RESCEU
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NEWSLETTER

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KEYNOTE

Peter Openshaw - Lead of WP5

Hunting the hidden effects of RSV

The twists of RSV disease have been a constant source of fascination to me since I first began working on it in 1985. We always knew it to be a very important infection in babies, causing a big surge in demand for beds every winter at a time when the healthcare facilities are already overstretched. What intrigued me was the delayed effects of RSV in older children and its importance in older adults. Largely through the meticulous work of Ann Falsey, Ed Walsh and others in Rochester, New York, it has become clear that RSV is not just a paediatric infection. As an adult chest physician I found this particularly important. It opened all sorts of questions about not only the relationship between bronchiolitis and babies and recurrent wheeze in older children (now, to my mind, at least in part a causal relationship), but also about the subtle and often hidden effects of RSV infection in ways that are not immediately obvious.

Traditionally, RSV infection is regarded as acute and transient, an example of the common cold viruses that last a few days and then resolve. But it's not that simple with RSV. It's a close relative of the measles virus and we know that measles can sometimes cause delayed or persistent effects. In addition

to causing an exanthematous acute illness, measles can rarely cause terrible and devastating diseases, subacute sclerosing panencephalitis (SSPE). Is there an equivalent of SSPE for RSV? Some years ago, I started to wonder if that SSPE equivalent could possibly be chronic lung disease in later life.

RSV is hard to find in adults. It specialises in infecting the respiratory epithelium and could infect cells hidden in the lung without simultaneously infecting the nose and throat. It might even remain hidden in local lymph nodes, as it seems to do in the equivalent disease in cattle. If this were the case, RSV could be missed by conventional sampling.

In studies we did some decades ago we found that it could indeed persist for at least several months in the lungs of mice and that it could evade cytotoxic T-cells that should be able to eliminate the virus. In collaboration with my old friend and colleague Jadwiga ('Wisia') Wedzicha, then at the Royal Free Hospital, we found that RSV could be detected by very sensitive molecular techniques (PCR) in the sputum of some patients with chronic obstructive pulmonary disease (COPD) and that these patients tended to have progressive loss of lung function, whereas patients without RSV were usually stable. Admittedly, others have not reproduced this finding but we haven't been able to explain these findings and really want to look further.

This is where our new collaboration under RESCEU comes in. We are again working with Wisia and her group, now at the Royal Brompton Hospital. We are both part of Imperial College's National Heart and Lung Institute and are delighted to have appointed a new clinical research fellow funded by RESCEU, Dexter Wiseman. He will be working on a well-established cohort of COPD patients with Professor Wedzicha, Dr Gavin Donaldson and their team.

There is great hope in the RSV community that we will soon have vaccines that can prevent RSV disease alongside antivirals that can be used to treat patients with infection. If these new clinical tools become available, we will at last be able to perform specific interventions and to discover what role RSV truly plays in adult disease. It's an exciting time, and RESCEU forms a key part of our future understanding of RSV and its many and varied roles.

Dr Dexter Wiseman, Prof Jadwiga 'Wisia' Wedzicha, Dr Gavin Donaldson, Raymond Sapsford

First RESCEU's clinical studies patients tested

RESCEU's clinical studies have started, with the aim of gathering data and addressing knowledge gaps on the impact of RSV infections. The investigation is building on the knowledge of a varied team of partners from universities and public health institutions, and includes 3 cohort studies on vulnerable populations (infants, older adults, COPD subjects) and one case-control study on infants after RSV infection.

The first symptomatic participants were tested and visited for Respiratory Syncytial Virus in the 3 mentioned clinical cohort studies. As the RSV season had not yet started, all tested patients were still RSV negative: we can expect that first RSV diagnosis and therefore more exhaustive results will be available only with the beginning of RSV season.

WP2 meeting in Amsterdam

WP2 will be holding a face to face meeting on the 23rd of January 2018 in Amsterdam to discuss the analysis plans 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. It aims to review the data availability for each partner, to discuss and agree the analysis plan and coding definitions and to work on the timescales for analysis for 2018. More information on the outcomes of the meeting will be provided on the next issue of the RESCEU newsletter and on the RESCEU website.

Join the RESCEU 2nd General Assembly in Oxford!

Registration is now open for the RESCEU 2nd General Assembly that will take place in Oxford on June 21st-22nd 2018. On this occasion, the meeting will be hosted by University of Oxford and it will be attended by the RESCEU's Scientific Advisory Group, Ethics Advisory Committee and Patient Advisory Board.

There will also be WorkPackage pre-meetings on June 20th:

- WP1: Systematic literature review of RSV and current estimates of burden disease
- WP2: Consolidation of health care systems data
- WP3: Retrospective resource use analyses from existing databases/networks
- WP4&5: Prospective data collection and presumed risk factors and biomarkers for RSV-related severe disease and related sequelae
- WP6: Project management and outreach to stakeholders

For more information about the registration please send an email to Núria Febrer (nfebrer@synapse-managers.com) and Anna Beltrami (abeltrami@synapse-managers.com).

Papers of the month

in collaboration with ReSViNET

October 2017

Pre-F-Stabilized Rsv Vaccine, A New Vaccine On The Horizon?

Liu X, Liang B, Ngwuta J, Liu X, Surman S, Lingemann M, Kwong PD, Graham BS, Collins PL, Munir S. Attenuated human parainfluenza virus type 1 (HPIV1) expressing the respiratory syncytial virus (RSV) fusion F glycoprotein from an added gene: effects of pre-fusion stabilization and packaging of RSV F. Journal of Virology, November 2017, vol. 91 no. 22 e01101-17 Available from: doi: 10.1128/JVI.01101-17

Summary

RSV vaccine development has come across many difficulties, with the instability of the pre-fusion RSV F protein being one of them. Xiang Liu and colleagues offer a potential solution to this problem by developing a pre-F-stabilized RSV vaccine based on an attenuated HPIV1 vector. The benefit of such a vaccine is that it specifically increases the immune response against the most effective RSV-neutralization epitopes, while the HPIV1 vector provides immunization against HPIV1. The authors developed four HPIV1 vectors. In hamsters, all of the vectors induced detectable RSV-neutralizing serum antibodies, but only the F1 vector was immunogenic for both RSV and HPIV1. It induced complement-independent high-quality RSV-neutralizing antibodies at titers similar to those of wild type RSV and provided protection against RSV infection.

This study describes a novel vector-based vaccine inducing robust protection against RSV, by developing immunity against the pre-fusion conformation of the RSV F glycoprotein.

This review was written by drs. Sjanna Besteman

Full article on PubMed.

October 2017

The first large case series of in-hospital RSV deaths

Scheltema NM, Gentile A, Lucion F, Nokes DJ, Munywoki PK, Madhi SA, Groome MJ, Cohen C, Moyes J, Thorburn K, Thamthitiwat S, Oshitani H, Lupisan SP, Gordon A, Sanchez JF, O'Brien KL, on behalf of the PERCH Study Group, Gessner BD, Sutanto A, Mejias A, Ramilo O, Khuri-Bulos N, Halasa N, de-Paris F, Rosane Pires M, Spaeder MC, Paes BA, Simoes EAF, Leung TF, da Costa Oliveira MT, de Freitas Lazaro Emediato CC, Bassat Q, Butt W, Chi H, Aamir UB, Ali A, Lucero MG, Fasce RA, Lopez O, Rath BA, Polack FP, Papenburg J, Roglić S, Ito H, Goka EA, Grobbee DE, Nair H, Bont LJ. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. *Lancet Glob Health*. 2017; 5: e984–91. Available from: doi: 10.1016/S2214-109X(17)30344-3 and doi: 10.1016/S2214-109X(17)30382-0 [errata corrige].

Summary

This is the first large descriptive study (case series) reporting 358 in-hospital deaths in children with community-acquired RSV infection. The study was conducted by Scheltema and colleagues using individual case records from hospitals. Nearly one third of children studied were from low income or lower middle income countries with high RSV-related mortality. A substantial proportion of children (28% in low and lower middle income, 47% in upper middle income and 70% in high income countries) had comorbidities. In low and middle income countries (LMICs), most children who died with RSV infection were aged younger than 6 months thus reinforcing the need to immunize children in this vulnerable age group. As the majority of the RSV related deaths in children occur outside hospitals, this study represents a small proportion of all RSV related deaths worldwide. Data on comorbidities and prematurity were missing for around one third of the children studied, mainly in LMICs. The results therefore need to be interpreted with caution.

Full Article on The Lancet Global Health website.

September 2017

C-reactive protein differentiates RSV from bacterial infection

Higdon MM, Le T, O'Brien KL, Murdoch DR, Prosperi C, Baggett HC, Brooks WA, Feikin DR, Hammitt LL, Howie SRC, Kotloff KL, Levine OS, Scott JAG, Thea DM, Awori JO, Baillie VL, Cascio S, Chuananon S, DeLuca AN, Driscoll AJ, Ebruke BE, Endtz HP, Kaewpan A, Kahn G, Karani A, Karron RA, Moore DP, Park DE, Rahman MZ, Salaudeen R, Seidenberg P, Somwe SW, Sylla M, Tapia MD, Zeger SL, Knoll MD, Madhi SA; for the PERCH Study Group. Association of C-Reactive Protein with Bacterial and Respiratory Syncytial Virus–Associated Pneumonia Among Children Aged <5 Years in the PERCH Study. *Clinical Infectious Diseases*. 2017 Jun 15; Suppl 3(64): S378-386. Available from: doi: 10.1093/cid/cix150.

Summary

As part of the Pneumonia Etiology Research in Child Health (PERCH) multi centre case control study, Higdon and colleagues evaluated the sensitivity and specificity of C-reactive protein (CRP) for

differentiating RSV and bacterial pneumonia. The comparison groups included "confirmed" bacterial pneumonia (positive blood / pleural fluid culture; or positive lung aspirate or PCR) and PCR confirmed RSV pneumonia. They observed that elevated CRP was positively associated with confirmed bacterial pneumonia and negatively associated with RSV pneumonia, with a sensitivity (77%) and specificity (82%) at a cut-point of 37.1 mg/L. They suggest that CRP could be useful to distinguish bacterial from RSV pneumonia. However, it was acknowledged that the cut-point varied by demographic and clinical factors, and might not be representative of other settings or other respiratory viral-associated pneumonia. Therefore, CRP should be complemented with other pathogen specific diagnostic tools to increase the performance.

Full Article on PubMed.

Upcoming major RSV/respiratory meetings

INTERNATIONAL SOCIETY FOR INFLUENZA AND OTHER RESPIRATORY VIRUS DISEASES, 2ND INTERNATIONAL MEETING ON RESPIRATORY PATHOGENS 2018

This meeting will focus on addressing these gaps through the sharing of recent advances in epidemiology, immunology, diagnostics, vaccines and therapeutics and clinical management. It will bring together clinicians, public health professionals, scientists, and policy makers to learn about respiratory pathogens, and discuss what are the next steps in reducing the burden of these diseases through research and policy initiatives. This includes specific sessions devoted to providing updates for policy makers to increase their understanding on respiratory diseases and to allow for better research-policy interactions that will accelerate translational research.

7th - 9th March, 2018

SINGAPORE

https://www.isirv.org/site/

List of recent RSV papers

November

Hu X, Li X, Hu C, Qin L, He R, Luo L, Tang W, Feng J. **Respiratory Syncytial Virus Exacerbates OVA-mediated asthma in mice through C5a-C5aR regulating CD4+T cells Immune Responses.** Sci Rep.;7(1):15207.

Homaira N, Briggs N, Pardy C, Hanly M, Oei JL, Hilder L, Bajuk B, Lui K, Rawlinson W, Snelling T, Jaffe A.**Association between respiratory syncytial viral disease and the subsequent risk of the first episode of severe asthma in different subgroups of high-risk Australian children: a whole-of-population-based cohort study.** BMJ Open.;7(11):e017936.

Li H, Callahan C, Citron M, Wen Z, Touch S, Monslow MA, Cox KS, DiStefano DJ, Vora KA, Bett A, Espeseth A.**Respiratory syncytial virus elicits enriched CD8+ T lymphocyte responses in lung compared with blood in African green monkeys.** PLoS One.;12(11):e0187642.

He L, Fan F, Hou X, Wu H, Wang J, Xu H, Sun Y. **4(3H)-Quinazolone regulates innate immune signaling upon respiratory syncytial virus infection by moderately inhibiting the RIG-1 pathway in RAW264.7 cell.**Int Immunopharmacol.;52:245-252.

Tripp RA, Power UF, Openshaw PJM, Kauvar LM. **Respiratory Syncytial Virus (RSV): Targeting the G Protein Provides a New Approach for an Old Problem.** J Virol., in press.

Eichinger KM, Kosanovich JL, Empey KM. **Localization of the T-cell response to RSV infection is altered in infant mice.** Pediatr Pulmonol., in press.

Goldstein E, Nguyen HH, Liu P, Viboud C, Steiner CA, Worby CJ, Lipsitch M. **On the relative role of different age groups during epidemics associated with respiratory syncytial virus.** J Infect Dis., in press.

Arbefeville S, Thonen-Kerr E, Ferrieri P. **Prospective and Retrospective Evaluation of the Performance of the FDA-Approved Cepheid Xpert Flu/RSV XC Assay.** Lab Med.;48(4):e53-e56.

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Lee SR, Kwok KL, Ng DKK, Hon KL. **Palivizumab for Infants < 29 Weeks in Hong Kong without a Clear-Cut Season for Respiratory Syncytial Virus Infection-A Cost-Effectiveness Analysis.** J Trop Pediatr., in press.

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Sendi P, Egli A, Dangel M, Frei R, Tschudin-Sutter S, Widmer AF. **Respiratory Syncytial Virus Infection Control Challenges with a Novel Polymerase Chain Reaction Assay in a Tertiary Medical Center.** Infect Control Hosp Epidemiol.;38(11):1291-1297

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