



The breadth of RSV Research in Utrecht, The Netherlands

The Utrecht RSV Research Group is led by Louis Bont, a paediatrician specialized in infectious diseases and immunology at the University Medical Center, Utrecht. The RSV Research Group which has produced more than 120 publications in peer reviewed journals since 2003 and is actively working with the Dutch RSV Patient Advisory Board. The RSV Research Group has led of a number of large well-defined RSV cohorts providing insight into the immuno-pathogenesis of RSV infection. The vision of the RSV Research Group is to combine clinical and basic research to decrease the global burden of RSV infection.

With an increasing worldwide awareness of the burden of disease of RSV infection grew the need for an international collaboration to address this issue. Until the establishment of ReSViNET in 2014 there was no international, integrated, multidisciplinary and translational research approach focused on RSV infections. ReSViNET was founded in Utrecht, The Netherlands in 2014 by 9 clinician scientists and Julius Clinical, an Academic Research Organization. ReSViNET is stimulating and performing research aiming to understand the burden of RSV infection, to advocate for better care for patients with RSV infection, to provide education related to RSV infection and to provide effective partnerships with relevant stakeholders. In the light of these core values of ReSViNET, the European RESCEU project was founded. Building on the existing ReSViNET consortium, RESCEU brings together leaders in RSV epidemiology and disease burden estimation, clinical RSV research, health economics, pathogenesis, immunology and vaccinology, key

opinion leaders with advisory roles in European and national public health bodies, health technology agencies and vaccine advisory groups.

As the leader of Work Package 4, the Utrecht RSV Research Group will coordinate the prospective clinical cohort studies which form the heart of the RESCEU project. With experience in leading more than ten clinical RSV-related studies, including burden of disease studies similar to those proposed by RESCEU, the Utrecht RSV Research Group has successfully included patients with the same rigor and attention for data quality as required in this study. Currently, the infant cohort study has already been approved by the local IRBs in the Netherlands, Spain and Finland. The COPD cohort study is already approved at all sites and the older adult cohort study is in the process of being submitted to the local IRBs. The case control study which starts in the winter months is currently being prepared for IRB submission. Together everyone is working hard to make sure the clinical studies can start including participants in the upcoming summer!



RESCEU WP3 meeting held in Antwerp

On May 16th and 17th 2017, a RESCEU WP3 workshop was organized in order to develop a framework of analysis for model-based estimation of the burden of RSV disease, and the cost-effectiveness of interventions to prevent and mitigate that burden. With 47 participants on day 1 and 56 on day 2, covering expertise in health economics, biostatistics, paediatrics, epidemiology, and other infectious disease/biomedical areas,

the workshop was well attended by European and US RESCEU Partners and Affiliated Partners (both academic and EFPIA, with representatives from WP1, WP2 and WP4 to discuss collaborative work with WP3), as well as by non-RESCEU organisations with relevant expertise. WP3 will ultimately incorporate the data generated from WP1, WP2 and WP4 to obtain and refine appropriate burden estimates by building a variety of mathematical and statistical models.

The group spent time analyzing the burden of RSV disease, understanding that there will be multiple data gaps along the way. Niel Hens (UA) provided a stimulating presentation, explaining how best to address these data gaps, including the appropriateness and accuracy of various methods to impute missing data, with special attention to multi-country disease burden estimates.

Mark Jit (London School of Hygiene & Tropical Medicine) walked the group through the differences and similarities among pivotal country specific guidelines for cost-effectiveness analysis. Philippe Beutels (UA), Chair of WP3, led a detailed discussion of a proposed framework for analysis, distinguishing perspective, costing, model choices (mainly static versus dynamic models), outcome choices and their valuation (eg, quality-adjusted life years (QALY) and disability-adjusted life years (DALY) arising both to patients and their caregivers), as well as issues around handling uncertainty and discounting.

After discussing the economic reviewing activities in WP1 (presented by Shanshan Zhang, UEDIN), a range of existing and draft economic models, both static and dynamic, were presented by industry and academic (affiliated) partners, as well as PATH, all of which helped identifying influential factors in different types of models, and will help prioritize data collection going forward.

A separate session was dedicated to cost and quality of life data collection in WP4. Joanne Wildenbeest (University Medical Centre Utrecht) provided an update from WP 4, addressing the various data collection protocols developed for the 4 observational studies coordinated by WP4. Building on this discussion, affiliated partner Thea Van Asselt (University Medical Centre Groningen) presented a new method to value quality of life in infants, and study plans using apps that could be linked in with RESCEU.

There was also a formal breakout session, during which the proposed framework for analysis was approved by the RESCEU Partners and Affiliated Partners. A formal report describing the agreed framework for analysis is currently being developed.

Overall this was a very successful meeting for RESCEU as Work Package 3 activities on

developing a framework for economic burden of disease were significantly advanced, and relationships among the RESCEU Partners were strengthened.



ESPID presentation: Systematic review of cytokines correlation with RSV disease severity

While the RESCEU clinical studies are waiting to get going from July 2017, another key aspect of WP5 is the development of systematic reviews of potential biomarkers of protection, disease severity and sequelae of RSV. From this ongoing work, a systematic review of studies of cytokines that correlate with RSV disease severity in children has been completed. An abstract formed from this work was accepted as a poster presentation at the European Society of Paediatric Infectious Diseases (ESPID) conference and was presented in Madrid in May 2017.

The key findings of the review were:

- In blood, the biomarkers G-CSF, IL-13, PDGF-BB, sCD25, TLR4, VEGF and IL-4/IFN- γ ratio were positively associated with RSV disease severity and CCL-5 and MIP-1 α negatively associated.
- In respiratory tract samples, the biomarkers CXCL8, EGF, GM-CSF, HGF, IFN- α , IL-15, MIP-1 α and IL-4/IFN- γ ratio were positively associated with RSV disease severity and FGF-b, PDGF-BB and SP negatively associated.

These findings will be used to shape the testing of biological samples collected in the clinical studies. Further results from these systematic reviews will be completed in the coming months!

The ESPID poster can be viewed [here](#).

The RESCEU Ethics Advisory Committee (EAC) holds its first meeting

The RESCEU EAC was brought together for the first time on the 20th of March 2017. This meeting was a good opportunity to introduce each other and get a comprehensive overview of the RESCEU Project and its ethical challenges from Dr. Harish Nair, the Project Coordinator.

The Ethics Advisory Committee is devised as an advisory body composed of renowned experts with detailed knowledge of ethical policies.

Dr. Sarah Chan

Dr. Mark Leslie Flear

Dr. Deborah Mascalzoni (Chairperson)

Dr. Martyn David Pickersgill

Dr. Ine Van Hoyweghen

The Ethics Advisory Committee participates in reviewing the proper application of the ethical rules; provides advice to RESCEU on ethical issues and on the compliance with European ethical laws and regulations and with different guidelines, laws and regulations of countries where studies are being performed.

Dr. Deborah Mascalzoni was appointed as chair of the EAC. The members of the EAC have now reviewed the RESCEU Ethics Policy Handbook.

RESCEU is now member of ISARIC



The RESCEU Project has recently joined the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). ISARIC is a global initiative aiming to ensure that

clinical researchers have the open access protocols and data-sharing processes needed to facilitate a rapid response to emerging diseases that may turn into epidemics or pandemics. ISARIC gathers over 70 research networks and individuals. The consortium is trying to understand the causes of severe acute respiratory diseases, discover how illnesses develop and progress in patients, and identify the most efficient treatments and the best way to prevent further transmission.

We look forward to a fruitful collaboration between both initiatives. More info about ISARIC: www.isaric.tghn.org/

4th ReSViNET Meeting

“Vaccines for the World”, the upcoming ReSViNET meeting, will be held on November 29th-December 1st 2017 in Malaga, Spain. This yearly RSV expert meeting is devoted exclusively to RSV infection prevention and treatment, and it is focusing on the scientific developments and demands in RSV field. Its main objective is to bring together the scientific data and expertise, connecting different stakeholders involved in RSV research. There will be ample full travel grants for young researchers.

To see the Preliminary Scientific Program, Please follow this [link](#). You will find the meeting brochure [here](#).

For more information regarding ReSViNET and the High-Level Expert meetings, please visit the website www.resvinet.org or contact Louis Bont (Chairman ReSViNET, l.bont@umcutrecht.nl) and Leyla Kragten-Tabatabaie (Network Manager ReSViNET, Leyla.kragten@juliusclinical.com)

Upcoming major RSV/respiratory meetings

- 5th ISIRV-AVG Conference, 14th-16th June 2017 - Shanghai, China

This Conference will be of interest to research investigators, clinicians and Public Health experts. It will focus on the progress in combatting respiratory virus infections (RVIs) with vaccines and therapeutics, including novel antiviral

approaches, and will address regional issues, like the impact of RVIs in Asia and the use/effectiveness of traditional Chinese medicines. A special symposium on novel coronaviruses (SARS/MERS) will be featured.

Info: www.isirv.org

- **16th Euro Global Summit and Expo on Vaccines & Vaccination, June 19th-21st 2017 - Paris, France**

The conference highlights the theme “Accelerating Next Generation Vaccines for Global Health” covering all important aspects in Vaccines and Vaccinations. The conference includes explicit keynote talks from distinguished scientists, plenary sessions, Poster competition, Young Researcher sessions, Symposiums, Workshop and Exhibitions.

Info: www.vaccines.global-summit.com/europe/

- **17th International Conference on Children Vaccines, August 21st-22nd, 2017 - Birmingham, UK**

17th International Conference with a comprehensive program covers an expansive array of matters such as Health Care, Immunology, Vaccines, Children Health, Vaccinology and Flu Vaccine, Children Vaccines 2017 will be a must-attend event.

Info: www.childrevaccines.conferenceseries.com/

- **ERS International Congress 2017, September 9th-13th, 2017 - Milan, Italy**

The European Respiratory Society 2017 (ERS) covers the topics of Medical, Health Care, Respiratory, Respiratory Medicine, Respiratory Care and Respiratory System and much more. The next annual ERS will be held in Milan, Italy, from September 9th-13th. More than 26000 attendees are expected to visit the ERS meeting this year.

Info: www.erscongress.org

- **International Neonatal and Maternal Immunization Symposia (INMIS), September 10th-12th 2017 - Brussels, Belgium**

The 4th International Neonatal and Maternal Immunization Symposia (INMIS) will take place in Brussels, Belgium, from September 10th-12th 2017 and will bring together scientists, clinicians and public health experts from all continents. The symposium will provide up to date information on key areas and latest progress on the basic science underpinning maternal and neonatal immunization, as well as

the most recent data from large vaccine trials and vaccines under development. The implementation of maternal and neonatal immunization worldwide will be debated.

Info: www.inmis.org

List of recent RSV papers

May 2017

Fretzayas A, Moustaki M. **Etiology and clinical features of viral bronchiolitis in infancy.** World J Pediatr., in press.

Leemans A, De Schryver M, Van der Gucht W, Heykers A, Pintelon I, Hotard AL, Moore ML, Melero JA, McLellan JS, Graham BS, Broadbent L, Power UF, Caljon G, Cos P, Maes L, Delputte P. **Antibody-induced internalization of the human respiratory syncytial virus fusion protein.** J Virol., in press.

Karatza AA, Kiaffas M, Rammos S. **Complete heart block complicating the acute phase of respiratory syncytial virus bronchiolitis.** Pediatr Pulmonol., in press.

Nyiro JU, Kombe IK, Sande CJ, Kipkoech J, Kiyuka PK, Onyango CO, Munywoki PK, Kinyanjui TM, Nokes DJ. **Defining the vaccination window for respiratory syncytial virus (RSV) using age-seroprevalence data for children in Kilifi, Kenya.** PLoS One:e0177803.

Piralla A, Mariani B, Rovida F, Baldanti F. **Frequency of respiratory viruses among patients admitted to 26 Intensive Care Units in seven consecutive winter-spring seasons (2009-2016) in Northern Italy.** J Clin Virol.;92:48-51.

Wang L, Cheng W, Zhang Z. **Respiratory syncytial virus infection accelerates lung fibrosis through the unfolded protein response in a bleomycin-induced pulmonary fibrosis animal model.** Mol Med Rep., in press.

Rezaee F, Linfield DT, Harford TJ, Piedimonte G. **Ongoing developments in RSV prophylaxis: a clinician's analysis.** Curr Opin Virol.;24:70-78.

Stobart CC, Hotard AL, Meng J, Moore ML. **BAC-Based Recovery of Recombinant Respiratory Syncytial Virus (RSV).** Methods Mol Biol.;1602:111-124.

Bruning A, Leeflang M, Vos J, Spijker R, de Jong MD, Wolthers KC, Pajkrt D. **Rapid tests for influenza, respiratory syncytial virus, and other respiratory viruses: a systematic review and meta-analysis.** Clin Infect Dis., in press.

Smith RJ, Hogan AB, Mercer GN. **Unexpected Infection Spikes in a Model of Respiratory Syncytial Virus Vaccination.** Vaccines (Basel).;5(2).

Graham BS. **Vaccine development for respiratory syncytial virus.** Curr Opin Virol.;23:107-112.

Villafana T, Falloon J, Griffin MP, Zhu Q, Esser MT. **Passive and active immunization against respiratory syncytial virus for the young and old.** Expert Rev Vaccines, in press.

Rojo GL, Goya S, Orellana M, Sancilio A, Rodriguez Perez A, Montali C, García C, Sosa L, Musto A8, Alvarez D, Castello A, Viegas M. **Unravelling respiratory syncytial virus outbreaks in Buenos Aires, Argentina: Molecular basis of the spatio-temporal transmission.** Virology;508:118-126.

Nyiro JU, Kombe IK, Sande CJ, Kipkoech J, Kiyuka PK, Onyango CO, Munywoki PK, Kinyanjui TM, Nokes DJ. **Defining the vaccination window for respiratory syncytial virus (RSV) using age-seroprevalence data for children in Kilifi, Kenya.** PLoS One:e0177803.

Jiao YY, Fu YH, Yan YF, Hua Y, Ma Y, Zhang XJ, Song JD, Peng XL, Huang J, Hong T, He JS. **A single intranasal administration of virus-like particle vaccine induces an efficient protection for mice against human respiratory syncytial virus.** Antiviral Res., in press.

Hosken N, Plikaytis B, Trujillo C, Mahmood K, Higgins D; Participating Laboratories Working Group. **A multi-laboratory study of diverse RSV neutralization assays indicates feasibility for harmonization with an international standard.** Vaccine, in press.

April 2017

Hause AM, Henke DM, Avadhanula V, Shaw CA, Tapia LI, Piedra PA. **Sequence variability of the respiratory syncytial virus (RSV) fusion gene among contemporary and historical genotypes of RSV/A and RSV/B.** PLoS One;12(4):e0175792.

Fonceca AM, Chopra A, Levy A, Noakes PS, Poh MW, Bear NL, Prescott S, Everard ML. **Infective respiratory syncytial virus is present in human cord blood samples and most prevalent during winter months.** PLoS One;12(4):e0173738.

Tang JW, Lam TT, Zaraket H, Lipkin WI, Drews SJ, Hatchette TF, Heraud JM, Koopmans MP; **INSPIRE investigators. Global epidemiology of non-influenza RNA respiratory viruses: data gaps and a growing need for surveillance.** Lancet Infect Dis., in press.

March 2017

Agoti CN, Munywoki PK, Phan MVT, Otieno JR, Kamau E, Bett A, Kombe I, Githinji G, Medley GF, Cane PA, Kellam P, Cotten M, Nokes DJ. **Transmission patterns and evolution of respiratory syncytial virus in a community outbreak identified by genomic analysis.** Virus Evol.;3(1):vex006.



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