another season, which is to be confirmed at the PROMISE General Assembly Meeting in May 2023.