PROMISE
Preparing for RSV Immunisation and Surveillance in Europe

innovative medicines initiative

101034339 – PROMISE

Preparing for RSV Immunisation and Surveillance in Europe

WP2 – Preparation of future RSV product assessment

D2.12 – Final Progress Report Task 2.2

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Document History

Version	Date	Description
V0.1	12/03/2024	First Draft
V0.2	20/04/2024	Comments
V1.0	24/04/2024	Final Version

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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
ARI	acute respiratory infection
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EQA	External quality assessment
ERVISS	European Respiratory Virus Surveillance Summary
EU/EEA	European Union and European Economic Area
FDA	USA Food and Drug Administration
GSK	GlaxoSmithKline
ILI	influenza-like illness
QCMD	Quality Control for Molecular Diagnostics
RSV	Respiratory syncytial virus
SARI	Severe acute respiratory infection
WHO	World Health Organization

Abstract

Task 2.2 of Work Package 2 focused on the establishment of the RSV Laboratory Network (RSV-LabNet), the standardisation/harmonisation of priorities, protocols, and ultimately the hand-over of progress and activities to the European Centre for Disease Prevention and Control (ECDC).

1. Introduction

Respiratory syncytial virus (RSV) is an important cause of acute lower respiratory tract infections and hospitalisations, especially among infants and elderly people. Due to a lack of harmonization, surveillance data of RSV is limited. Collecting quality diagnostic data becomes even more vital due to three major developments during the past few years.

1. Many immunisation strategies against RSV are being developed, and some have already entered the market. The European Medicines Agency (EMA) approved in October 2022 the use of the monoclonal antibody nirsevimab (Beyfortus®) for the prevention of serious lower respiratory tract disease caused by RSV in newborns and children during their first RSV season. A few European countries (France, Spain, Luxembourg) have already implemented the application of the antibody in their national programs for the winter of 2023/2024. Furthermore, the vaccine of Pfizer was approved by the EMA and the US Food and Drug Administration (FDA) in the summer of 2023 as maternal vaccine and for older adults. The older adult vaccine of GlaxoSmithKline (GSK) was approved in April 2023.
2. In spring 2024, a revised legal implementing act for notifiable diseases will be drafted by the ECDC. This includes a proposal to add RSV to the list of communicable diseases and related special health issues to be notified at the EU/EEA level.
3. Following the COVID-19 epidemic and the above mentioned developments on RSV prevention and reporting, the European Centre for Disease Prevention and Control (ECDC) and World Health Organisation (WHO) Regional Office for Europe have jointly developed an RSV surveillance platform; i.e., the European Respiratory Virus Surveillance Summary (ERVISS) for the integrated reporting of influenza, RSV and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well as the clinical syndromes of influenza-like illness (ILI), acute respiratory infection (ARI) and severe acute respiratory infection (SARI).

In order to support these developments a laboratory network for RSV (RSV-LabNet) was established to determine, advise, and advocate improved (high-quality) diagnostics for RSV across Europe.

2. Methods

2.1. Establishment of RSV-LabNet

In 2019 a survey was performed in Europe regarding surveillance and diagnostics for RSV. We developed an updated, new survey that focused more on the diagnostics of RSV, and we used this survey to develop the first phase of RSV-LabNet. The update survey was published in J Infect Dis. 14 August 2023 PMID: 37578049. Since the establishment of RSV-LabNet, the network has had quarterly meetings with an average attendance of 45 people from 23 institutes in 17 countries. One working group was established to develop a unified genotyping system for RSV (further discussion in section 2.2).

Additionally, we had joint meetings between the Laboratory Network and the EPI RSV network. One online meeting was jointly organized, and there has been a number of presentations given in either the Laboratory Network (given by epidemiologists) or at the EPI RSV Meetings (given by Laboratory Network members). Also, a physical meeting was hosted at RIVM where virologists and members of the RSV-LabNet attended with epidemiologists and members of the EPI RSV network.

2.2. Harmonisation and sharing of protocols for RSV diagnostics

There were numerous ways that RSV-LabNet worked to harmonize and share items for RSV-LabNet. Through the RSV-LabNet website, we were able to share important new literature that was published. Additionally, through the website, we shared protocols from other RSV-LabNet partners (after we transcribed the received protocols onto standard PROMISE templates).

RSV-LabNet also established a working group to work on the harmonization of an RSV genotyping system. We linked with an international group working on the project and overall worked as a large global team of RSV and sequencing experts to develop an updated, (hopefully) standard, genotyping system for RSV. This work has not yet been published at the time of this writing but the title for submission is "*The unified proposal for respiratory syncytial virus classification below the subgroup level*".

RSV-LabNet is also working on an external quality assessment (EQA) report using current and historical EQA data from Quality Control for Molecular Diagnostics (QCMD). This will be an update to the 2008 *Clin Microbiol Infect* manuscript "*The impact of laboratory characteristics on molecular detection of RSV in a European multicentre quality control study*". This EQA analysis is necessary due to the wide range of diagnostic workflows in European laboratories (as shown in the RSV-LabNet survey manuscript) and multiple international EQA programs.

2.3. Sustainability and transfer to ECDC

There is still some uncertainty and ongoing discussion around what the handover of PROMISE RSV-LabNet materials to ECDC will look like. Briefly the items we intend to transfer are:

1. List of contact persons at network laboratories
2. List of contact persons for the sequencing working group
3. List of contact persons for the global genotype working group
4. Literature database
5. Protocol database
6. Survey database (raw data from survey; for discussion)
7. Papers produced under PROMISE
    a. Survey (complete)
    b. QCMD EQA analysis (in progress)
    c. Genome analysis (in progress)
    d. Collaboration with Unified Genotype System Group (submitted)

3. Results

- Respiratory syncytial virus (RSV) is a common pathogen causing mostly cold-like symptoms, but in very young infants and elderly individuals it can lead to severe disease and even death. There are currently promising developments both in vaccine development and in therapeutics that are expected to be approved soon. To get an impression within European countries of the laboratory diagnostics and surveillance activities, in anticipation of these developments, we queried the members of the European Respiratory Syncytial Virus Laboratory Network (RSV-LabNet, under the umbrella of the PROMISE project) via an online survey. The answers from the consortium members showed scattered monitoring and the application of a broad array of techniques in the laboratories. A majority of the members expressed strong interest in harmonization and collaboration for setting up surveillance programs and the need for sharing laboratory protocols. The additional value of RSV whole-genome sequencing is broadly appreciated, but implementation requires further development and closer collaboration. The RSV-LabNet can have an important responsibility in establishing contacts and exchange of expertise and providing a platform for communication to advance diagnostics, preparedness, and surveillance.
    - J Infect Dis. 2024 - Respiratory Syncytial Virus European Laboratory Network 2022 Survey: Need for Harmonization and Enhanced Molecular Surveillance
- A globally implemented unified classification for human respiratory syncytial virus (HRSV) below the subgroup level remains elusive. Here, we formulate the global consensus of HRSV classification based on the challenges and limitations of our previous proposals and the future of genomic surveillance. From a high-quality dataset of 1,480 HRSV-A and 1,385 HRSV-B genomes submitted to NCBI and GISAID up to March 2023, we categorized HRSV-A/B sequences into lineages based on phylogenetic clades and amino acid markers. We defined 24 lineages within HRSV-A and 16 within HRSV-B, providing guidelines for prospective lineages definition. Our classification demonstrated robustness in its applicability to both complete and partial genomes. In addition, it allowed the observation of notable lineage replacements and the identification of lineages exclusively detected since the COVID-19 pandemic. We envision that this unified HRSV classification proposal will strengthen and facilitate HRSV molecular epidemiology on a global scale.
    - medRxiv 2024 - The unified proposal for classification of human respiratory syncytial virus below the subgroup level. https://www.medrxiv.org/content/10.1101/2024.02.13.24302237v1
- In progress – RSV EQA analysis

4. Discussion

Not applicable.

5. Conclusion and next steps

The diagnostic landscape continues to evolve for RSV and other respiratory diseases across Europe. And, as the development of therapeutics and vaccines also continues, it will remain important to have high quality diagnostics, and to develop new surveillance and diagnostic systems

Laboratories will need to perform quality checks via EQAs on a regular basis.

Sequencing capacity and capability will also continue to develop for RSV across Europe. It will be important for laboratories to develop these capacities further, our publication on the unified RSV genotyping system will guide that development.

We anticipate ECDC developing futher program(s) for RSV diagnostics and surveillance, but at this point in time it is still uncertain how those programs will be designed, or function.

ANNEXES

- J Infect Dis. 2024 - Respiratory Syncytial Virus European Laboratory Network 2022 Survey: Need for Harmonization and Enhanced Molecular Surveillance
- medRxiv 2024 - The unified proposal for classification of human respiratory syncytial virus below the subgroup level. https://www.medrxiv.org/content/10.1101/2024.02.13.24302237v1