RESCEU
REspiratory Syncytial virus Consortium in EUrope

NEWSLETTER

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Contents

KEYNOTE

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Staying the course on delivering the next-generation of RSV preventative

medicines

Despite more than 60 years of research and numerous clinical trials evaluating vaccines in both the young and old, there still only remains one medicine currently approved for the prevention of RSV: palivizumab (Synagis®, AstraZeneca/MedImmune). Although it's the only available prophylaxis option, palivizumab is not widely used, primarily because it is only approved for use in infants considered to be high-risk: those born prematurely, or with congenital heart or lung disease.

The limited preventative and treatment options represent a significant unmet medical need and an opportunity for the healthcare research community to develop more effective medicines to help prevent RSV in a much broader population. Fortunately, numerous biopharmaceutical companies and research entities, including AstraZeneca/MedImmune, remain committed to advancing development of new, innovative RSV prevention options with the potential for use in a far larger patient population. These continued efforts are now bringing us closer than ever before to delivering new preventive RSV medicines.

MedImmune has been active in the RSV field for more than 25 years, having first developed RespiGam® IVIG in 1996, Synagis® in 1998, and tested several live-attenuated and vector-based vaccines and mAbs (**Figure 1**). We are currently optimistic about and moving full steam ahead on development of MEDI8897, an extended half-life mAb being evaluated in a Ph2b placebo-controlled study in approximately 1,500 pre-term infants. We look forward to sharing the full results of this pivotal trial with the RSV community in 2019.

The development of 8897 represents an important and meaningful step toward delivering a next-generation preventive RSV mAb to all infants in need. It offers significant advantages over Palivizumab, which we believe will allow it to make a much bigger impact in the fight against RSV. Notably, MEDI8897 is being developed for use in a broader infant population, not only those considered to be high-risk for RSV, and it only requires one dose for an entire RSV season. We are hopeful that MEDI8897 can help address the significant unmet medical need and we expect to share the results in the 1H next year at an upcoming meeting.

I have been involved in vaccine R&D for more than 20 years. I did my graduate work on influenza, post-doctoral training at the AIDS vaccine program at the NIH and worked at Merck Vaccines prior to joining MedImmune. At Merck, I was privileged to be part of the team that developed GARDASIL®, the first vaccine for the prevention of cervical cancer. I experienced firsthand how it important is was for researchers from around the world to come together to better understand the epidemiology, develop diagnostic assays and international reference standards and work towards identifying a correlate of protection. All these endeavors were important to get the vaccine approved for females and eventually males. More recently, I have had the opportunity to work on the IMI-COMBACTE programs for the prevention of ventilator-associated *S. aureus* and *P. aeruginosa* pneumonias (VAP). In addition to epidemiology studies, COMBACTE is performing two clinical trials to evaluate antibodies developed by MedImmune to prevent *S. aureus* and *P. aeruginosa* VAP. COMBACTE has shown the power of bringing together scientists with diverse backgrounds and interests to do science on a scale that could not be achieved individually.

IMI-RESCEU follows IMI-COMBACTE in that it facilitates the interactions between academic, government and industry researchers to:

1. Understand the disease burden of RSV in infants, elderly and subjects with COPD
2. Identify biomarkers that may be associated with long-term consequences of RSV
3. Establish a study network and data platform to engage with public health authorities

With more than a dozen vaccines/mAbs in clinical development RESCEU is playing an important role in

creating and disseminating key information that will hopefully lay the foundation for approval of the first vaccine or mAb for all infants or the elderly.

I am proud to be a part of this prestigious group that is working diligently to advance innovative preventive RSV medicines and remain inspired by all the work being done to deliver a next-generation medicine that will significantly strengthen our capability to fight RSV. I feel that now more than ever, we are getting closer to making that vision a reality.

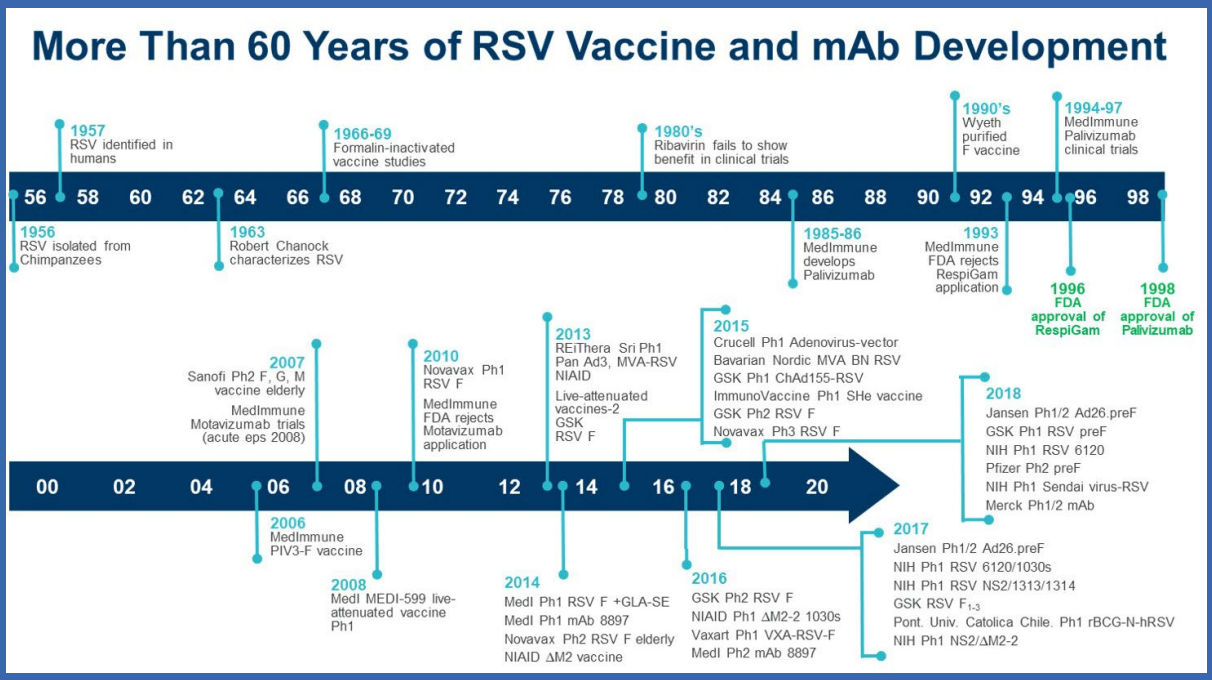

Figure illustrating more than 60 years of vaccine and monoclonal antibody development for the prevention of RSV infections.

WP2 preparing the first RESCEU RSV Surveillance Meeting in collaboration with the European Centre for Disease Prevention and Control (ECDC)

The main aim of RESCEU Work Package 2 *Consolidation of health care systems data*, Task 2.2 *National / large scale surveillance systems in Europe* is to develop a proposal for a European RSV enhanced surveillance framework. One of the deliverables to achieve this aim is to organise consensus building meetings of RSV surveillance experts in Europe. Anne Teirlinck (RIVM) and Thea Kølsen Fischer (SSI) in collaboration with Pasi Penttinen from ECDC have set up a workshop to be held in Copenhagen on 20th-21st March 2019. The workshop will bring together experts from Public Health agencies and academic bodies as a follow-on from the RSV sessions at the 2017 Annual ECDC Influenza meeting in Stockholm, with the aim to develop a proposal for aligning national RSV surveillance systems in Europe.

A report of the workshop will be written for the next RESCEU newsletter.

RESCEU Older Adults Clinical Study achieves complete recruitment

The Older Adults Clinical Study has recently become the first clinical study in RESCEU to achieve full recruitment

rate, according to schedule and with the appropriate age distribution. The study focuses on Respiratory Syncytial Virus (RSV) in older adults aged 60 years and above, and it is one of 4 Clinical Studies conducted by RESCEU across Europe (Birth cohort study, Infant case-control study, Older adults study and Chronic Obstructive Pulmonary Disease (COPD) study), to address the lack of knowledge on the burden of RSV in certain populations and provide substantial insights on the impact of RSV on health systems and societies throughout Europe.
A total of 8 Clinical Centres are participating, under the coordination of the University Medical Center Utrecht.

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.

Xiao Li (University of Antwerp)

Xiao Li is a doctoral researcher in the Centre for Health Economics Research & Modelling Infectious Diseases (CHERMID) at the University of Antwerp. Her primary research topic is economic evaluation of interventions against respiratory infections, with a focus on Respiratory Syncytial Virus (RSV) in European and Gavi-eligible countries.

Tell us about your professional career.

Modelling and cost-effectiveness analyses of vaccination strategies against infectious diseases have always been my great interest and passion. After I obtained my master's degree in International Health Policy (Health economics) from London school of Economics and Political Science, I moved to Belgium and started my career in consultancy and pharmaceutical industry. I have more than seven years of experience conducting health economics evaluations on several vaccines, including hepatitis B, human papillomavirus, rotavirus, pertussis, varicella and influenza. My previous professional experience includes: burden of disease studies, systematic literature reviews, cost-effectiveness and budget impact analyses, quality of life studies, dynamic transmission models, development of

reimbursement dossiers, project management, and communication with various stakeholders. In September 2017, I joined CHERMID at the University of Antwerp as a doctoral researcher with the the opportunity to become a member of RESCEU team, and to advance my research skills and pursue a Doctor of Philosophy degree.

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

Most health providers and policy-makers in the healthcare sector are interested to know not only whether an intervention against RSV infection is effective, but also whether it is cost-effective, in the other words, is it worth what you pay for. As a health economist working on RESCEU Work Package 3 (WP3) under the supervision of Professor Philippe Beutels at the University of Antwerp, my role is to use a range of techniques to assist with answering these economic questions. I am currently working collaboratively with WP2 to determine the RSV-associated economic, financial, and health burden and whether the potential new interventions provide better value for money than standard care. Using the data collected from different work packages (systematic reviews conducted by WP1, retrospective database analyses performed by WP2 and prospective cohort studies led by WP4), our team will calculate the health care and societal costs, as well as quality-of-life measures, from the perspective of patients and caregivers. Together with WP3 affiliate partner, Professor Mark Jit from the London School of Hygiene and Topical Medicine (LSHTM), CHERMID developed MC MARCEL (Multi-Country Model Application for RSV Cost-Effectiveness poLicy), a model to assess the key drivers of the cost-effectiveness of potential strategies against RSV in children under 5 years of age. We have applied this model in Gavi-eligible countries, and our next step is to populate the model with EU country-specific data. In the future, our team will also develop other simulation models in order to extend the analysis to different target groups (i.e. COPD and elderly population) to inform decision-makers.

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

I believe that RESCEU provides a unique opportunity for researchers with different backgrounds to collaborate and gain a thorough understanding of RSV infections. I foresee enormous new evidence will be generated through the consortium, and novel ways of synthesizing the evidence will inevitably emerge from such a diverse group of collaborators. We will be able to have a comprehensive understanding of RSV disease burden in Europe, especially on the proportion of all RSV cases in the community that are hospitalised and the RSV-associated fatality rate outside of the hospital.

With the clinical trials of the upcoming RSV interventions which inform our estimates of the efficacy and duration of protection of new technologies, we will be able to predict the reduction of RSV-associated disease burden in Europe and worldwide in both the short- and long-run. It may also allow us to better understand the RSV transmission and the impact of each strategy in a specific target group as well as in the general population.

I think the RESCUE studies will be invaluable references for years to come because we aim to systematically assess the landscape of the current evidence in the epidemiology of RSV and resource-use of treatment. By using the same methods of analysis across countries, we will come to understand how the new prophylaxes may have different economic and epidemiological impacts in different countries, and therefore how these new tools can be used to the best advantage of these respective countries . As a first step, our assessment to which extent the

various gaps in knowledge drive the uncertainties for policy-making provides a basis for prioritising further research on RSV.

Simon Drysdale (University of Oxford)

Simon Drysdale is a consultant and researcher in paediatric infectious diseases at St George's University Hospital NHS Foundation Trust and St George's, University of London.

Tell us about your professional career.

I am consultant and honorary senior lecturer in paediatric infectious diseases at St George's University Hospital NHS Foundation Trust and St George's, University of London. I am also a researcher at the University of Oxford working with Andrew Pollard and Matthew Snape on the RESCEU project. I graduated from St George's Hospital Medical School in 2003 and in 2008 undertook a PhD at King's College London (KCL) investigating factors predisposing prematurely born infants to viral lower respiratory tract infection (LRTIs) (including RSV) and chronic respiratory morbidity after viral LRTIs. I completed a postgraduate diploma in paediatric infectious diseases at the University of Oxford in 2016 and started as a consultant at St George's in March 2018. RSV and other viral respiratory illnesses have been my main research interest since undertaking my PhD and I am an investigator on several clinical trials and laboratory and observational studies, mainly relating to RSV infection.

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

I have been involved in work packages (WP) 4 and 5 from the outset of the RESCEU project. These WPs aim to improve the understanding of RSV epidemiology, using clinical cohorts, and to identify biomarkers that will predict RSV disease severity or sequelae. I helped to develop the clinical and laboratory protocols for the four clinical studies in conjunction with the other clinical sites and EFPIA partners, and have been the local principal investigator for the infant cohort and case-control studies in Oxford. I have also been leading the systematic

reviews of biomarkers of RSV disease in infants and adults and in animal studies undertaken as part of WP5. I co-supervise two University of Oxford DPhil students who are working within the RESCEU consortium to investigate RSV sequencing and susceptibility to RSV disease via host transcriptomics. In addition, I am a member of the editorial board for the RESCEU newsletter!

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

The RESCEU project will provide important data on many aspects of RSV infection across Europe including epidemiology, healthcare utilisation and associated costs and clinical and biological data. Having a better understanding of the burden of RSV disease, particularly in groups where data is currently scare, will aid academics, researchers and policy makers to identify targets groups for interventions such as antiviral medications and vaccines. In addition, the identification of biomarkers to predict disease severity or sequelae may provide the basis for a clinical test to aid clinicians or will provide a large dataset which can be used to validate biomarkers identified in other future studies. In addition, the biobank of collected samples that is being stored will allow future work to be undertaken. The RESCEU project will leave a lasting legacy of a network of researchers allowing international collaboration in Europe and beyond for future RSV and other respiratory virus projects.

Papers of the month

in collaboration with ReSViNET

November 2018

Patterns of respiratory pathogen circulation in rural coastal Kenya

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. 2018 Oct 30;67(10):1559-1567. doi: 10.1093/cid/ciy313.

Summary

A household-based active surveillance during RSV season was conducted in 47 households in Kilifi Kenya. This study showed that 93.4% of the study participants had at least 1 virus detected. Adenovirus (AdV), human coronavirus (HCoV) and rhinovirus (RV) were the most prevalent during the RSV season. The individual attack rates declined with increasing age for most pathogens. Coinfection detection was common (13.4%-17.4%) and was higher among the symptomatic cases. The prevalence of RSV (and HMPV, PIV3 and RV) were higher among the hospital cases than in the community. Therefore, the frequency distribution of viruses could differ between community and hospital settings. Studies with a longer surveillance (particularly with multiple years) and studies investigating a wider range of respiratory viruses would provide more comprehensive data on virus circulation and year-to-year variation.

Full article on Pubmed.

Papers of the month

in collaboration with ReSViNET

November 2018

The significance of Human Respiratory Syncytial Virus (HRSV) in children from Ghana with acute lower respiratory tract infection: a molecular epidemiology analysis

Obodai E, Odoom JK, Adiku T, Goka B, Wolff T, Biere B, Schweiger B, Reiche J. The significance of human respiratory syncytial virus (HRSV) in children from Ghana with acute lower respiratory tract infection: A molecular epidemiological analysis, 2006 and 2013-2014. PLoS One. 2018 Sep 10;13(9):e0203788. doi: 10.1371/journal.pone.0203788. eCollection 2018.

Summary

The molecular epidemiology of RSV infection is increasingly thought to be essential to understand how the virus spreads around the world every year. RSV molecular epidemiology also informs developers of therapeutics about potential sensitivity or resistance of the virus to specific drugs. Altogether, data of about 1000 specimens have been published, most from developed countries. The World Health Organization has started a pilot to perform RSV surveillance, probably including viral sequencing. Data from poor resource settings have been prioritized. To that end it is important to note this paper form researchers from Ghana and Germany who were able to provide valuable sequence data from a study performed in 2006-2014 in which 127 RSV positive children were included. The results show the evaluation of RSV-A (ON1) and RSV-B strains (BA9) in Ghana. These data will add significantly to our understanding of viral behaviour over time in low and middle income countries (LMIC).

Full article on Pubmed.

Papers of the month

in collaboration with ReSViNET

October 2018

Implications of viral genomic variability for RSV immunisation programs

Vicente Mas, Nair H, Campbell H, Melero JA, Williams TC. Antigenic and sequence variability of the human respiratory syncytial virus F glycoproteincompared to related viruses in a comprehensive dataset. Vaccine. 2018 Oct 3. pii: S0264-410X(18)31325-2. doi: 10.1016/j.vaccine.2018.09.056; in press.

Summary

In this study Williams and colleagues examined variability in the RSV F glycoprotein from published data virus strains sequenced in different locations worldwide. Looking at the specific parts of the protein targeted by human

antibodies, they compared variability at these sites to that in the closely related viruses bovine RSV and human metapneumovirus. They found some regions that were very similar between related viruses, suggesting that these were evolutionarily conserved and therefore might be good targets for future vaccines, and other areas that were highly variable, suggesting a high degree of evolutionary change, that might therefore be less effective targets for immunisation campaigns. They concluded by recommending that efforts should be made to establish a global baseline dataset to identify potential evolutionary changes in the virus driven by any immunisation programs, and have in fact already taken steps towards this. The DIVERGE (Diversity in RSV Genomes) consortium, led by researchers at the UoE, is already sequencing samples from 6 countries around the world to improve our understanding of RSV genetic variability: https://www.ed.ac.uk/mrc-human-genetics-unit/diversity-in-rsv-genomes. The output from this sequencing project will contribute towards discussions amongst stakeholders about which type of RSV vaccines are most likely to be effective in reducing the burden of this global disease.

Abstract on Pubmed.

Papers of the month

in collaboration with ReSViNET

September 2018

Respiratory viral epidemiology in rural Kenya

Nyiro JU, Munywoki P, Kamau E, Agoti C, Gichuki A, Etyang T, Otieno G, Nokes DJ. Surveillance of respiratory viruses in the outpatient setting in rural coastal Kenya: baseline epidemiological observations. Wellcome Open Res. 2018 Jul 25;3:89. doi: 10.12688/wellcomeopenres.14662.1. eCollection 2018.

Summary

This paper reports the epidemiological data of respiratory viruses at nine outpatient health facilities in rural coastal Kenya as well as in hospital settings. More than half (53.7%) of participants with ARI symptoms were from children younger than 5 years. The most common respiratory viruses detected were rhinovirus, influenza virus, coronavirus, parainfluenza virus, respiratory syncytial virus (RSV) and adenovirus. In hospital settings with young children admitted to hospitals, the frequency of RSV and adenovirus was significantly higher, indicating they were more commonly associated with severe disease. More data tracking temporality and seasonality of viral prevalence over multiple years as well as discussion on viral co-infections would strengthen the evidence.

Abstract on Pubmed.

Upcoming major RSV/respiratory meetings

2nd ISIRV EPIDEMIOLOGY GROUP CONFERENCE

The next Epidemiology Group conference is planned to take place at the new ECDC facilities in Stockholm. This is

an interdisciplinary meeting bringing together epidemiologists, clinical researchers, as well as experts in public health, risk analysis, big data and global health. The focus will be on severe disease presentations with influenza and other respiratory viral infections. In particular, the programme will address 6 key topics:

- Linking clinical research and surveillance
- What happens outside the hospital?
- Learning from individual clinical and patient-reported outcomes
- Predicting outcomes on the individual and population level
- Advancing public health surveillance of severity
- Epidemiological methods and challenges in high and low resource settings

More details are available on the ISIRV website.

JANUARY 16-18, 2019
STOCKHOLM, SWEDEN

2nd WORLD CONGRESS ON PEDIATRICS & CHILD CARE 2019

Abstract submission is now open for the 2nd World Congress on Pediatrics &Child care that will take place in Malmo, Sweden, on June 17-18, 2019. This international congress will provide a platform for Pediatrics professionals, researchers, students, and healthcare industrialists to meet and share their creative ideas and thoughts on children health. The congress focus on important topics with 30 scientific sessions, including infectious diseases, neonatology, bronco pneumo allergology, pediatric patient safety and quality improvement, pediatric emerging medicine and many others.

Further information on scientific sessions and abstract submission process can be found at www.pediatricsconference.org.

JUNE 17-18, 2019
MALMO, SWEDEN

List of recent RSV papers

November

Noor A, Krilov LR. Respiratory syncytial virus vaccine: where are we now and what comes next? Expert Opin Biol Ther., in press.

Reuter SE, Evans AM, Ward MB. Reducing palivizumab dose requirements through rational dose regimen design. CPT Pharmacometrics Syst Pharmacol., in press.

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October

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