INTRODUCTION AND UPDATE

Prof Harish Nair
University of Edinburgh
RESCEU Co-ordinator

@RESCEUproject

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RESCEU - introduction

€ 29M (2017-2021) Innovative Medicines Initiative (IMI) Project to build evidence base on RSV disease burden and associated economic impact in Europe to

- inform vaccine policy
- inform and improve clinical management of RSV cases
- build pan European stakeholder community for RSV; actively engage stakeholders to improve strategic planning and decision making
- create a powerful new bio-repository for future research using existing and prospectively collecting clinically annotated biological specimens
- collaborate with regulatory authorities (EMA and FDA) to ensure required regulatory input for clinical platform development and to conduct clinical trials
RESCEU - objectives (1)

- To conduct systematic reviews and assemble unpublished data to inform RSV epidemiology, disease burden (including sequelae) and resulting economic burden.
- To develop a sustainable data platform to quantify healthcare and economic impact of RSV (all ages and key risk groups) including sequelae at regional and national levels.
- To report available RSV surveillance data from Europe; and in collaboration with WHO/ECDC define best practice and SOPs for a European RSV surveillance network.
- To provide (overall and per risk group) estimates of RSV attributable economic burden and potential cost-effectiveness of RSV vaccines.
- To establish an effective GCP study network for prospective studies and develop SOPs.

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RESCEU - objectives (2)

- To conduct GCP multi-centre prospective studies to establish incidence of RSV disease and document resource utilisation by severity in various risk groups.
- To establish biobank for identifying potential biomarkers of RSV disease severity for further validation.
- To establish an ethics/governance framework that will allow wide stakeholder engagement including national and international public health agencies, pharmaceutical industry and regulators.
- To provide high-quality, sustainable, robust data collection systems that link closely with public health/regulatory bodies/health care providers for informing policy and regulatory processes.
- To promote dissemination of knowledge to a wide range of stakeholders, raise awareness, foster connectivity and promote appropriate action.
- Consortium formed with ReSViNET as nucleus
- RESCEU partners – Academic, Public Health Agencies and EFPIA
- RESCEU Affiliate partners – Inner and outer circle (all stakeholders)
- Linkages to existing consortia
- International Scientific Advisory Group
- RESCEU Ethics Advisory Committee
### WP Leaders

<table>
<thead>
<tr>
<th>Work Package</th>
<th>Academic Lead</th>
<th>EFPIA Lead</th>
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<tbody>
<tr>
<td>WP-1</td>
<td>University of Edinburgh, GB - Harish Nair</td>
<td>Scott Gallickhan, Sanofi</td>
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<td>WP-2</td>
<td>University of Edinburgh, GB - Harry Campbell Dutch Public Health Authority (RIVM), NL – Adam Meijer</td>
<td>Charles Knirsch, Pfizer</td>
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<tr>
<td>WP-3</td>
<td>University of Antwerp, BE - Philippe Beutels</td>
<td>Brian Rosen, Novavax</td>
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<tr>
<td>WP-4</td>
<td>University Medical Centre Utrecht, NL - Louis Bont</td>
<td>Antonio Gonzalez Lopez, GSK</td>
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<tr>
<td>WP-5</td>
<td>University of Oxford, GB - Andrew Pollard Imperial College London, GB - Peter Openshaw</td>
<td>Jeroen Aerssens, Janssen</td>
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<tr>
<td>WP-6</td>
<td>Synapse, SP - Eva Molero</td>
<td>Judith Hackett, AZ</td>
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<tr>
<td>Overall Coordination</td>
<td>University of Edinburgh, GB - Harish Nair</td>
<td>Judith Hackett AZ</td>
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Additional Partners

- Servicio Galego de Saúde, SP (Federico Martinon-Torres)
- University of Turku, FI (Terho Heikkinen)
- Statens Serum Institut, DK (Thea Fischer)
- University Medical Centre Groningen, NL (Maarten van den Berge)
- Fondazione PENTA for the treatment and care of children with HIV-ONLUS (Carlo Giaquinto)
## Affiliated Partners

<table>
<thead>
<tr>
<th><strong>Academic (Inner Circle)</strong></th>
<th><strong>Public Health Institutions (Inner Circle)</strong></th>
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<tbody>
<tr>
<td>Barcelona Institute for Global Health (ES)</td>
<td>National Institute for Health and Welfare THL (FI)</td>
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<tr>
<td>Queen's University Belfast (UK)</td>
<td>Norwegian Institute of Public Health (NO)</td>
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<tr>
<td>Emma Children’s Hospital, Academic Medical Centre (NL)</td>
<td>Public Health Institute Slovenia (SL)</td>
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<tr>
<td>Erasmus Medical Centre (NL)</td>
<td>National Centre for Epidemiology Department of Respiratory Viruses (HU)</td>
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<tr>
<td>Institut Pasteur (FR)</td>
<td>Center for Health Policies and Services (RO)</td>
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<tr>
<td>London School of Hygiene &amp; Tropical Medicine (UK)</td>
<td>Netherland Institute for Health Services Research (NL)</td>
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<tr>
<td>Ospedale Bambino Gesù di Roma (IT)</td>
<td>Xunta de Galicia, Consellería de Sanidade (ES)</td>
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<tr>
<td>Royal Manchester Children's Hospital (UK)</td>
<td><strong>Patient Societies (Inner Circle)</strong></td>
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<tr>
<td>U. Valencia / Global Influenza Hospital Surveillance Network (ES)</td>
<td>ReSViNET Patient Advisory Board (UK)</td>
</tr>
<tr>
<td>Université de Versailles Saint-Quentin (FR)</td>
<td><strong>Clinical Societies (Inner Circle)</strong></td>
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<tr>
<td>University of Cambridge (UK)</td>
<td>RCGP Research &amp; Surveillance Centre (UK)</td>
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<tr>
<td>University of Groningen (NL)</td>
<td>Royal College of Physicians of Edinburgh (UK)</td>
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<tr>
<td>University of Leuven (BE)</td>
<td>World Association of Perinatal Medicine (WAPM) (INT)</td>
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<tr>
<td>University of Lille (FR)</td>
<td><strong>Academic Institutions (Outer Circle)</strong></td>
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<tr>
<td>Instituto de Medicina Molecular (PT)</td>
<td>Nationwide Children's Hospital in Columbus (USA)</td>
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<tr>
<td>University of Liverpool (UK)</td>
<td>Fundación INFANT (ARG)</td>
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<tr>
<td>University of Perugia (IT)</td>
<td>Pontificia Universidade Católica do Rio Grande do Sul (BRA)</td>
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<td>University of Surrey (UK)</td>
<td><strong>Public Health Institutions (Outer Circle)</strong></td>
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<tr>
<td>Utrecht University (NL)</td>
<td>Canada Immunization Research Network (CAN)</td>
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<tr>
<td>University Children's Hospital Sant Joan de Deu (ES)</td>
<td>PATH - Center for Vaccine Innovation and Access (USA)</td>
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<tr>
<td>Université Libre de Bruxelles (BE)</td>
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<tr>
<td>Medical Faculty of the Martin-Luther University Halle-Wittenberg (DE)</td>
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RESCEU Structure

- WP1 – Literature review
- WP2 – Retrospective data integration
- WP3 – Resource use analysis
- WP4 – Prospective studies
- WP5 – Biomarkers
- WP6 – Project Management & outreach to stakeholders

Advisory Groups:
- International Scientific Advisory Group
- Patient Advisory Board
- Ethics Advisory Committee
RESCEU Governance

Consultative bodies for ethical, scientific and technical matters

ISAG, PAB, EAC

Decision powers on technical development, work plan updates, and resource re-allocation. Bi-monthly meetings.

Leading participants of each work package, coordinating their WP activities

Result-oriented efforts with a clear and exclusive mission of studying/resolving interfacing problems between WPs

Day-to-day operational/technical aspects

Forum for scientific discussion with all stakeholders

Partners. Overall project supervision and orientation, decisions requiring unanimity.

Decision powers on technical development, work plan updates, and resource re-allocation. Bi-monthly meetings.

Day-to-day management of the project

Forum

General Assembly

All partners

Steering Committee

WP leaders

Operations Team

PMO

WP1
Academia/EFPIA leads

WP2
Academia/EFPIA leads

WP3
Academia/EFPIA leads

WP4
Academia/EFPIA leads

WP5
Academia/EFPIA leads

WP6
Academia/EFPIA leads

Task Force

Task Force

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RESCEU Advisory Boards

- **International Scientific Advisory Group (ISAG):** experts on scientific/technical matters relevant to the Project; non-binding advice to the General Assembly and the Steering Committee as decision making support.

- **Ethics Advisory Committee (EAC):** ethics experts; advice on ethical issues & compliance with European ethical laws, regulations and guidelines.

- **Patient Advisory Board (PAB):** independent senior external experts who are representative of the patient community. Participates in the General Assembly meetings.

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<thead>
<tr>
<th>Board</th>
<th>Composition</th>
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<tbody>
<tr>
<td>ISAG</td>
<td>Prof. Ann R. Falsey</td>
<td>EAC</td>
<td>Dr. Sarah Chan</td>
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<td></td>
<td>Prof. Larry Anderson</td>
<td></td>
<td>Dr. Mark Leslie Flear</td>
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<td></td>
<td>Prof. Janet A. Englund</td>
<td></td>
<td>Dr. Deborah Mascalzoni</td>
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<td></td>
<td>Prof. Ruth A. Karron</td>
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<td>Dr. Martyn David Pickersgill</td>
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<td></td>
<td>Dr. José A. Melero Fondevila</td>
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<td>Dr. Ine Van Hoyweghen</td>
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<td>Prof. Shabir Ahmed Madhi</td>
<td>PAB</td>
<td>Nicole Derksen-Lazet</td>
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<td>Dr. Mark A. Miller</td>
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<td></td>
<td>Prof. Eric A.F. Simões</td>
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<td></td>
<td>Dr. Pasi Penttinen/Dr. Eeva Broberg</td>
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To conduct large-scale systematic literature reviews to consolidate all available published and unpublished data (at the global level) to synthesise evidence to inform:

- **RSV epidemiology**, particularly correlation between meteorological factors and activity of respiratory pathogens
- **Clinical consequences of RSV infection** (morbidity by severity and mortality) by age group and other high risk populations and by regions (including by income levels)
- **Medium to long term consequences** of RSV infection
- **Direct and indirect costs** related to RSV infection and societal impact
Conceptual model of RSV healthcare burden

- develop conceptual framework to assess RSV healthcare impact in young children, elderly and other risk groups
- identify relevant data from national / regional routine health services databases and RSV disease registries (DK, NL, FI, UK, IT, NO) and primary care databases (e.g. UK Clinical Practice Research Datalink (CPRD), Italian Pedianet) - (many with individual level data linkage capability)
- obtain the necessary data governance and ethical approvals to access data and conduct data linkage annually

- hospital inpatients and outpatients; accident and emergency; intensive care (including neonatal intensive care); mortality registers; prescription databases; general practitioner / community services records; virology databases

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WP2- Integrating routine health service data in Europe

Data linkage and time series modelling

- develop SoPs - case definitions, ICD /DRG codes, minimum datasets
- develop an agreed analysis plan to be used by all sites to:
  - estimate RSV healthcare burden: all age groups, young children, adults with chronic medical conditions (including COPD), elderly (>65 years) [Fleming 2015]
  - describe association between (RSV) bronchiolitis episodes and subsequent wheeze / asthma [Green 2015] and pneumococcal disease [Weinberger 2015]
  - encourage the wider generation of comparable data across Europe

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RIVM (lead), SP (co-lead), UEDIN, SSI, TUCH, PENTA

National Public Health Agencies

- RIVM as designated lead National Public Health Agency to facilitate interactions with and seek collaboration from national public health agencies across Europe to promote data sharing on RSV
- seek to further strengthen our close collaboration with ECDC to help them develop European RSV surveillance
- seek to raise awareness and promote the use of these data by national public health / regulatory bodies / health care providers

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WP2- Surveillance systems in Europe

- Support ECDC in establishing regular European RSV surveillance meetings (with ECDC convenorship)
  - Participation in initial meetings in Nov 2015, Feb 2017
  - ECDC have identified RSV surveillance data from 21 European countries (in 2014/15)
WP2- Surveillance systems in Europe

- Assist in the development of SOPs for a European RSV surveillance framework / operational plan
  - case definitions, sampling strategies, coverage of high risk groups, specification of a common core dataset
- Report seasonality and other available RSV data from European countries
- Wider international collaboration
  - form links with other major international efforts to quantify the healthcare consequences of RSV disease building on our links with US CDC (HAIVEN, NVSN) and Canadian CIRN / IMPACT networks to identify and share best practices, promote common case definitions
WP2- Surveillance systems in Europe

UEDIN (lead), Pfizer (co-lead), RIVM, SSI, TUCH, PENTA, GSK Bio, SP

- form links with other major international efforts to quantify the healthcare consequences of RSV disease to share best practices, develop common case definitions / core datasets
- coordinate with WHO as it develops global plans for RSV surveillance

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WP2- RSV prevention and treatment practices in Europe

UEDIN (lead), GSK Bio (co-lead), RIVM, SSI, TUCH, PENTA, AZ, JPNV

- Conduct systematic reviews and surveys of relevant (inter) national clinical associations and professional bodies to describe current RSV treatment and prevention practices across Europe [in collaboration with ERS]
- Make available existing clinical guidelines and care pathways and will describe and critically review the variation in practices across Europe
WP3 - Objectives

- To estimate health care resource use and direct costs to health care systems and patients from various databases and data repositories across Europe (with WP1 and WP2) using advanced statistical and health economic methods
- To estimate the indirect time costs (to patients, their family and their employers) associated with RSV illness
- To estimate costs and Health Related Quality of Life scores prospectively in collaboration with WP4
- To estimate the economic burden of disease by modelling risk group and country-specific estimates
- To explore the parameter space for which different options for interventions against RSV infection would be deemed cost-effective in EU countries using different simulation models
Different simulation models will be developed and populated with RESCEU data to study the potential effectiveness and cost-effectiveness of interventions in different age and risk groups on RSV morbidity and mortality.

1. A static model (by London School of Hygiene and Tropical Medicine). This model will be adapted to explore the parameter space for which RSV interventions (e.g. maternal immunization) may be cost-effective in different country settings.

2. A static model developed for the US (by Novavax) focusing on the elderly, will be adapted to the European context

3. A static population model (by GSK Bio) to assess childhood, maternal and elderly RSV vaccination

4. A dynamic transmission model for the US (by SP) to investigate interventions that are expected to have a substantial impact on the transmission dynamics of RSV (such as childhood immunization)
Primary Objectives

- Construction of a sustainable, GCP-compliant database
- To determine the burden, including long-term wheeze and cost, of RSV infection in healthy term baby’s
  - hospitalization
  - medical care
- To determine the incidence of moderate to severe RSV infection in older adults >65y
- To determine the incidence and long-term consequences of moderate to severe RSV infection in COPD patients

Secondary Objectives

- To establish an Intensive Care Unit registry
Clinical Study 1
Birth cohort
Active surveillance, n=1000*
Passive surveillance n=9,000

Clinical Study 2
Infant Case-Control* n=480

Clinical Study 3
Elderly n=1,000

Clinical Study 4
COPD (n=500)

RSV season

* Blood sampling during acute and convalescent phase of RSV RI in 480 infants
WP4 - Infant cohort

Fig.1 Expected flowchart of patients included in the RESCEU infant birth cohort

- UO XF N= 2000
- UEDIN N= 2000
- UMCU N= 2000
- TUH N= 2000
- SERGAS N= 2000

RESCEU Birth Cohort N= 10,000

- Passive monitoring N= 9000
- Active monitoring N= 1000

Active monitoring:
- No RSV N= 800
- Mild RSV N= 100
- MA-RSV N= 100 (=10%)
- Any RSV N= 200 (=20%)
- No hospitalization N= 92

Passive monitoring:
- RSV-hospitalization N= 80 (=0.8%)
- N= 72

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In addition, samples from:

- SSI biobank (Danish Neonatal Screening Biobank with DNA on filter paper from heel bleeding of newborns)
- Kilifi (Kenya) biobank (Prospective cohort study; samples: NP/OP swabs, sera, peripheral blood mononuclear cells (PBMC) and in some cases, Paxgene whole blood RNA tubes)
• Are there serological or mucosal biomarkers (type, level or function of antibody; soluble immune mediators) that predict, correlate with protection from or susceptibility to infection?

• Are there virological factors (viral load, sequence) associated with severe disease?

• Can a transcriptomic, proteomic, metabolomic or epigenetic signature be found that is associated with susceptibility to disease, severe disease or wheezing sequelae?

• Are there RSV-specific T cell biomarkers (phenotype or function) or markers of innate immunity that correlate with susceptibility, recovery, or protection from infection?

• Are alterations in the respiratory microbiome associated with susceptibility to, or severity of disease or sequelae?

• By analysing stored host DNA, can we find genetic associations with susceptibility to, or severity of disease or wheezing sequelae?
• Are there serological or mucosal biomarkers (type, level or function of antibody; soluble immune mediators) that correlate with susceptibility to disease or protection from infection or slow recovery?

• Are there virological factors (viral load, sequence, persistence) associated with severity of disease, slow recovery or progressive deterioration?

• Are there RSV-specific immune biomarkers that correlate with susceptibility to infection, severity of exacerbation or long-term effects of RSV?

• Is there a transcriptomic signature that is predictive of or associated with severe RSV disease, greater or more severe or prolonged exacerbation?

• Are alterations in the respiratory microbiome associated with severe disease or sequelae?
## WP5 – Sample Collection

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<tr>
<th>Sample</th>
<th>Existing biobank</th>
<th>RESCEU biobank</th>
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<tbody>
<tr>
<td>SSI Biobank</td>
<td>Kilifi biobank</td>
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<tr>
<td>Infant, RSV and no RSV (2)</td>
<td>Infant pre-disease, disease (2)</td>
<td>Infant birth cohort (from WP4)</td>
</tr>
<tr>
<td>9000 (3000 + 6000)</td>
<td>200 (100+100)</td>
<td>1000</td>
</tr>
<tr>
<td>Total No. of individuals</td>
<td>500 (226+226)</td>
<td>480</td>
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<tr>
<td>Total No. of samples available</td>
<td>9000</td>
<td>1000</td>
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<tr>
<td>Airway samples</td>
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<tr>
<td>Stool</td>
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<td>Airway (RSV PCR)</td>
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<tr>
<td>Serum</td>
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<td>Plasma</td>
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<td>PBMCs</td>
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<tr>
<td>Host DNA (once only)</td>
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<tr>
<td>Host RNA</td>
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WP5 – Communication and outreach

- Newsletter, RESCEU website – make available a wide range of information and data on RSV healthcare burden; aim to meet the needs of policy makers, healthcare workers and the general public
- Organise RSV Science Policy Forum in year 5 of RESCEU to engage more widely with policy makers
- Session at Annual Health Forum in Gastein
- Interaction with VENICE, HTA network of EU HTA agencies
- Engaging with clinicians (e.g. ERS)
  - RSV Observatory

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WORKING TOGETHER FOR EXCITING 5 YEARS OF RSV RESEARCH