KEYNOTE

Andrew Pollard
RESCEU WP5 Principal Investigator and WP Co-Leader

Time for RESCEU

There are tremendous pressures for paediatricians working in hospital wards each year during the RSV season. The estimated annual hospital admission rate for bronchiolitis in England and Wales has risen to an astonishing 46.1 (95% CI 45.6 to 46.6) per 1,000 babies under 1 year of age (in 2011). 1-2 per 1,000 are admitted to intensive care. With a birth cohort of 700,000, babies per year, this is over 30,000 admissions per year and a lot of expensive intensive care cots occupied. If there was no RSV, there would be a lot less bed occupancy in paediatric hospitals and intensive care units and winter pressures would fall substantially, perhaps even beds/cots could be closed.

With the massive pipeline of potential products in development, and several candidates moving to phase 3 trials, we are closer today than we have ever been, to having a safe and effective vaccine that has a substantial impact on the RSV problem. However, there remains much that we don’t know about RSV vaccines, notably when to give them, how well they will work, will they induce herd immunity and how long the effects would last. For a start, which target age group: maternal immunisation using a purified protein with the risk of rapid antibody waning and reduced disease impact; or immunise the neonate through use of a monoclonal antibody, which could have similar properties to palivizumab but with more stable antibody with a longer half-life, but we don’t know if it will be powerful enough or long enough to protect against all infant disease; immunise the infant with a live-attenuated or viral vector vaccine which means missing the early cases if following the routine schedules in Europe; or vaccinate toddlers to protect them and reduce spread to siblings via herd
We won't know the answers to these questions until we start seeing some efficacy data for products that are in development. For now, we must prepare the ground for a future vaccine, develop the data that should underpin policy recommendations, for or against. In RESCEU, many of the outstanding issues are being identified and considered to inform models of the potential disease impact and the potential economic impact. With this momentum control of RSV could be just around the corner.

EMA ITF Briefing Meeting with RESCEU representatives in London

Since its very beginning, RESCEU was aware of the importance of establishing an early and continuous dialogue with regulatory bodies to ensure a lasting impact to the project. In the specific case of RESCEU, interaction with regulators is crucial to identify the most critical regulatory issues and bottlenecks for the development of medicinal products intended for the treatment and prophylaxis of RSV infection.

As a first step, a Briefing Meeting with the EMA Innovation Task Force was held on March 16th at the EMA premises in London. On a general level, the objective of ITF briefing meetings is to provide for a preparatory discussion on scientific and regulatory topics relevant to the development of new medicinal products and technologies complementing and reinforcing existing formal procedures.

Both RESCEU representatives from the academia and the industry participated to the meeting, presenting RESCEU objectives and structure and addressing questions to EMA's experts on different topics related to different RESCEU Work Packages. Even if the project was still at an early stage at the moment of discussion, preliminary feedback was obtained and suggestions were formulated on the kind of outputs that could be of most value for informing EMA policy guidance for assessment on new vaccines. On the other hand, EMA experts queried RESCEU representatives on topics such as data that will be or have been produced, clinical studies and practical tools resulting from the project.
In summary, the meeting was a valuable chance for mutual understanding and exchange on how RESCEU can contribute to inform the EMA about science and how EMA can feed into RESCEU to promote that the outcome of the consortium’s work has value to the public and others. Follow up discussions between RESCEU and specific EMA working groups have been scheduled to deepen into some of the topics.

RESCEU representatives at the EMA premises in London. From the left: Eva Molero (Synapse), Francesca Rocchi (PENTA), Brian Rosen (Novavax), Harry Campbell (University of Edinburgh), Jeroen Aerssens (Janssen), Harish Nair (University of Edinburgh) and Louis Bont (University Medical Center Utrecht).

NEW SECTION: Get to Know the RESCEU Team!

*These are the first of a series of interviews to members of the RESCEU team, where they are interviewed on their vision of RESCEU, their current position and how they contribute to the Project.*

Koos Korsten (UMCU)
Koos Korsten is a PhD candidate in paediatric infectious diseases at the Wilhelmina Children’s Hospital, University Medical Centre Utrecht, The Netherlands. His research focuses on the burden of disease caused by the Respiratory Syncytial Virus (RSV) in infants and the elderly as part of the European RESCEU trial.

**Tell us about your professional career.**

I am proud to be the first junior consortium member to introduce myself in the RESCEU newsletter. I am Koos Korsten, PhD candidate in the research group of Louis Bont in the Wilhelmina Children’s Hospital in the Netherlands. During my medical training I’ve been working as a research assistant in the research group of Louis and subsequently performed a scientific internship on the prediction of severe RSV infection in preterm infants. After graduating from medical school I was thrilled to be involved in the upcoming RESCEU project which led to my current position as a PhD candidate in RESCEU. However, medical school did not fully prepare me for the job. That is why I am currently obtaining a Master’s degree in Epidemiology at the University of Utrecht. This Master has a special focus on epidemiology in clinical research and already provided useful insights which helped me in my work on the RESCEU project.

**Can you please explain a bit about your role at the University Medical Centre Utrecht as part of the RESCEU project?**

In the RESCEU consortium, I am involved in the clinical studies which are part of work package 4. For both the older adults cohort study and the infant cohort study I am working with Louis Bont and Joanne Wildenbeest to make sure everything runs smoothly in the execution of these studies in all the participating countries. After months of careful preparation, IRB submissions and being involved in designing the questionnaires, constructing the online database Research Online and developing the practical execution of the studies, I am excited to see everything is working out at all sites. By being a contact person for the infant cohort and older adult cohort studies, I had the advantage of being in contact with most of the researchers involved in these studies during last winter (at least by email or phone). I look forward meeting everyone in person as well during the upcoming General
How do you foresee the future of RSV infection after RESCEU project?

I am convinced that the RESCEU project will help to bridge the gaps of knowledge about some of the most basic, but nevertheless very important questions concerning RSV-infections: how often does RSV occur and which individuals are at increased risk of severe infection? While the majority of the general population is not considered to be at high risk for a severe RSV infection, it is still of vital importance to see how frequent RSV-infections occur and who is at increased risk on an individual level, despite being part of the overall ‘low-risk’ population. Additionally, the collection of data on the burden of disease outside the hospital setting in the older adult study and in the active cohort of the infant cohort study will be an important contribution to our understanding of the true burden of disease of RSV. I believe that RESCEU will provide us with more accurate estimates of the impact of RSV-infection in the general population.

Angéline Denouel (SP)

Angéline Denouel is a Research Assistant in Epidemiology who works for the Global Vaccine Epidemiology & Modelling department at Sanofi Pasteur. She is currently collaborating with RESCEU WP1 at the University of Edinburgh. She holds a Master’s Degree in Public Health with a focus on Methods in Epidemiology and Clinical Research.

Tell us about your professional career.

During my Master in Public Health I’ve done two internships at the French National Institute of Health and Medical Research in cancer area. I was involved in a literature review on biomarkers associated with cognitive impairment in treated cancer patients (published in Frontiers in


article (currently in process of publication). After my graduation I’ve been hired by the pharmaceutical company Sanofi Pasteur as bio-statistical coordinator in the United States for a year in order to initiate scientists to biostatistics and help them perform their own statistical analyses. Since August 2017 I work as research assistant in epidemiology (still for Sanofi Pasteur) in collaboration with the University of Edinburgh as part of the RESCEU project. I’m involved in WP1 - Systematic literature review on RSV and current estimate of burden of disease - and I closely work with Dr. Ting Shi in systematic literature reviews, data extractions and meta-analyses elaboration.

Can you please explain a bit about your role in Sanofi Pasteur as part of the RESCEU project?

First of all, I was exclusively employed by Sanofi Pasteur to work physically at the University of Edinburgh as part of RESCEU project and more particularly in WP1. As an employee of Sanofi Pasteur my first mission was to extract data from clinical trials on RSV associated acute respiratory infections (ARI) cases provided by the company to share with the consortium. With the supervision of Prof. Harish Nair and Dr. Ting Shi, my second mission was to perform a systematic literature review on all-causes of hospitalisations for pneumonia in older adults. I was one of two reviewers extracting the data of included studies and I had the chance to be involved in the meta-analysis and in the manuscript: Global and regional burden of hospital admissions for pneumonia in older adults in 2015. I’ll also be involved in the same work for the next RESCEU WP1 deliverable about the global and regional burden of RSV-associated ARI in older adults.

How do you foresee the future of RSV infection after RESCEU project?

After RESCEU project I would expect a perfect understanding of RSV infection burden for young children, adults and elderly, as well as the economic impact of RSV. All this knowledge would be useful to provide insights on health decision-making in order to improve patient care and prevention.

RSV infection is still underestimated and I would expect a better estimation of the infections due to RSV with an increasing number of tests for RSV like those for influenza in healthcare. RSV would be known as a major cause of respiratory illness in scientific community but also in global community like flu and would be associated with efficient preventive campaigns.

And finally I foresee the development of an effective vaccine for all age categories in order to decrease the number of severe respiratory infections and the number of deaths due to RSV.

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**Papers of the month**

*in collaboration with ReSViNET*

**April 2018**

**Epidemiology of respiratory virus infection in preterm infants in a tropical area**

Summary

A 11-year retrospective cohort data linkage study was performed in one hospital from Singapore to investigate the epidemiology of respiratory viral infections (RVIs). This study included 1,854 preterm infants (born with ≤32 weeks of gestational age) admitted with laboratory confirmed RVIs before 2 years old. Overall 14.5% infants had at least one RVI. The hospitalisation rate of RVI was 116 per 1,000 infants per year with the highest rate in 3-5 months age group (200). Respiratory syncytial virus (RSV) was the most common pathogen identified (56.8%) and a similar peak in 3-5 months age group was found. Infants with RVIs were more likely to be born with ≤27 weeks of gestational age, have received treatment of postnatal steroids and be diagnosed with bronchopulmonary dysplasia. However, this study only included symptomatic infants admitted to hospitals, which might have missed infants with mild symptoms or were asymptomatic and infants who were not hospitalised. Also, some social and environmental factors which might increase the risk of RVI were not included in this analysis. Study interpretation should also take into consideration the testing strategy and laboratory methodology.

Abstract on Pubmed.

Papers of the month

in collaboration with ReSViNET

April 2018

Subcutaneous treatment with diabetes drug liraglutide (Victoza®) is effective treatment of RSV infection


Summary

The glucagon-like peptide(GLP)-1 receptor agonist liraglutide has the potential to be an effective treatment of RSV bronchiolitis. This is the conclusion from a mouse study from researchers from the Vanderbilt University (Nashville, TN) and Emory (Atlanta, GA). Mucus production is a hallmark of severe RSV bronchiolitis. Mucus production is mediated by the production of Th2 cytokines, in particular IL-13. To date, no treatment has proven to prevent mucus production during RSV infection. Liraglutide is a registered and commercially available diabetes GLP1-R agonist to suppress glucagon secretion. As it was known to be immunosuppressive, this study aimed to assess the drug’s
potential as an RSV therapeutic. Liraglutide treatment decreased mucus production, airway hyperresponsiveness and lung pathology without affecting viral replication. This favorable outcome coincided with decreased IL-13 production and type 2 innate lymphoid cells (ILC) in the airways. The relevance for human RSV infection was supported by a SNP in the THADA gene which is known to define the beta-cell response to GLP-1. This study reveals a novel therapeutic pathway to improve the outcome of patients with RSV infection.

Abstract on Pubmed.

Papers of the month

in collaboration with ReSViNET

March 2018

RSV during infancy and childhood asthma: the puzzle remains


Summary

A 6-year single-blind, randomised, placebo-controlled trial (MAKI) was carried out to evaluate the effect of RSV prevention during infancy on asthma and lung function at age 6 years. 429 infants born at 32-35 weeks of gestation (otherwise healthy) randomly received either palivizumab or placebo during RSV season of their first year of life and were followed up at age 6 years. This study indicated that RSV prevention in otherwise healthy preterm infants reduced the risk of parent-reported asthma at age 6 years, which was mainly explained by differences in infrequent wheeze. However, RSV prevention had no effect on the risk of physician-diagnosed asthma or lung function at age 6 years. The result of this study should be interpreted with caution due to potential information bias from parents, missing data for lung function, and limited power of the study. We should also be careful when generalising the results to term infants or lower income regions or assessing the impact of RSV prevention by using other immunisation strategies.

Abstract on Pubmed.

Papers of the month

in collaboration with ReSViNET

February 2018

RSV hospitalisation: preterm infants with CLD compared to term infants

Winterstein AG, Choi Y, Meissner HC. Association of Age With Risk of Hospitalization for Respiratory Syncytial Virus in Preterm Infants With Chronic Lung Disease, JAMA Pediatr. 2018 Feb 1;172(2):154-
Summary
American Academy of Pediatrics guidelines recommends RSV prophylaxis with palivizumab up to 24 months age for infants with chronic lung disease (CLD). Winterstein and colleagues conducted a retrospective cohort study consisting of 1,018,593 healthy term infants and 5181 preterm infants with CLD (42.7% vs 0.1% using palivizumab) using Medicaid billing records for 12 seasons, linked to birth and death certificates. The study indicated that when preterm infants with CLD were at 18.5 (95% CI 15.6-22.8) months, the risk of hospitalisation for RSV was similar to that of 1-month term infants with siblings. During a sensitivity analysis when the presence of young siblings was not considered, the age threshold increased to 25.5 months. This study supports the current American Academy of Pediatrics guidelines. However, interpretation should take into consideration of the inherent differences in the source population, seasonality, misclassification bias by using ICD-9-CM coding, and the trends in RSV hospitalisation over study period.

Abstract on Pubmed.

Upcoming major RSV/respiratory meetings

7th CONGRESS OF THE EUROPEAN ACADEMY OF PAEDIATRIC SOCIETIES
The Congress is organised by the European Academy of Paediatrics (EAP), the European Society for Paediatric Research (ESPR) and the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). In addition, ten other important European paediatric societies have joined as collaborating societies, among them the European Respiratory Society (ERS), the European Association for Pediatric and Congenital Cardiology and the European Association of Palliative Care. The central feature of the Congress will be the scientific papers, with focus on the topics considered vital for the advancement of high-quality paediatric care and training worldwide. The comprehensive programme of the event, which can be navigated interactively online, offers educational symposia, interactive sessions and the possibility of attending pre-congress training courses and courses for continuing professional development/education. The latest will be held on October 29 and 30, 2018 and are sponsored by the organising societies. Deadline for online registration is October 17, 2018. The scientific programme and full list of speakers are available on www.eaps.kenes.com

OCTOBER 30 - NOVEMBER 3, 2018
PARIS, FRANCE

INTERNATIONAL RESPIRATORY SYNCYTIAL VIRUS SYMPOSIUM
Since its inception in 1996, the International RSV Symposium remains the longest ongoing meeting to discuss RSV, and has seen continual growth in both meeting attendance and abstracts over the years, with more than 300 attendees and over 200 posters and abstracts presented in the last two editions
The 11th edition will take place next fall at Omni Grove Park Inn, Asheville, North Carolina. The symposium will bring together leading scientists, students, non-profits, regulators, sponsors, and leaders in industry from all over the world to discuss past and current efforts to understand, treat, and prevent RSV disease. Abstracts are invited in the fields of Clinical Studies, Evolution and Epidemiology, Virology and Immunology, with deadline for submission on June 30. A limited number of travel awards will be made available.

Further details can be found on [www.rsvsymposium.com](http://www.rsvsymposium.com)

**OCTOBER 31 - NOVEMBER 4, 2018**
**OMNI GROVE PARK INN, ASHEVILLE, NC, USA**

**6th INTERNATIONAL SOCIETY FOR INFLUENZA-ANTIVIRAL GROUP CONFERENCE**

The 6th edition of ISIRV-AVG focusing on *Advances in Respiratory Virus Therapeutics*, will take place in Washington DC on November 2018. This edition will build on the previous conference held in Shanghai in June 2017, when it became clear that new data would be forthcoming in 2018 from ongoing clinical trials of investigational therapeutics for influenza, RSV and other respiratory viruses. The programme will encompass the following topics:

- Preclinical Topics
- Clinical Trial Design Issues
- Clinical Trial and Regulatory Issues
- Clinical Trial Papers

Abstracts are invited in the areas of pre-clinical, regulatory and clinical. Applications are invited for travel awards supported by the Bill & Melinda Gates Foundation and by ISIRV, for applicants from a low to middle income country as defined by the [World Bank](http://www.worldbank.org).

Further details and agenda can be found on [www.isirv.org](http://www.isirv.org)

**NOVEMBER 13 - NOVEMBER 15, 2018**
**WASHINGTON DC, USA**

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**List of recent RSV papers**

**May**


Hicks SN, Chaiwatponsakorn S, Costello HM, McLellan JS, Ray W, Peeples ME. [Five Residues in the Apical Loop of]


Mora AL, Detalle L, Gallup JM, Van Geelen A, Stohr T, Duprez L, Ackermann MR. **Delivery of ALX-0171 by inhalation greatly reduces respiratory syncytial virus disease in newborn lambs.** MAbs. 1-59, in press.


**April**


Ivanciuc T, Sbrana E, Casola A, Garofalo RP. **Protective Role of Nuclear Factor Erythroid 2-Related Factor 2 Against Respiratory Syncytial Virus and Human Metapneumovirus Infections.** Front Immunol.;9:854.


Munywoki PK, Koech DC, Agoti CN, Cane PA, Medley GF, Nokes DJ. Continuous invasion by respiratory viruses observed in rural households during a respiratory syncytial virus seasonal outbreak in coastal Kenya. Clin Infect Dis., in press.


Kunzmann S, Krempl C, Seidenspinner S, Glaser K, Speer CP, Fehrholz M. Increase of CTGF mRNA expression by respiratory syncytial virus infection is abrogated by caffeine in lung epithelial cells. Influenza Other Respir Viruses., in press.


March


Haber N. Respiratory syncytial virus infection in elderly adults. Med Mal Infect., in press.


Patel MC, Shirey KA, Boukhvalova MS, Vogel SN, Blanco JCG. Serum High-Mobility-Group Box 1 as a Biomarker and a Therapeutic Target during Respiratory Virus Infections. MBio.;9(2).


For more information, visit us at [www.resc-eu.org](http://www.resc-eu.org)

Sign up for RESCEU-Newsletter [here](https)! Next issue in September.

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