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**KEYNOTE**

Harry Campbell
RESCEU WP2 Principal Investigator and WP Co-Leader

Working to improve data on RSV to raise awareness and inform policy decisions

I co-lead Work-package 2 in RESCEU together with Chuck Knirsch. This aims to assemble evidence on the importance of RSV infection and present this to policymakers so that we can raise awareness and knowledge of RSV and make available information that will be needed for vaccine decisions. It is hoped that when an effective vaccine becomes available we will be able to shorten the time that policymakers take to make informed decisions.

We are assembling national data of health service use associated with RSV from 6 European countries within RESCEU in a coordinated manner. We aim to then present these at a high-level policy summit to European policymakers. In parallel, we are supporting European Centre for Disease Control (ECDC) in taking actions to promote consensus on surveillance approaches to RSV across Europe. Improved surveillance systems would generate data which could monitor RSV healthcare burden and its reduction following the introduction of the vaccine. It would
also improve our knowledge of RSV seasonality across Europe and of RSV sequence variation across Europe and over time. We are also studying existing guidelines for the management of bronchiolitis and the use of preventive treatments (Palivizimab) in preterm and other high-risk infants across Europe. We hope then to hold workshops with paediatricians to discuss the reasons for variation and to try to improve and harmonise practices across Europe.

At the same time as working on RESCEU I am helping WHO set up pilot RSV surveillance projects in GAVI-eligible countries based on the influenza surveillance platform and am, with my colleague Thomas Williams, studying global RSV sequence variation with support from NIH. It is hoped that this will give further information on RSV transmission, evolution over time and associations between sequence and disease severity. It is a pleasure to work as one of the team members of RESCEU and make a contribution to improving our understanding of RSV and to controlling this important disease.

![Image of the Respiratory Viral Epidemiology Group, University of Edinburgh, including RESCEU early career researchers, Harry Campbell (in the center) and Harish Nair (the RESCEU Coordinator, third from the left).](image)

**WP2 team meeting in Amsterdam to discuss health service data**

WP2 will be holding a face-to-face meeting on the 2nd and 3rd of April 2019 in Amsterdam to discuss the ongoing analysis for Task 2.1 “National and regional routine health service data”. The meeting will be attended by around 20 people ranging from RESCEU academic partners, EFPIA companies and Affiliated Partners. In this occasion, the team will review the preliminary analysis of routinely collected data to explore the healthcare burden of RSV in seven European countries, and discuss the future work towards this task. More information on the outcomes of the meeting will be provided on the next issue of the RESCEU newsletter.

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**Get to Know the RESCEU Team!**
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.

You Li (UEDIN)

You Li (Leo) is a PhD student and part-time research fellow at The University of Edinburgh, Scotland. He has a Master of Science in epidemiology and biostatistics, and a Bachelor of Medicine in Peking University, China. His research interests include modelling global burden of RSV and other respiratory viruses, their transmission, and interaction with bacterial infection.

Tell us about your professional career.

I received training on epidemiology and quantitative analytic skills, and obtained my Master of Science degree in epidemiology and biostastics in the Institute of Reproductive and Child Health, Peking University, China. After that, I moved to Scotland in 2016 and started doctoral study at the Centre for Global Health Research, The University of Edinburgh. My PhD project contains two parts: one is the global seasonality of RSV and other respiratory viruses, which includes description and modelling of the seasonality; and the other one is the association between viral respiratory infection and subsequent pneumococcal diseases using the Scottish data. Apart from PhD projects, I have been actively involved in modelling global influenza mortality in young children. I was also involved in projects related to the global distribution of Neisseria meningitidis serotypes among healthy carriers and those with meningococcal diseases. Last year, I started my post as a part-time research fellow at The University of Edinburgh and worked as a co-investigator on the WHO research project about RSV seasonality for countries planning of introduction of RSV prevention strategies. I co-supervised MPH and medical students on topics related to the coinfections of respiratory pathogens, and I am currently supervising online MPH students.

Can you please explain a bit about your role at the University of Edinburgh as part of the RESCEU project?

I have been involved in Work Package 1 and 2 of the RESCEU project. For WP1, I am responsible for
the Task 1.6, global seasonality of RSV. This task, as part of my PhD project, describes and models
the global seasonality of RSV, aiming to provide important information for health-care planning and
vaccine/mAb strategies. I am also leading the update of global paediatric RSV disease burden
estimates (Task 1.10). My role in this task is mainly about the improvement of modelling for global,
regional and national estimates of RSV disease burden, especially the overall RSV mortality. For
WP2, I am involved in Task 2.1, which assesses the burden of RSV in European countries using
routine health databases. I work with Dr. Rachel Reeves and the other WP2 partners on the Task 2.1
analysis plan and provide general advice related to statistical questions.

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

RESCEU project has created a multi-disciplinary and multi-stakeholder community, and has brought
together a diverse group of collaborators. As a researcher, I think RESCEU provides good
opportunities for researchers from different parts of EU and beyond, to work more closely on
reducing RSV infections. I would foresee that after RESCEU project, many important gaps in
knowledge related to RSV infection would be addressed and sustainability will be one of the
treasures that RESCEU leaves for us. For example, a sustainable data platform across EU and beyond
will be developed at regional and national levels and will help better quantify the healthcare and
economic impact of RSV.

Sabine Tong (Sanofi Pasteur)

Tell us about your professional career.

Holding a master of biostatics, biomathematics, bioinformatics and health from Claude Bernard
University (Lyon, France), I have 5 years of experience with programming and statistics in the
pharmaceutical sector. Working in contract research organizations, I had the opportunity to carry
out different pharmaceutical industries’ projects in various diseases area such as oncology,
neurology, or rheumatology, and to be involved at different steps of the clinical development. Since January 2017, I have been working as a Real World (RW) analyst consultant for Sanofi Pasteur, providing evidences on disease burden and economic burden using different sources of claims databases (Marketscan, CPRD) to support medical decision-making and prevention strategies in infectious diseases area such as respiratory syncytial virus (RSV), acute otitis media, pneumonia, and meningococcal disease.

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

I have been involved in the RESCEU Work Package 2 (WP2) which aims to assemble existing routinely collected health and RSV data across Europe (Denmark, Netherlands, Finland, United Kingdom / Scotland, Italy, and Norway) to inform economics models for WP3. Sanofi Pasteur is supporting the RESCEU WP2 for data in the United Kingdom (UK) using the combination of primary care from the Clinical Practice Research Datalink (CPRD), linked to secondary care Hospital Episode Statistics (HES) and mortality data from the Office for National Statistics (ONS). Having technical and analytical expertise in RW studies and claims databases, I have supported and adapted the data analysis plan to the UK data identifying their strengths and limits. As a Real world analyst, my operational role is to carry out the analyses to provide the estimates of RSV disease burden, including childhood sequelae (asthma/wheeze), and the economic burden in the UK.

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

I think that the RESCEU project is an impressive mobilization of capacity and resources:

- By gathering clinicians, epidemiologists, scientists, health economists, statisticians, public health professionals and industries with a strong history of RSV research allowing a close interaction and collaboration on the questions of RSV impact on health systems and societies throughout Europe.
- By building an expanding data platform gathering sustainable knowledge base on RSV through existing data integration and analysis and via prospective studies and surveillance systems.

Thus, I believe that the combination of a multidisciplinary approach, the availability of several data sources and the use of similar methods of analysis across EU countries will provide new and robust evidences, an improved understanding, and a wider awareness of RSV-associated burden of disease that will contribute to improve health and wellbeing.

Papers of the month

in collaboration with ReSViNET

February 2019

Respiratory syncytial virus and influenza hospitalisations by HIV status in South African children

https://mailchi.mp/bf8964e78ae0/resceu-newsletter9

Summary

McMorrow and colleagues conducted a six-year prospective surveillance for severe respiratory illness (SRI) in young children under five years old in 3 South African hospitals. Both respiratory syncytial virus (RSV) and influenza associated hospitalisations were laboratory confirmed. The median age of children admitted with RSV and influenza was 4.4 months vs 13.9 months, with highest annual hospitalisation rate in infants aged 0-2 months vs 6-11 months respectively. This indicates that a maternal immunisation could serve as an effective strategy for reducing RSV associated hospitalisations. HIV exposure increased both RSV and influenza associated hospitalisation in infants aged 0-5 months with relative risk (RR) of 1.4 and 2.2 while HIV infection was in association with them in all age group (0-59 months) with RR of 3.8 and 2.7 respectively. However, the impact of the duration of maternal antiretroviral exposure on RSV or influenza associated hospitalisation was not measured which could strengthen the study finding.

Abstract on Pubmed.

February 2019

The endangered future of Syngem, a novel bacterium-like particle based, needle-free, RSV vaccine

Summary

Despite numerous years of research we are still lacking a safe and effective RSV vaccine. This process is hindered by numerous problems: the lack of a correlate of protection being one of them. That this has major consequences for vaccine development, is illustrated by the study performed by Stephanie Ascough, Peter Openshaw and colleagues. In their paper they describe the results of a randomized controlled, phase 1 trial of a novel needle-free RSV vaccine: SynGEM. The vaccine is based on a stable pre-fusion F antigen of the virus, and uses a bacterium-like-particle (BLP) as an immune-enhancing carrier. The study confirms that the vaccine is safe and that it is capable of inducing a mild (about 2 to 3-fold), but prolonged, increase in RSV-specific antibodies. However, the study didn’t reach the endpoint threshold and for now, SynGEM is withheld from proceeding to next phase trials.
This study illustrates, that the lack of a correlate of protection brings an uncertainty to the table, which could lead to the premature termination of a potentially effective RSV vaccine. The use of a human challenge model (HCM) in RSV vaccine development would offer the possibility to circumvent this insecurity. Furthermore it might accelerate RSV-vaccine development.

**January 2019**

**Sample size required to detect the effect of RSV vaccination on recurrent wheezing**


**Summary**

Riddell and colleagues investigated the feasibility of utilizing maternal RSV vaccine trials to detect the effect of RSV vaccine on childhood recurrent wheezing. The model inputs came from systematic reviews and meta-analyses, including the following parameters: vaccine efficacy, allocation ratio, rate of early severe RSV illness, risk of recurrent wheezing at age 3, and increased risk of RSV infection on recurrent wheezing. The result showed that among the plausible scenarios the lowest sample size required was 6196 mother-infant pairs per trial arm, and 75% and 47% of plausible scenarios required more (>31,060 and >100,000). Unfortunately all these scenarios exceed the size of the only current phase III trial of RSV vaccination in pregnant women, which indicated the impossibility of demonstrating an effect on recurrent wheezing. Further efforts are needed to plan for post-licensure studies to inform the impact of RSV vaccines given during pregnancy on long term respiratory illness.


**January 2019**

**Miniature lungs: the road towards a better model to study RSV disease.**


Summary
Sachs from UMC Utrecht developed human airway organoids (miniature lungs) that offer the possibility to study RSV in an human in vitro model. The authors show that RSV replicates well in human airway organoids and that infection can be inhibited after pre-treatment with palivizumab. Furthermore, RSV caused epithelial changes that mimic disease characteristics such as epithelial shedding, syncytia formation and alterations of the cytoskeleton. Also, there was an upregulation of antiviral genes and an enhanced secretion of cytokines such as IP-10. Both of these findings reflect the immune responses following RSV infection in infants. Lastly, human airway organoids offer the possibility to study the interaction between immune cells and the RSV infected epithelium. The latter is of major importance to increase the knowledge on RSV immune signalling.
Altogether, RSV - infected airway organoids offer the possibility to study numerous aspects of RSV disease, including airway remodelling, immune cell interaction and treatment possibilities.

Written by Sjanna Besteman

Abstract on PubMed

December 2018

Severy Morbidity and Mortality Associated with Respiratory Syncytial Vires versus Influenza Infection in Hospitalized Older Adults


Summary
A large cohort of adults >=60 years hospitalised with laboratory confirmed RSV or influenza infection during 5 consecutive seasons were investigated. The study showed that older adults hospitalised with RSV were slightly older and more likely to have baseline co-morbidity conditions than those with influenza. Regarding hospitalisation outcome, they had longer length of hospital stay, greater odds of pneumonia, ICU admission, COPD exacerbation, chronic bronchiolitis, emphysema and one-year mortality than those with influenza, even after adjustment for baseline comorbidities. This might reflect the increased use of antiviral therapies for influenza in recent years and differences of clinical severity in RSV and influenza infection. The findings highlight the substantial morbidity and mortality associated with RSV infection in hospital settings in the expanding population of older adults who could benefit from RSV vaccines and antivirals.

Abstract on PubMed
December 2018

Proinflammatory Effects of Respiratory Syncytial Virus–Induced Epithelial HMGB1 on Human Innate Immune Cell Activation

Kempaiah Rayavara,* Alexander Kurosky,† Susan J. Stafford,† Nisha J. Garg,* Allan R. Brasier,‡,x Roberto P. Garofalo and Yashoda M. Hosakote*, J Immunol 2018; 201:2753-2766; Prepublished online 1 October 2018; http://www.jimmunol.org/content/201/9/2753
doi: 10.4049/jimmunol.1800558

Summary

The first epithelial molecular events upon infection define the size and direction of the inflammatory response, which ultimately defines disease in RSV infected patients. Rayavara and colleagues shed a light on this complex process. Previously, this group showed that RSV promotes the release of high mobility group box 1 (HMGB1) by airway epithelial cells. HMGB1 is a nuclear protein, which becomes an alarmin after secretion to the extracellular space to induce an inflammatory response.

In the current study they show, that HMGB1 forms a link between the infected respiratory epithelium and the response by immune cells. After RSV infection, HMGB1 is expressed by airway epithelial cells. This process is dependent on TLR4 and is mediated by the MAPK and NF-kB pathway. Blocking of TLR4 or the NF-kB pathway in AECs, decreases the expression of HMGB1. Next they show that HMGB1 stimulates primary immune cells, such as monocytes and macrophages, to produce inflammatory cytokines and chemokines.

Blocking the HMGB1 pathway, under an umbrella of antiviral treatment, might limit immune pathology and thereby ameliorate the course of disease in children with RSV infection.

Abstract on PubMed

Upcoming major RSV/respiratory meetings

WP2 RSV SURVEILLANCE MEETING ON THE DEVELOPMENT OF A HARMONIZED RSV SURVEILLANCE SYSTEM IN EUROPE

As previously announced, we are on the eve of the Surveillance Meeting, where WP2 team is gathering experts from Public Health agencies and academic bodies to discuss and develop a suggested framework for an RSV surveillance protocol in Europe, basing discussions on the 2017 ECDC RSV surveillance survey. In this occasion, RESCEU partners, SSI, RIVM, UEDIN, PENTA, and Affiliated Partners, NiPH (N), THL (FIN), NIVEL (NL), will meet representatives of ECDC - updating on RSV Atlas and ECDC perspective on RSV surveillance -, WHO - giving updates on ongoing RSV pilot surveillance project -, and many more National Health institutes in Europe.
Updates on feasibility assessments for various surveillance systems, framework design and further strategical content, after the meeting.

MARCH 20 - 21, 2019
COPENHAGEN, DENMARK

IMMUNOLOGICAL ASSAYS AND CORRELATES OF PROTECTION FOR NEXT GENERATION INFLUENZA VACCINES
The Conference on Immunological assays and Correlates of Protection for Next Generation Influenza Vaccines, taking place in Siena (IT) in the end of March, will gather scientists from academia, industry, and government public health, standardisation and regulatory agencies that develop and evaluate seasonal and pandemic influenza vaccines, to focus on relevant steps to develop next-generation influenza vaccines. More information, agenda are available on the website and registration is possible till the 21st of March.

MARCH 31 - APRIL 2, 2019
SIENA, ITALY

10TH EDITION OF THE OPTIONS FOR THE CONTROL OF INFLUENZA IRSV CONFERENCE
The 10th edition of the ISRV Conference on Options for the Control of Influenza, will be held between the 28th of August and the 1st of September in Singapore. This is the largest international conference exclusively dedicated to influenza prevention, control and treatment, including seasonal flu and pandemic preparedness. Highlights of the meeting include: new tracks on influenza co-infections with other viral pathogens and key issues for policy making - special sessions to showcase the latest developments in Chinese-speaking countries - pre-conference workshops on a wide variety of topics including technology, mathematical modelling and bioinformatics. Registration are opening soon. See website.

AUGUST 28 - SEPTEMBER 1, 2019
SINGAPORE

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List of recent RSV papers

February

Cullen LM, Schmidt MR, Torres GM, Capoferri AA, Morrison TG. Comparison of Immune Responses to Different Versions of VLP Associated Stabilized RSV Pre-Fusion F Protein. Vaccines (Basel). 15;7(1).

Manley GCA, Parker LC, Zhang Y. Emerging Regulatory Roles of Dual-Specificity Phosphatases in Inflammatory
**Airway Disease**, Int J Mol Sci. 5;20(3).


Alansari K, Toaimah FH, Almatar DH, El Tatawy LA, Davidson BL, Qusad MIM. **Monoclonal Antibody Treatment of RSV Bronchiolitis in Young Infants: A Randomized Trial.** Pediatrics, in press.


Voelker DR, Numata M. **Phospholipid regulation of innate immunity and respiratory viral infection.** J Biol Chem., in press.


Battles MB, McEllan JS. **Respiratory syncytial virus entry and how to block it.** Nat Rev Microbiol., in press.


Sarkar I, Zardini Buzatto A, Garg R, Li L, van Drunen Littel-van den Hurk S. **Metabolomic and Immunological Profiling of Respiratory Syncytial Virus Infection after Intranasal Immunization with a Subunit Vaccine**
January


Kuyipers J. Impact of rapid molecular detection of respiratory viruses on clinical outcomes and patient management, J Clin Microbiol., in press.


Oh DS, Kim TH, Lee HK. Differential Role of Anti-Viral Sensing Pathway for the Production of Type I Interferon Bin Dengdritic Cells and Macrophages Against Respiratory Syncytial Virus A2 Strain Infection, Viruses.15;11(1).


Sonawane AA, Shastri J, Bavdekar SB. Respiratory Pathogens in Infants Diagnosed with Acute Lower Respiratory...
Tract Infection in a Tertiary Care Hospital of Western India Using Multiplex Real Time PCR. Indian J Pediatr., in press.


Ayegbusi OT, Ajagbe OA, Afromowe TO, Aransi OA, Olusola BA, Awogbindin IO, Ogunsemore OO, Faneye AO, Odaibo GN, Olaye JO. *Virus genes and host correlates of pathology are markedly reduced during respiratory syncytial and influenza virus co-infection in BALB/c mice*, Helinyon 3;5(1):e01094.


December


Hurley LP, Allison MA, Kim L, O'Leary ST, Crane LA, Brtnikova M, Beaty BL, Allen KE, Poser S, Lindley MC, Kempe
A. **Primary care physicians’ perspectives on respiratory syncytial virus (RSV) disease in adults and a potential RSV vaccine for adults.** Vaccine. 21;37(4):565-570.


Kombe IK, Munywoki PK, Baguelin M, Nokes DJ, Medley GF. **Model-based estimates of transmission of respiratory syncytial virus within households.** Epidemics, in press.


Johnson JK, Harris FL, Ping XD, Gauthier TW, Brown LAS. **Role of zinc insufficiency in fetal alveolar macrophage dysfunction and RSV exacerbation associated with fetal ethanol exposure.** Alcohol., in press.


Ban J, Lee NR, Lee NJ, Lee JK, Quan FS, Inn KS. **Human Respiratory Syncytial Virus NS 1 Targets TRIM25 to Suppress RIG-I Ubiquitination and Subsequent RIG-I-Mediated Antiviral Signaling.** Viruses.;10(12).


Groves HE, Shields MD. RSV and asthma inception - cause and effect or shared susceptibility? J Infect Dis., in press.


For more information, visit us at www.resc-eu.org
Sign up for RESCEU-Newsletter here! Next issue in June.

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