RESCEU
REspiratory Syncytial virus Consortium in EUrope

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innovative medicines initiative

NEWSLETTER
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KEYNOTE

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Health economics can help answer important policy questions

When new health care technologies become available, two pivotal questions arise: (1) If we use the new technology, how can we use it to the best advantage of our population and our health care system? (2) Should using the new technology be subsidized by the taxpayer, and at what price?

These questions can partly be addressed by health economic evaluation, which studies the comparative effectiveness, cost-effectiveness and budget-impact of different intervention options.

With RSV we have reached an exciting juncture in technological advancement. RESCEU is paving the way in anticipation of new RSV interventions showing their efficacy and safety. WP3 is making a giant

jigsaw puzzle based on the various data and insights from RESCEU to estimate the health and economic RSV burden in Europe and beyond. We can then combine trial efficacy data with country-specific burden data to estimate population-level effectiveness and cost-effectiveness. To this end, WP3 is developing a series of simulation models that can explore the potential consequences of using new RSV interventions in various ways (e.g. different target groups, schedules, uptake levels) in terms of their health impacts, resource use (e.g. hospitalisations), as well as their monetary costs and benefits, all in comparison with current practice for RSV, and at the population level. By investigating how different options of using RSV interventions compare to each other we try to provide objective answers to the first pivotal question. By analyzing how the value for money for these new RSV interventions compares with that of other interventions in health care we further support policy makers in the complex prioritization tasks they face through the second question.

As a researcher I have been involved in these kinds of analyses since the early 1990s when the first - then - expensive vaccine, recombinant hepatitis B vaccine, was slowly being introduced in Europe. Since then, data sources have become richer and more accessible, analytical standards dealing with uncertainty and herd immunity improved, and many new vaccines were successfully introduced. Policy making for preventive interventions has been difficult where there is substantial biomedical uncertainty and/or the burden of disease is perceived to be mild. This, along with budget-impact considerations, seems to have played a role in the relatively slow introduction of childhood vaccination against chickenpox, rotavirus and influenza in many countries.

RESCEU has the opportunity to facilitate the policy making process by generating novel data-driven evidence in a timely manner. If the new RSV interventions prove to be sufficiently efficacious and are competitively priced, I expect that any remaining uncertainties will not obfuscate the decision-making process on RSV.

WP2 representatives participating to the International Population Data Linkage Network's Conference in Alberta, Canada

Rachel Reeves (University of Edinburgh) successfully submitted an abstract for a workshop at the International Population Data Linkage Network's (IPDLN) Conference, which took place on 12-14 September, 2018, at the Banff Centre, in Banff National Park, Alberta, Canada.
The conference theme was Linking Data – Improving Lives, with the aim of providing a forum for the

presentation and discussion of research and innovation in the area of Linked Population Data Science and Policy Impact.
The title of the workshop was 'Using linked health data in international comparisons of infectious disease burden' and was based on the work involved in WP2 Task2.1 *Assessing RSV healthcare burden using routine linked health data*. Rachel and some other RESCEU colleagues, from Telethon Kids Institute, Perth, Australia (which recently became a RESCEU Affiliate Partner) and from Sanofi Pasteur worked together to lead the workshop at the conference. A report on the conference and how the workshop went will be available in the next RESCEU newsletter.

Two RESCEU abstracts accepted for presentation at the IMI 10th Anniversary Scientific Symposium

The IMI Scientific Symposium will take place on 22 and 23 October 2018 in Brussels to celebrate the 10th anniversary of the programme. During the two days, partners from different IMI projects will be showing more than 80 poster displays, over 25 oral presentations and several panels on topics ranging from personalised medicine to patient-centric approaches in drug development.

This is the result of a call for abstracts launched by IMI during the spring with the double intent of presenting the spectrum of IMI's projects, while highlighting young researchers' contributions; in fact, PIs could only participate as co-authors, as only proposals with researchers in the early stage of their career as main authors were admitted to the call.
RESCEU will be participating to the event with a poster and an oral presentation; the poster will focus on "Developing a robust evidence base on RSV disease and economic burden using a multi-disciplinary approach", and will be elaborated by means of a transversal collaboration between Rachel Reeves (UEDIN, WP2), Xiao Li (UA, WP3) and Ting Shi (UEDIN, WP1), to be displayed during the event session "New targets, tools and pathways".

The oral presentation on "Prospective data collection on burden of RSV infection in Europe – paving the way for an RSV vaccines and therapeutics", will be given by Joanne Wildenbeest (UMCU, WP4), during the event session "Patient engagement along the value chain".

NEW SECTION: 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.

Deniz Öner (Janssen)

Deniz Öner is a postdoctoral researcher in the Translational Biomarkers / Infectious Diseases Department at Janssen Pharmaceutica, Belgium. She is primarily focusing her research on the identification of biomarkers of RSV infection in the scope of the RESCEU project. She holds a PhD degree in Public Health from KU Leuven, Belgium.

Tell us about your professional career.

I obtained my M.Sc. in Pharmaceutical Technology from Istanbul University. During my master, I volunteered in several public health and internship projects in the European Pharmaceutical Students Association. These experiences motivated me to work in international and multi-centred projects in Pharmaceutical Industries.
My experience in research continued with a year as a research assistant in the Molecular Biology and Genetics laboratory at VIB (Flemish Institute for Biotechnology), KU Leuven, Belgium. The following year, I started my PhD in the Faculty of Public Health and Primary Care, Department of Environment and Health in Respiratory Toxicology – Pneumology laboratory at KU Leuven. For four years, I focused on the

investigation of predictor genetic markers of occupational and environmental respiratory exposures, namely nanoparticles and asbestos. I was thrilled to work with cells, animals and human samples and using sophisticated sequencing techniques and bioinformatic tools.

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

Currently I am a postdoctoral researcher at Janssen Pharmaceutica combining my pharmacy and research experience in the RESCEU project. I work together with Jeroen Aerssens, part of the WP5 – presumed risk factors and biomarkers for RSV-related severe disease and related sequelae.
My role is to lead the project in identifying transcriptional biomarkers for RSV susceptibility and severity in infant- and adult-cohorts within the RESCEU project. In addition, I am actively involved in viral diagnostics and immune response to RSV infection studies on the samples collected from clinical sites. Therefore, I am working closely with the EFPIA partners and WP4 in the RESCEU consortium. This gives me the opportunity to learn epidemiological and experimental aspects of the RSV infection while improving my communication skills.
I am proud to be part of this consortium involving so many top-notch scientists in the RSV field from both academia and industry.

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

Currently, it is not known why some individuals are having severe infection and are being hospitalised in intensive care unit whilst others have mild to moderate infections. We are in a critical period with (several) new vaccines in the pipeline, but we do not know when or whom to vaccinate, especially when the economic impact of massive vaccination trials and campaigns should be taken into consideration. With the RESCEU project, both academics and industries came together to tackle this problem. I see RESCEU as a tremendous opportunity to improve our chances in winning our battle against RSV infections. Having met many of the scientific, regulatory and public health partners during the General Assembly in Oxford, I am confident that many of the obstacles in RSV infection will be overcome. I foresee that after RESCEU project, clinicians will be able to identify the high-risk segments of the population and reduce intensive care hospitalisations in RSV-infected infants and adult patients with appropriate prevention programs. Finally, I hope to see the effect of our hard work both in developed and developing countries to reduce the negative impact of RSV infection on global health.

Rachel Reeves (UEDIN)

Rachel Reeves is a Research Fellow at The University of Edinburgh, Scotland. She holds a PhD in Epidemiology from University College London and a Master's degree from Newcastle University, UK. Her research interests include exploring the healthcare burden of Respiratory Syncytial Virus (RSV) to inform policymaking and regulatory decisions regarding preventative measures and interventions.

Tell us about your professional career.

My research career has centred on epidemiological research using routinely collected data, and I have a particular interest in RSV. I completed my PhD at University College London on the epidemiology and burden of RSV in young children in secondary care in England. Understanding the health burden of RSV (e.g. how many people are infected, what the characteristics of those infected people are, and how severe their illness is) is vital in order to identify target populations for interventions. However, it is difficult to determine how many patients are infected with RSV each year – respiratory infections can be caused by many different viruses and bacteria, but only a small number of patients with respiratory symptoms are tested to identify which virus or bacteria is causing the infection. During my PhD, I estimated the national burden of hospital admissions for RSV infection in infants and young children in England using multiple methods (including a novel method utilising linked laboratory surveillance and hospital admissions data for RSV), and highlighted the strengths and limitations of using routinely collected data for RSV research. After completing my PhD, I was excited to be able to build on the skills and expertise I had developed by joining the RESCEU team at the University of Edinburgh. Here, I work

on RESCEU Work Package 2, analyse national data on acute respiratory infections, and co-supervise students who carry out projects exploring respiratory infections in high-risk populations in Scotland.

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

My main role at the University of Edinburgh is working on RESCEU Work Package 2. Work Package 2 is assembling existing data on RSV healthcare burden to inform policy-making and regulatory decisions, and is promoting widespread cooperation, data sharing and surveillance across Europe. One of the key tasks of Work Package 2 is Task 2.1, which assesses the healthcare burden of RSV in at least six European countries using national routine health databases. In this task, I lead the development of the analysis plan that each country is following in order to produce comparable results. I also carry out the analysis of the Scottish health databases – including linked hospital, laboratory, maternity, birth, death and prescribing databases. I very much enjoy working closely with the other Work Package 2 partners to overcome the complexities of working with these types of data; one of our main challenges is producing comparable results despite the many differences between countries – such as differences in thresholds for admission, diagnostic coding and RSV testing practices, to name but a few. I am also involved in the other tasks in Work Package 2, which include RSV surveillance activities, systematic reviews of RSV prevention and treatment guidelines, and coordinating RESCEU activities with those undertaking RSV research and surveillance outside Europe.

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

RESCEU will fill many important gaps in knowledge of the health and economic burden of RSV, including generating evidence of the short- and long-term consequences of RSV infection. This evidence will allow policymakers and regulatory agencies to make decisions regarding potential future interventions and treatment options for RSV. Nevertheless, there will still be many unanswered questions – such as on transmission of RSV, the drivers of RSV's distinct seasonality, and why the immune response to RSV is so short-lived that we can all be re-infected throughout our lives. I hope that the RESCEU network will facilitate the answering of these further questions in the future (and that I can play a part in helping to answer them too!). However, ultimately, I believe that the future of RSV infection relies on the success of potential vaccines candidates (and other interventions) in Phase III clinical trials; only with that success will we have a real chance at reducing the impact of RSV worldwide.

Papers of the month

in collaboration with ReSViNET

July 2018

New insights into aetiology of neonatal infections

Saha SK, Schrag SJ, El Arifeen S, Mullany LC, Shahidul Islam M, Shang N, Qazi SA, Zaidi AKM, Bhutta ZA, Bose A, Panigrahi P, Soofi SB, Connor NE, Mitra DK, Isaac R, Winchell JM, Arvay ML, Islam M, Shafiq Y, Nisar I, Baloch B, Kabir F, Ali M, Diaz MH, Satpathy R, Nanda P, Padhi BK, Parida S, Hotwani A, Hasanuzzaman M, Ahmed S, Belal Hossain M, Ariff S, Ahmed I, Ibne Moin SM, Mahmud A, Waller JL, Rafiqullah I, Quaiyum MA, Begum N, Balaji V, Halen J, Nawshad Uddin Ahmed ASM, Weber MW, Hamer DH, Hibberd PL, Sadeq-Ur Rahman Q, Mogan VR, Hossain T, McGee L, Anandan S, Liu A, Panigrahi K, Abraham AM, Baqui AH. Causes and incidence of community-acquired serious infections among young children in south Asia (ANISA): an observational cohort study. Lancet. 2018 Jul 14;392(10142):145-159. doi: 10.1016/S0140-6736(18)31127-9. Epub 2018 Jul 6.

Summary

Aetiology of Neonatal Infections in South Asia (ANISA) study is a prospective case-control study at five sites in Bangladesh, India and Pakistan. This study showed that the causal attribution among babies with possible serious bacterial infections (pSBI) episodes was 28% (16% bacterial and 12% viral). The leading pathogen in the first two months of life was respiratory syncytial virus with 5.4 (4.8-6.3) episodes per 1000 live births, followed by Ureaplasma spp with 2.4 (1.6-3.2) episodes per 1000 livebirths. Among babies who died, a cause could be attributed in 46% of pSBI episodes, among which 92% were bacterial. However, interpretation of this study should take into consideration of the following aspects: (i) There is a substantial percentage (72%) of pSBI episodes and (54%) fatal pSBI deaths without attribution of a cause; (ii) There could be other organisms beyond the 28 agents under study; (iii) The definition of pSBI has relatively low specificity.

Abstract on Pubmed.

Papers of the month

in collaboration with ReSViNET

July 2018

The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates

Mazur NI, Higgins D, Nunes MC, Melero JA, Langedijk AC, Horsley N, Buchholz UJ, Openshaw PJ, McLellan JS, Englund JA, Mejias A, Karron RA, Simões EA, Knezevic I, Ramilo O, Piedra PA, Chu HY, Falsey AR, Nair H, Kragten-Tabatabaie L, Greenough A, Baraldi E, Papadopoulos NG, Vekemans J, Polack FP, Powell M, Satav A, Walsh EE, Stein RT, Graham BS, Bont LJ; Respiratory Syncytial VirusNetwork (ReSViNET) Foundation. The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. Lancet Infect Dis. 2018 Jun 15, in press. Available from doi: 10.1016/S1473-3099(18)30292-5.

Summary

The global burden of disease caused by respiratory syncytial virus (RSV) is increasingly recognised, not only in infants, but also in older adults (aged ≥65 years). Advances in knowledge of the structural biology of the RSV surface fusion glycoprotein have revolutionised RSV vaccine development by providing a new target for preventive interventions. The RSV vaccine landscape has rapidly expanded to include 19 vaccine candidates and monoclonal antibodies (mAbs) in clinical trials, reflecting the urgency of reducing this global health problem and hence the prioritisation of RSV vaccine development. The candidates include mAbs and vaccines using four approaches: (1) particle-based, (2) live-attenuated or chimeric, (3) subunit, (4) vector-based. Late-phase RSV vaccine trial failures highlight gaps in knowledge regarding immunological protection and provide lessons for future development. In this Review, we highlight promising new approaches for RSV vaccine design and provide a comprehensive overview of RSV vaccine candidates and mAbs in clinical development to prevent one of the most common and severe infectious diseases in young children and older adults worldwide.

Full article available on ReSViNETt's website.

Papers of the month

in collaboration with ReSViNET

May 2018

RSV burden in HIV-infected mothers

Madhi SA, Cutland CL, Downs S, Jones S, van Niekerk N, Simoes EAF, Nunes MC.Burden of Respiratory Syncytial Virus Infection in South African Human Immunodeficiency Virus(HIV)-

Infected and HIV Uninfected Pregnant and Postpartum Women: A Longitudinal Cohort Study. Clin InfectDis. 2018 May 17;66(11):1658-1665. Available from: doi: 10.1093/cid/cix1088.

Summary

A longitudinal cohort study from South Africa investigated the RSV burden in HIV-infected and HIV-uninfected women (from mid-pregnancy until 24 weeks of postpartum). The incidence of RSV illness in 2011 among HIV-infected women was slightly higher than the rate in HIV-uninfected women (3.4 (95% CI 1.4-8.1) vs. 1.2 (95% CI 0.6-2.2) per 1000 person-months). RSV infection during pregnancy was not associated with adverse pregnancy outcomes. Postpartum RSV infection in mothers was commonly associated with concurrent RSV infection in their infants. However, this study was based on a limited sample size. Also, geographic and temporal differences with different intensity and virulence of the circulating RSV virus, significant year-to-year variability in RSV incidence, case definition under research, and healthcare seeking behaviour in local study sites might result in further uncertainty of the true estimates. More research is required to determine the potential benefit from maternal RSV vaccination in this high-risk population.

Abstract on Pubmed.

Upcoming major RSV/respiratory meetings

9th ASIAN CONGRESS OF PEDIATRIC INFECTIOUS DISEASE

The 2018 edition of the Asian Congress of Pediatric Infectious Disease (ACPID) will take place in Fukuoka, Japan, on November 10-12. The congress is entitled *Global Prospects, Local Progress and Eternal Promise for Children's Health* and will be the first-ever joint meeting of the 9th ACPID and the 50th Japanese Society for Pediatric Infectious Diseases (JSPID). The Congress will focus on a range of topics and diseases, with specific session for poster and oral presentations dedicated to respiratory viral infections. Deadline for pre-registration is October 31st. More information, including the list of accepted posters and oral presentations and program, are available on the ACPID website.

NOVEMBER 10 - 12, 2018
FUKUOKA, JAPAN

INTERNATIONAL CONFERENCE ON VIROLOGY, BACTERIOLOGY & INFECTIOUS DISEASES

This international conference will take place in Rome from November 26-28, 2018, with the highlight theme: "A step towards advancement in the research and treatment of Infectious Diseases". The event will host a variety of sessions focusing on topics such as Virology and Immunology, Infectious Diseases Epidemiology, Pediatric Infectious Diseases and Infectious Disease Vaccines. A specific session is also dedicated to Respiratory tract Infections and RSV. The conference will host Keynote Presentations, Special Sessions, Workshops, Symposiums, Oral talks, Poster Presentations and Exhibitions. Information for abstracts submission and registration are available on www.infectiousdiseasesconference.org

NOVEMBER 26 - 28, 2018
ROME, ITALY

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. Further details will be available shortly on the website.

JANUARY 16-18, 2019
STOCKHOLM, SWEDEN

List of recent RSV papers

August

Ortiz-Hernández AA, Nishimura KK, Noyola DE, Moreno-Espinosa S, Gamiño A, Galindo-Fraga A, Valdéz Vázquez R, Magaña Aquino M, Ramirez-Venegas A, Valdés Salgado R, Andrade-Platas D, Estevez-Jimenéz J, Ruiz-Palacios GM, Guerrero ML, Beigel J, Smolskis MC, Hunsberger S, Freimanis-Hence L, Llamosas-Gallardo B; Mexico Emerging Infectious Diseases Clinical Research Network (La Red). Differential risk of hospitalization among single virus infections causing influenza like illnesses. Influenza Other Respir Viruses, in press.

Falsey AR, Walsh EE, Esser MT, Shoemaker K, Yu L, Griffin MP. Respiratory Syncytial Virus (RSV)-associated Illness in Adults with Advanced Chronic Obstructive Pulmonary Disease and/or Congestive Heart Failure. J Med Virol., in press.

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Fordyce EAF, Fraser Hunt S, Crepin D, Onions ST, Parra GF, Sleigh CJ, King-Underwood J, Finch H, Murray J. Conformationally restricted benzothienoazepine respiratory syncytial virus inhibitors: their synthesis, structural analysis and biological activities. Medchemcomm.; 9(3):583-589.

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July

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