# RSVVW'21

6TH RESVINET CONFERENCE 10-12 NOV 2021 ONLINE VIRTUAL

A GLOBAL CONFERENCE ON NOVEL RSV PREVENTIVE AND THERAPEUTIC INTERVENTIONS

# ABSTRACT BOOKLET

ReSViNET
RESPIRATORY SYNCYTIAL VIRUS NETWORK
FOUNDATION

6TH ReSViNET CONFERENCE
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## RSV PROPHYLAXIS IN THE ERA OF COVID-19; CHALLENGES & SOLUTIONS

Adel Alharbi

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and viral pneumonia in pediatrics worldwide. In the Kingdom of Saudi Arabia (KSA), the prevalence of RSV is 23.5% in pediatric patients with acute lower respiratory tract illness. Coronavirus disease (COVID-19) poses critical public health and socioeconomic challenges in KSA. The Saudi Pediatric Pulmonology Association (SPPA), a subsidiary of the Saudi Thoracic Society (STS), developed a task force to determine the potential challenges and barriers to the RSV immunoprophylaxis program during the era of COVID-19 and to compose a practical, nationwide, and multidisciplinary approach to address these challenges. Some of the recommendations to manage these challenges include increasing the number of RSV immunoprophylaxis clinics, drive-thru visits, home-care services, and swift referrals to the RSV immunoprophylaxis program specialists. Additional training is required for healthcare personnel to add RSV immunoprophylaxis to the regular immunization schedule.

**Table 1 -** Saudi Initiative of Bronchiolitis Diagnosis, Management, and Prevention recommendations on using Palivizumab across different patients' categories.[11]

| Patient segment | Recommendations | Level of evidence |
|---|---|---|
| Early preterm (=28 weeks, 6 days GA) | ≤12 months of age | 1B |
| Mid preterm (29 weeks GA, 0 days to 32 weeks, 6 days GA) | ≤6 months of age | 1B |
| Late preterm (33 weeks, 0 days weeks GA to 35 weeks, 0 days GA) | ≤6 months of age at the start of the RSV season OR born during RSV season with at least one of the following risk factors:<br>Attendance at child care<br>Children <5 years of age who live permanently in the same household (including siblings)<br>Exposure to environmental air pollutants | 1B |
| Infants and children with CLD | <12 months for all; <24 months if still receiving medications for CLD within 6 months from the beginning of the epidemic season | 1B |
| Infants and children with hemodynamically significant CHD | <12 months for all; <24 months if still receiving medications for the cardiac condition <6 months from the beginning of the epidemic season.<br>Postoperative dose after cardio bypass | 1B |
| Children with anatomic pulmonary abnormalities or neuromuscular disorders | <24 months may be considered for infants with impaired ability to handle respiratory secretions. | 3B |
| Immunocompromised children | <24 months may be considered for children who are profoundly immunocompromised during the RSV season | 2B |
| Children with down syndrome | Recommended for children with accompanying qualifying heart disease, CLD, airway clearance issues, or premature birth (<35 weeks, 0 days GA) | 2B |
| Children with cystic fibrosis | <12 months with clinical evidence of CLD and/or nutritional compromise for <24 months with manifestations of severe lung disease or weight for length <10$^{th}$ percentile | 2A |
| Special situations: If an infant who is receiving prophylaxis experiences a breakthrough of RSV | If an infant who is receiving prophylaxis experiences a breakthrough of RSV, the monthly prophylaxis should continue as planned until a maximum of 5 doses have been administered | 3B |

RSV: Respiratory Syncytial Virus, CLD: chronic lung disease, CHD: congenital heart disease, GA: gestational age

## UNRAVELING SPECIFIC MECHANISM OF COMMUNITY DEATHS DUE TO RSV IN BUENOS AIRES, ARGENTINA

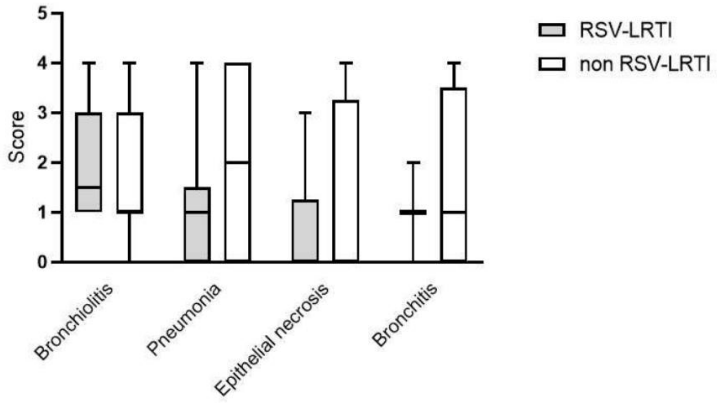
Paola X. De La Iglesia

Respiratory syncytial virus (RSV) is a major cause of respiratory tract illness in infants (LRTI). Its contribution to child mortality has been underestimated. Uncertainty related to RSV death attribution
or bacterial coinfection can bias RSV burden estimation.

We designed an approach based on active surveillance, minimal invasive tissue sampling technique (MITS), verbal autopsy (VA), molecular methods,and cause of death (COD) attribution based on determination of Cause of Death (DeCoDe) process. This study aimed to define the mechanistic role of RSV in lungs of community deaths of children under 5.

Active surveillance population-based prospective study in a catchment area of 40,027 live births in the Southern region of Buenos Aires were conducted. Tissue samples were subjected to routine processing procedures and immunohistochemistry (IHC) was performed for RSV, CD3, CD20 and MPO. Patterns of lung disease were evaluated and scored.

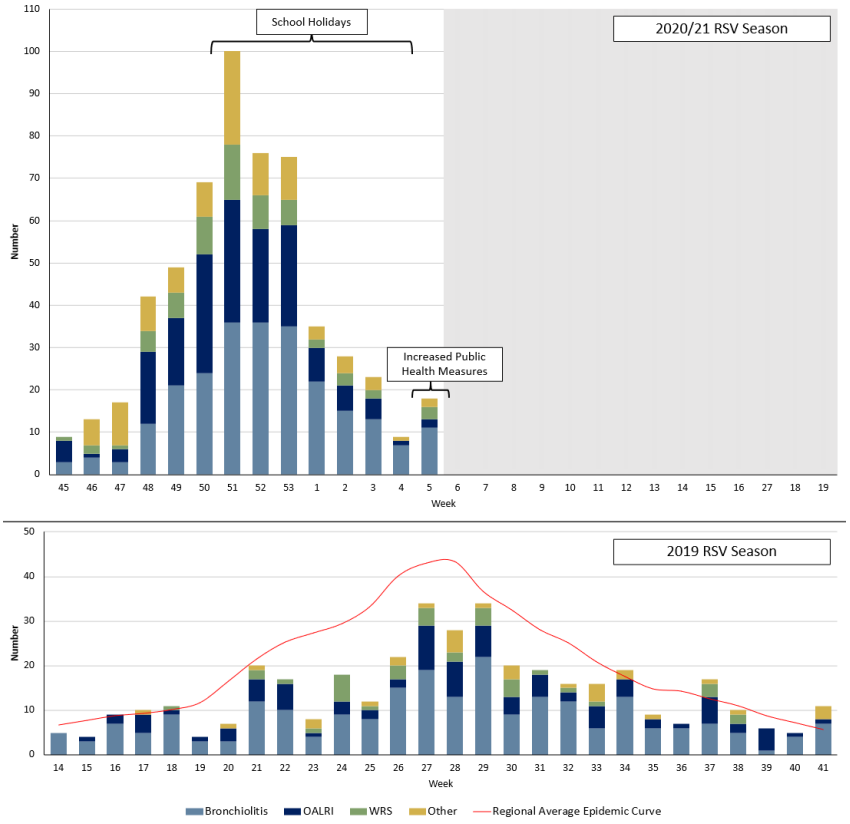
In 2019, 63 subjects were enrolled, RSV infection was found in the causal chain of 11/13 cases with positive molecular biology results in respiratory samples. The estimated mortality rate due to RSV among infants was 0.27 deaths/1000 live births. We found in 8/12 (66.7%) deaths a mixed histopathology pattern of mild bronchiolitis and interstitial pneumonia and no RSV case had the characteristic syncytia in lung parenchyma. From all the RSV deaths, only 16.7% had severe acute lung disease by histopathology. When we compared lung injury patterns with non RSV LRTI we found that there weren't significant differences in severity between groups (figure 1).



## EXAMINING THE INTERSEASONAL RESURGENCE OF RESPIRATORY SYNCYTIAL VIRUS IN WESTERN AUSTRALIA

David Foley

**Background** Following an absence in winter, a summer resurgence of respiratory syncytial virus (RSV) occurred in Western Australia towards the end of 2020, in the setting of minimal SARS-CoV-2 related non-pharmaceutical interventions (NPIs). We compared the epidemiology and clinical presentation in 2019 and the delayed 2020/21 season.
**Method** RSV season onset/offset threshold was defined as ⩾1.2% of year detections. For 2020/21, the year was centred on the peak four weeks. Respiratory coded admissions >12hrs at a single tertiary paediatric hospital were linked to laboratory testing data from 1st January 2019 to 31st March 2021. Epidemiological and clinical data were collected. Admissions were stratified into bronchiolitis, other acute lower respiratory infection (OALRI), wheeze responsive to salbutamol (WRS) and other.
**Results** The 2020/21 season was shorter (14 vs 28 weeks) with more admissions (n=563 vs n=398). There were 320 admissions in the peak four weeks in 2020/21, 2.7 times the 2019 peak (n=118). The median age in 2020/21 was 14.7 months (IQR 4.4-24.8), compared with 7.5 months (IQR 2.2-22) in 2019. Bronchiolitis numbers were similar (2020/21 n=242, 2019 n=236). OALRI (n=167 vs n=94) and WRS (n=93 vs n=31) admissions were higher in 2020/21. The median length of stay was shorter, and ICU utilisation was lower in 2020/21.
**Conclusion** The 2020/21 season was shorter, with higher numbers and more prominent peak. The seven-month delay was associated milder clinical phenotype, associated increased infection in older RSV-naïve children. Resurgence in other regions will be shaped by contemporary NPIs and interval from last season.



## CLINICAL OUTCOMES OF A MULTIDISCIPLINARY PROGRAM TO OPTIMIZE PALIVIZUMAB PROPHYLAXIS IN IMMUNOCOMPROMISED PATIENTS

Diego R. Hijano[1], Delia Carias[2], Hailey Skonhovd[1], Jose A. Ferrolino[1], Ronald H. Dallas[1], Ted H. Morton[2], William L. Greene[2], Josh Wolf[1], Pat M. Flynn[1], and Shane J. Cross[2]

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**Introduction** The American Academy of Pediatrics recommends that children younger than 24 months who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis. However, the costs associated with palivizumab make this broad recommendation prohibitive for many institutions.

**Methods** Since 2015, routine palivizumab prophylaxis is recommended for all patients ⩽ 24 months of age with acute myeloid leukemia, severe combined immunodeficiency, or receiving hematopoietic cell transplant (HCT) (including pre-HCT conditioning) and all patients ⩽ 12 months of age with a diagnosis of acute lymphoblastic leukemia. A performance improvement program, comprising requirement for pre-authorization for palivizumab, proactive identification of eligible recipients, and tracking of administered and due doses was developed to ensure administration only to eligible patients. We subsequently performed a single center retrospective review of the effectiveness and outcomes of our performance improvement for palivizumab administration in immunocompromised patients.

**Results** During four consecutive winter seasons (2015-2019), 185 patients were evaluated for palivizumab eligibility. Of these, 72 (38.91%) met institutional criteria and received palivizumab. Two patients had RSV upper respiratory tract infection and none of the patients developed lower respiratory tract infection. Of the 113 patients who did not receive palivizumab, 2 developed RSV upper respiratory tract infection and none of the patients developed lower respiratory tract infection. Implementation of a performance improvement program resulted in over $1.8 million in savings to the institution.

**Conclusion** A multidisciplinary program to optimize palivizumab in immunocompromised children was feasible and reduced the financial cost of palivizumab to the institution.

Table: Clinical outcomes of immunocompromised children with and without palivizumab prophylaxis.

| Season | Screened | Palivizumab | | RSV Infection | RSV LRTI | RSV Hospitalization |
|---|---|---|---|---|---|---|
| 2015-16 | 33 | Yes | 12 (36.3%) | No | No | 1 patient URTI^ |
| | | No | 21 (63.6%) | No | No | 0 |
| 2016-17 | 56 | Yes | 24 (42.9%) | No | No | 1 patient URTI |
| | | No | 32 (57.1%) | No | No | 1 patient URTI |
| 2017-18 | 51 | Yes | 19 (37.3%) | No | No | 0 |
| | | No | 32 (62.7%) | No | No | 0 |
| 2018-19 | 45 | Yes | 17 (37.7 %) | No | No | 0 |
| | | No | 28 (62.2%) | No | No | 1 patient URTI |

* LRTI: Lower respiratory tract infection; ^ URTI: Upper respiratory tract infection

## RESPIRATORY INFECTION INTENSITY AND IMPACT QUESTIONNAIRE (RIIQ™) SHOWS INCREASED SYMPTOM SEVERITY IN ADULTS WITH UNDERLYING RISK FACTORS HOSPITALISED WITH ACUTE VIRAL RESPIRATORY TRACT INFECTIONS

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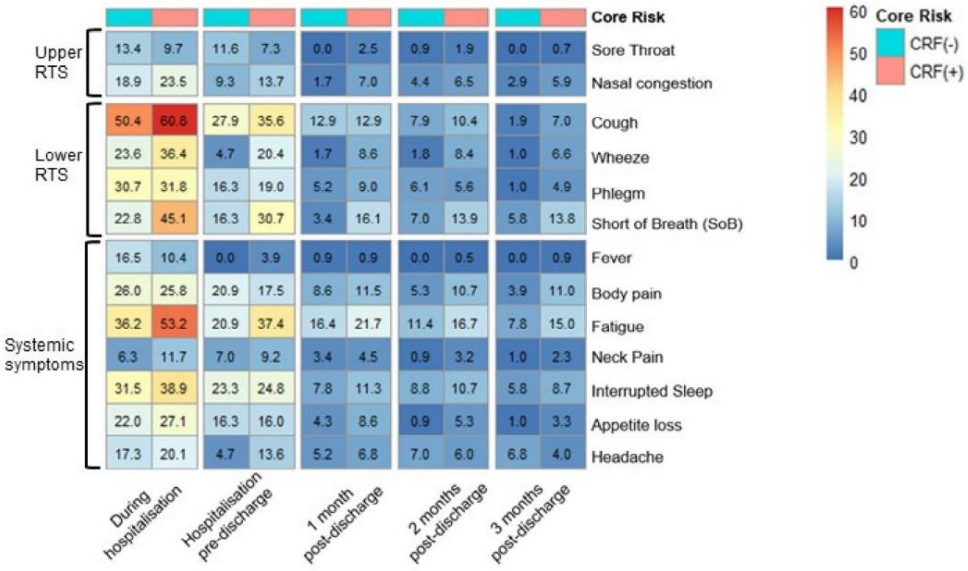
**Background** Influenza, respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) can cause acute respiratory tract infection (ARTI) requiring hospitalisation in adults, particularly those with core risk factors (CRFs) for severe illness. We report symptom burden and disease severity in CRF(+)/(-) adults during and after hospitalisation.

**Methods** In this prospective study across 12 countries, adults aged ≥18 years hospitalised with influenza, RSV or hMPV ARTI completed the RiiQ™ during hospitalisation and 1, 2 and 3 months post-discharge. The RiiQ™ includes upper and lower respiratory tract symptoms (RTS) and systemic symptoms (Figure) rated from 0–3 (none–severe). Analyses were performed by presence of CRFs (aged ≥65 years, chronic heart disease, COPD, chronic renal disease, asthma).

**Results** Data comprised 667 patients with influenza (346 [52%]), RSV (224 [34%]) or hMPV (97 [15%]); 535 patients were CRF(+) and 132 were CRF(-). RiiQ™ scores were significantly higher at all timepoints for lower RTS versus upper RTS and systemic symptoms ($p<0.0001$) particularly among CRF(+) patients. Most common moderate–severe symptoms during hospitalisation were cough (CRF(+)/(-), 60.8%/50.4%; $p=0.044$), short of breath (45.1%/22.8%; $p<0.001$), wheeze (36.4%/23.6%; $p=0.009$) and phlegm (31.8%/30.7%; $p=0.902$) for lower RTS, and fatigue (53.2%/36.2%; $p=0.001$) and interrupted sleep (38.9%/31.5%; $p=0.156$) for systemic symptoms (Figure). Most common moderate–severe symptoms 3 months post-discharge were fatigue (CRF(+)/(-), 15.0%/7.8%; $p=0.079$), short of breath (13.8%/5.8%; $p=0.040$) and body pain (11.0%/3.9%; $p=0.044$) (Figure).

**Conclusions** Moderate–severe symptoms persisted post-discharge across all viruses, particularly in CRF(+) patients who had greater symptom burden (especially lower RTS) than CRF(-) patients.

*Respiratory Syncytial Virus; Influenza; Human Metapneumovirus; Patient-Reported Outcomes; RiiQ*




CRF, core risk factor; RTS, respiratory tract symptoms; SoB, short of breath.

## SURVEILLANCE OF COMMON RESPIRATORY VIRUSES, INCLUDING RSV AND SARS-COV2 DURING THE COVID-19 PANDEMIC IN URBAN AND RURAL SETTINGS OF THE GAMBIA

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**Introduction** At the start of the COVID-19 pandemic, there was no surveillance system in The Gambia to monitor the evolution of the SARS-CoV2 virus. We set up a one year observational study to detect SARS-CoV2, RSV and other respiratory viruses from participants presenting influenza like-illness (ILI).
**Methods** Between April 2020 and May 2021, we conducted a prospective, observational, non- intervention surveillance study for SARS-CoV2, RSV and other common respiratory viruses in an urban and rural setting of Gambia in order to evaluate community prevalence of these pathogens in individuals of all ages presenting with ILI.
**Result** A total of 948 participants presented with ILI and were recruited into the study. We identified at least one respiratory virus in 445 (46.9%) individuals. Of the 948 , RSV A was detected in 20(2.1%) and SARS-CoV2 140(14.8%). There were 115 participants under 5 years of age, of whom 14 (12.2%) were RSV A positive. Of these, 7 (50.0%) were of age group 24-59 months, 5(35.7%) were 6-23 months and 2(14.3%) were > 6months. Of all RSV A, 3(21.4%) were coinfected with SARS-CoV2 and 6(42.8%) coinfected with rhinovirus. RSV A was mostly detected during the rainy months of August-November.
**Conclusions** During the COVID-19 pandemic, RSV A continued to circulate in individuals with influenza-like symptoms, during the rainy season and mostly under the age of 5 years. Further surveillance to investigate SARS-CoV2 coinfection and impact of COVID-19 pandemic on prevalence of RSV will play a role in our understanding of the dynamics of virus-virus interactions.

**Acknowledgement** We acknowledged funding from Gates Foundation funding.



## INVESTIGATIONAL MATERNAL RESPIRATORY SYNCYTIAL VIRUS VACCINE (RSVPREF3) BOOSTS MATERNAL IMMUNITY AGAINST RSV-A AND RSV-B, WITH TRANSPLACENTALLY ACQUIRED ANTIBODIES PERSISTING IN INFANTS UNTIL SIX MONTHS POST-BIRTH

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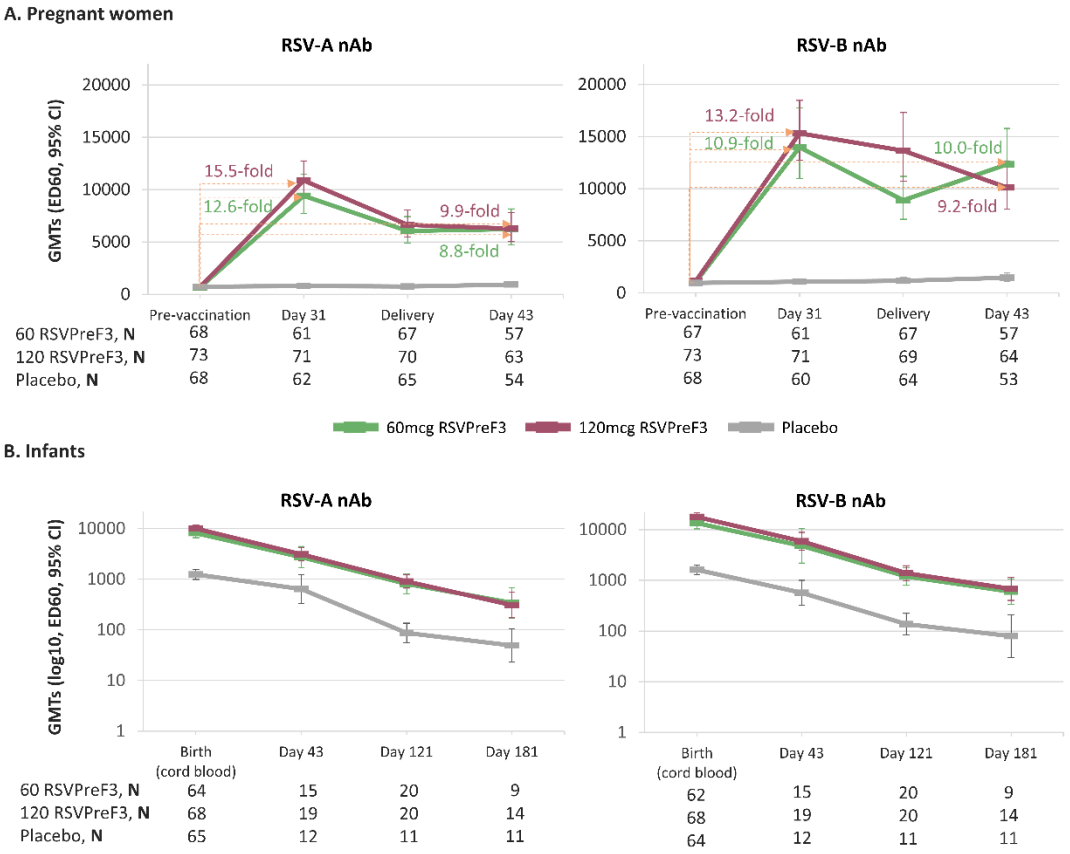
**Background** The investigational maternal RSVPreF3 vaccine is immunogenic, with successful antibody transfer to the fetus (NCT04126213). Here we evaluated the persistence of maternally acquired RSV-specific antibodies among infant sub-cohorts until six months after birth.
**Methods** In this phase II, observer-blind, multi-country trial, 18-40-year-old pregnant women, randomised 1:1:1, received one 60mcg or 120mcg dose of RSVPreF3 or placebo on gestation weeks 280/7-336/7. Anti-RSVPreF3 IgG, RSV-A and RSV-B neutralising antibodies (nAb) were measured among mothers/infants.
**Results** Among the 213 mothers, anti-RSVPreF3 IgG antibody geometric mean concentrations (GMCs) were higher in vaccine than placebo recipients on day (D)31 post-vaccination, delivery and D43 post-delivery, remaining higher than pre-vaccination on D43. Among the 206 infants, anti-RSVPreF3 IgG GMCs were highest at birth and declined thereafter. Among the mothers, RSVPreF3 induced

robust increases in RSV-A and RSV-B nAb geometric mean titres (GMTs) with titres 10.9-15.5-fold higher on D31, and 8.8-10.0-fold higher on D43 than pre-vaccination (Figure A). Among the infants, high RSV-A and RSV-B nAb GMTs in cord blood indicated efficient placental transfer; GMTs declined over time but remained higher in vaccine versus placebo groups on D181 post-birth (Figure B).
**Conclusions** RSVPreF3 induced robust increase in maternal RSV-specific antibody responses and RSV-A/RSV-B nAb titres. Transplacentally acquired antibody levels/titres were high in cord blood and declined in infants until six months post-birth, with a similar decreasing RSV-A and RSV-B nAb GMTs and kinetics. Antibody levels/titres remained higher among the RSVPreF3-vaccinees' infants versus placebo at all timepoints through D181.

**Funding** GlaxoSmithKline Biologicals SA




**RSV-A**, respiratory syncytial virus type A; **nAb**, neutralising antibodies; **GMT**, geometric mean titre; **RSV-B**, respiratory syncytial virus type B; **N**, number of women/infants with available results; **CI**, confidence interval; **ED60**, serum dilution inducing 60% inhibition in plaque forming units. The cut-off used for these assessments are: ≥18 ED60 (RSV-A nAb) and ≥30 ED60 (RSV-B nAb) Coloured values on the graphs indicate the increase in nAb, calculated as the geometric mean of individual ratio of antibody titres at each post-vaccination timepoint over pre-vaccination.

Note: A part of RSV-A results (Pre-vaccination, Day 31, Delivery [pregnant women] and Birth [infants]) were presented at ESPID 2021, Abstract 470.

## REVIEW OF CLINICAL OUTCOMES ASSESSMENTS TO DESCRIBE HEALTH-RELATED QUALITY OF LIFE OF CAREGIVERS OF CHILDREN WITH RSV

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**Background** Respiratory syncytial virus (RSV) is a leading cause of pneumonia and bronchiolitis among young children, and a leading cause of morbidity and mortality in children under age 5.[1] The health-related quality of life (HRQL) impacts experienced by caregivers of young children with RSV is not well-documented. Understanding the health status of caregivers is an important facet of future RSV epidemiology studies.
**Objective** This study aimed 1) to describe the HRQL impacts on caregivers of young children with RSV; and 2) to identify the most appropriate clinical outcomes assessments (COAs) for assessing caregiver impacts.
**Methods** A targeted literature review (TLR) identified qualitative studies with caregivers of children with RSV, pneumonia, bronchiolitis or respiratory tract infections under 2 years old, which informed the development of a conceptual model (CM) of caregiver impacts.
**Results** Sixteen COAs were mapped against the CM, then narrowed to six for an in-depth review and gap analysis. The CM identified multiple domains of caregiver HRQL impact: emotional, physical, family, work, and financial. All literature focused on impact of hospitalization, with no data on impacts of caring for a child treated in an outpatient setting. None of the short-listed COAs were specific to RSV nor had been fully validated in the target population.
**Conclusion** Additional work is needed to better understand the impact of caring for a young child with RSV in both inpatient and outpatient settings. Additional validation work on existing COAs or development of a de novo COA is needed.

1. Lisa Staadegaard, Saverio Caini, Sonam Wangchuk, Binay Thapa, Walquiria Aparecida Ferreira de Almeida, et. al. The Global Epidemiology of RSV in Community and Hospitalized Care: Findings from 15 Countries. *Open Forum Infectious Diseases*, Volume 8, Issue 7, July 2021, ofab159, https://doi.org/10.1093/ofid/ofab15

*Disease (Respiratory Syncytial Virus, RSV), Population (Caregivers), Impacts, Quality of Life*



## SEVERE RSV INFECTION AMONG CHILDREN YOUNGER THAN 2 YEARS ADMITTED TO THE PICU IN LMICS: INTERIM RESULTS OF THE RSV GOLD III– ICU NETWORK STUDY

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**Introduction** There is a lack of individual clinical data of children with life-threatening RSV infection in low- and lower-middle-income countries (LMICs). The RSV GOLD III - ICU Network study aims to describe clinical, demographic and socioeconomic characteristics of children admitted to the pediatric intensive care unit (PICU) with life-threatening RSV infection in 10 LMICs. Here we present the interim results of this prospective observational study.
**Methods** Children younger than 2 years of age with respiratory symptoms fulfilling the World Health Organization (WHO) "extended severe acute respiratory infection (SARI)" case definition are tested for RSV using a molecular point-of-care diagnostic device during local respiratory seasons. Patient characteristics are collected through a questionnaire. The study duration is 2 years at each study site.
**Results** Between April – September 2021, a total of 284 children have been tested at 7 study sites (Tanzania, Sudan, Mozambique, Nigeria, Ghana, Nepal, Cameroon). Of these, 93 (33%) were RSV-positive. Median age at testing was 134 days and 66 (60%) were males. Nine (8%) children had been born prematurely and 13 (12%) had a comorbidity. Median length of stay was 6 days. In total, 18% of parents had heard about RSV before.
**Conclusion** RSV is responsible for one third of respiratory-related PICU admissions in young children in LMICs. Given the estimated duration of protection of 3 months after birth for maternal vaccination, we expect that extended half-life monoclonal antibodies will have most impact in preventing life-threatening RSV infection in LMICs.

## RSV CLINICAL BURDEN AND HEALTHCARE USE IN PRIMARY CARE IN CHILDREN AGED LESS THAN FIVE YEARS IN TWO ITALIAN REGIONS, 2019/20 WINTER SEASON

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**Background** Respiratory syncytial virus (RSV) is well recognized as a cause of lower respiratory tract infections hospitalization in children aged less than 5 years, but the burden of RSV infection in primary care in young children is still not clearly defined.
**Methods** As part of the RSV ComNet study, we conducted a prospective cohort study during the 2019/20 winter season in the Lazio (Central Italy) and Puglia (Southern Italy) regions in Italy. Children aged <5 years who consulted their paediatrician with an acute respiratory infection (ARI) were eligible for swabbing and all swabs were tested using a multiplex PCR. The primary outcomes were the clinical burden defined as symptoms at day of enrollment and after 14 days; duration of illness and healthcare usage after 14 days.
**Results** A total of 293 children met the ARI case definition and 119 (41%) were RSV positive and 116 (97%) completed the day 14 questionnaire. Recruited children had a median of one extra visit to their paediatrician (IQR: 0-2) and 7 days of illness (IQR: 5-10). Seven children (6%) were hospitalized (6 out of 7 children were aged.
**Conclusions** Our study highlights the burden of RSV in young children in primary care in Italy.

**Funding** This collaborative study was funded by Sanofi Pasteur and AstraZeneca. Project activities were organised and planned in collaboration with the team from Sanofi Pasteur, but all implementation work was done by the Italian research team and Nivel. Datasets are held by Nivel and the Italian research team and are not shared with the funding parties. There is an agreement that all epidemiological analyses are completed in collaboration with the team from Sanofi Pasteur, but all public health implications and conclusions are determined by the Italian research team and Nivel.



## ASSESSING THE ROLE OF HOST EPIGENETIC CHANGES AFTER RSV INFECTION IN RESPIRATORY MORBIDITY DEFINED AS WHEEZING AND/OR ASTHMA

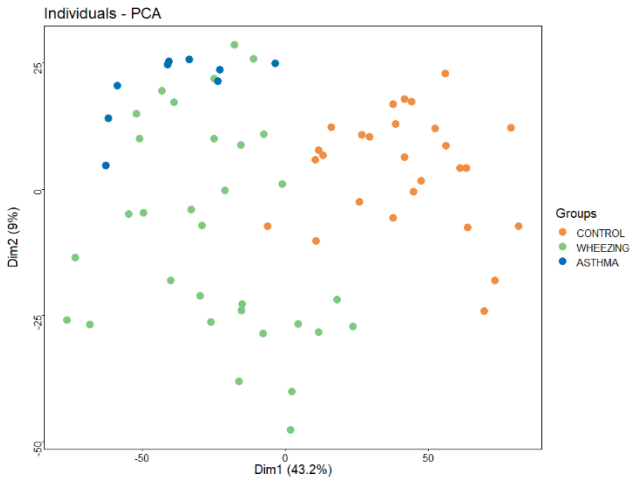
Sara Pischedda

Respiratory syncytial virus (RSV) is a common pathogen that infects virtually all children by two years of age and is the principal cause of acute lower respiratory infections (ALRI) in young children. RSV infection in infants has been associated with the subsequent development of recurrent wheezing and asthma, although the mechanisms involved are not well established. The objective of the present study is to assess whether there are differences in the methylation pattern after an RSV infection among children who have recurrent wheezing, children with subsequent asthma and children with complete recovery.

We perform a prospective, observational study of 77 infants admitted for a respiratory infection due to RSV. Patients were selected according to their clinical course and after 3 years of follow-up, were classified into three different subgroups: recurrent wheezing RSV cases; asthma RSV cases; not-wheezing/asthma RSV cases (here onwards, the control group). The genome-wide methylation pattern was measured in whole blood, using the Illumina Infinium Methylation EPIC BeadChip.

We identified a consistent number of significant differentially methylated positions (DMPs) comparing the control group with the wheezing group, and the control group vs the asthma group. The functional analysis of the results obtained by comparing the three groups together showed significant enrichment in signaling pathways related to immune response processes and cellular processes.

Our study demonstrates that epigenetic mechanisms can play a fundamental role in the development of asthma after RSV infection, contributing to explain the different phenotypes that children can develop after infection.






## ANALYSIS OF MULTIPLE ENDPOINTS IN CLINICAL TRIALS FOR RSV VACCINES

Ottavia Prunas

An increasing number of vaccines against respiratory syncytial virus (RSV) are in the clinical development pipeline. Typically, it is required to demonstrate efficacy against a primary outcome, with a lower 95% confidence interval above 0. However, the choice of which clinical outcome should be the primary outcome is somewhat arbitrary, and a wrong choice can lead to the failure of the trial (e.g., Novavax maternal trial). A key question is how to incorporate data from multiple, overlapping endpoints and how to use this information to optimize sample size, efficacy, and Type 1 error.

In our work, we aim to explore methodological issues surrounding the design and analysis from vaccine trials through simulated data. Our goal is to use simulations to demonstrate how we might combine information from multiple endpoints for a composite analysis to improve the likelihood of detecting an effect.

We simulated a trial population of ~4600 individuals that resembles data from the Novavax maternal vaccine trial. For these individuals, we generated random observations of different overlapping clinical endpoints, assuming that efficacy is similar to the point estimates reported in the trial. We also tested scenarios where the endpoints were not correlated or where they were highly correlated. We then investigated different approaches to measuring VE, including permutation-based methods, and Bayesian model-based approaches and compared these methods based on performances with type I error and power.

We found that the results from the permutation model were robust to the correlation structure of the data. Besides, the permutation model led to a satisfying trade-off between power and type I error. In conclusion, the permutation approach provides robust results with both highly correlated and non-correlated outcomes.

## DESCRIBING PEDIATRIC RSV DISEASE AT INTENSIVE CARE UNITS IN NEPAL USING MOLECULAR POINT-OF-CARE DIAGNOSTICS [ONGOING STUDY]

Shrestha Rupesh

**Background** Respiratory Syncytial Virus (RSV) is one of the common pathogens causing acute lower respiratory infection in young children requiring hospital admission worldwide. A substantial proportion of RSV related morbidity and mortality is known to occur in low and lower-middle-income countries and infants are most vulnerable group. With introduction increasing number of vaccines against bacterial pneumonia, the contribution of viral pathogen like RSV is likely to rise.
**Methods** This is a prospective observational study being carried out in High Dependency Units (HDUs) and Pediatric Intensive Care Units (PICUs) of two Pediatric Hospitals in Nepal to obtain clinical data in severely ill children with RSV infection. This study is a part of multi-center study, RSV GOLD III, being conducted in 10 countries globally. The total study period is for 2 years. All the children less than 2 years of age admitted to HDUs and PICUs will be tested for RSV using point-of-care molecular diagnostic test. Clinical characteristics and outcome of the children infected with RSV will be recorded.
**Results** Till now 34 children were enrolled in study. Out of them, 11 (32.3%) tested positive for RSV. About three fourth of children who tested positive were below 1 year of age.
**Expected Impact** This study will provide additional information regarding the clinical characteristics and outcome of critically ill children less than 2 years infected with RSV in LMICs. These results will give better idea on global RSV disease burden and will help policy makers to plan and implement RSV prevention strategies



## GENETIC CHARACTERIZATION OF RSV IN ARGENTINA BEFORE AND DURING THE SARS-COV-2 PANDEMIC

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**Background** The implementation of community mitigation measures in response to SARS-CoV-2 pandemic have impacted on the circulation of the most frequent respiratory viruses. In Argentina in 2020, the decrease in circulating RSV not only led to the absence of pediatric hospitalizations due to RSV, but it was also not detected in pediatric outpatients. However, in 2021 the beginning of the annual RSV outbreak was detected in the month of April, as usual ones. In this work we study in a comparative manner the genetic characteristics of the RSV circulating in the pediatric population before and after 2020, the year when SARS-CoV-2 totally displaced RSV.
**Methodology** Nasopharyngeal aspirates from pediatric patients admitted to Hospitals due to respiratory tract infections positive for RSV between 2018 and 2021 in Buenos Aires. The ectodomain of the G gene was sequenced and evolutionary analyses were performed.
**Results** A total of 121 G ectodomain sequences were obtained, RSVB predominated during 2018 and 2021 whereas RSVA in 2019. All RSV-A sequences were ON1-like strains and all RSV-B were BA-like. The genetic lineages before and after 2020 were the same, but the phylogenetic analyses of these sequences with sequences reported other countries in 2020 and 2021, revealed that Argentine viruses from 2021 correspond to different viral introductions. The genetic knowledge of RSVs that have overcome the 'bottleneck' of the COVID pandemic is essential in view of a future a RSV vaccine

## QUANTIFYING UNDER ASCERTAINMENT IN EXISTING OLDER ADULT RSV DISEASE INCIDENCE ESTIMATES BASED ON USE OF RT-PCR OF NASOPHARYNGEAL/NASAL SWAB ALONE

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1. Older Adult RSV Vaccine Program, Global Medical Development Scientific and Clinical Affairs, Pfizer Vaccines.

**Background** Many potential sources of under estimation exist for RSV-related hospitalization incidence including sole use of reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal (NP) swabs collected at hospital admission or study enrolment to identify RSV infections. We sought to quantify the increase in RSV infection identification associated with addition of sputum or paired serology specimens to NP/nasal swabs.

**Methods** We reviewed published literature to identify data reporting results from NP or nasal swab with RT-PCR plus either paired serology specimens (4-fold rise) or sputum RT-PCR. We calculated the RSV-infection prevalence ratio associated with adding the 2nd specimen type.

**Results** We identified three studies reporting NP swab plus serology and two reporting NP/nasal swab plus sputum (Table). Serology increased RSV detection by 29 to 64% over NP swab RT-PCR alone, with the highest value coming from a prospective cohort study of acute respiratory infection incidence where the first specimen was collected at pre-RSV season baseline for all subjects rather than illness onset/hospital admission. Sputum RT-PCR increased RSV detection by 28 to 32% over NP/nasal swab RT-PCR alone.

**Conclusions** Our data suggest that studies relying on NP/nasal swab RT-PCR will substantially underestimate the proportion of ARI associated with RSV and thus RSV incidence, thereby underestimating the value of preventive interventions such as vaccines. Models, such as those used for cost-effectiveness analyses, should take this into account. Future studies should simultaneously compare the RSV infection yield from multiple matched specimen types (NP/nasal, sputum, saliva, serology).

| Study/Year/ Country* | Population | Respiratory Swab Type for RT-PCR | Additional Specimen | Prevalence Ratio** | Pathogens | Comments |
|---|---|---|---|---|---|---|
| Falsey (2012)/ US Rochester | Adults Hospitalized with ARI – 183 positives out of 556 events | nasal (nares/flocked) & throat swabs (2 swabs in same tube) ≤24 hours of admission | Sputum | 1.68 | All viral pathogens | RSV prevalence ratio underestimated because unable to remove all NP positives without sputum available |
| | | | Sputum | 1.28 | RSV | |
| Jeong (2014)/ Korea | Adults Hospitalized with ARI: 154 paired specimens | NP swab (flocked) | Sputum | 1.32 | RSV | |
| Zhang (2016)/ US CDC | CAP hospitalizations (all ages; 936 adults) | Combined NP/OP swabs ≤3 days of admission | Serology: admission & convalescent (2–10 weeks later) | 1.50 | RSV | 18 to 64 years |
| | | | | 1.29 | RSV | ≥65 years |
| | | | | 1.38 | RSV | ≥18 years |
| Falsey (2002)/ US Rochester | Adults with ARI (1,112 with both serology and swab) – included inpatients and outpatients | Bilateral NP & OP swabs (3 swabs in same tube) ≤48 hours of admission | Serology: baseline or admission & convalescent (4–6 weeks later) | 1.34 | RSV | complex cohort – part prospective (mainly outpatient events) and part persons enrolled at hospitalization |
| Korsten (2020)/ Netherland/ UK/Belgium | 1040 adults ≥60 years enrolled in prospective cohort across 2 seasons (59 ARIs; no hospitalizations) | NP swab for incident ARI events (home visit within 72 hrs) | Serology: preseason and post season serology within 2 months of RSV season | 1.64 | RSV | Prevalence ratio for 2-fold rise was 2.58 |

Abbreviations: ARI= acute respiratory infection; CAP = community-acquired pneumonia

* References: Korsten K et al. Eur Respir J. 2021 Apr 1;57:2002688; Zhang Y et al. J Clin Microbiol. 2016 Dec 28;55:79-89; Jeong JH et al. J Med Virol. 2014 Dec;86:2122-7; Branche AR et al. J Clin Microbiol. 2014 Oct;52:3590-6; and Falsey AR et al. J Clin Microbiol. 2002 Mar;40:817-20.

**Note: Prevalence ratio indicates percentage increase, eg 1.68 is consistent with 68% increase in prevalence with adding sputum specimen. Prevalence Ratio = [RSV prevalence based on NP/nasal swab and 2nd specimen type]/[ RSV prevalence based on NP/nasal swab alone]

## ESTIMATION OF RESPIRATORY SYNCYTIAL VIRUS (RSV) BURDEN IN SECONDARY CARE HOSPITAL RECORDS IN IRELAND 2015-2019 USING ICD-10 DIAGNOSIS CODES

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**Background** RSV is a notifiable disease in Ireland and the second most common respiratory virus after Influenza. (1, 2) RSV is one of the leading causes of lower respiratory tract infections and a major burden on society. (3,4,5,6)
**Objective** To estimate the RSV-related hospital admissions in infants < 2 years of age in Ireland using ICD-10 definitions.
**Method** ICD-10 specific hospitalisations due to RSV were obtained from the Hospital Inpatient Enquiry (HIPE) database for infants<2 years of age between 2015-2019 codes were J12.1, J20.5, J21.0, B97.4. (7) Hospital costs were estimated by the number of admissions multiplied by an adjusted unit cost based on the cost per day for an inpatient stay from the ABF 2020 admitted price list for minor respiratory infection (€2,568.07). (8)
**Results** Table 1. RSV hospital admissions < 2 years, 2015-2019.

| ICD-10 | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|
| J12.1 | 7 | 13 | 6 | 12 | 14 |
| J20.5 | ~ | ~ | ~ | ~ | ~ |
| J21.0 | 1,096 | 1,345 | 1,102 | 1,403 | 1,515 |
| B97.4 | 0 | 0 | 0 | 0 | 0 |
| **Total** | **1,103** | **1,358** | **1,108** | **1,415** | **1,529** |

~ too few numbers to report

- There were 1,529 hospitalisations due to RSV in children.
- This represents a 39% increase in discharges due to RSV since 2015.
- Estimation of the cost of secondary care admissions was €3,926,577 in 2019.

**Conclusion** RSV imposes a major clinical and economic burden in Ireland, particularly at a time when hospitals are at maximum capacity. It is crucial the burden of disease is understood to inform future policy decisions.

**Acknowledgements** Funding for this study was provided by Sanofi

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## PREVALENCE, SEVERE OUTCOMES, AND COSTS ASSOCIATED WITH RESPIRATORY SYNCYTIAL VIRUS (RSV) IN ADULTS ≥ 50 YEARS OF AGE HOSPITALIZED WITH RESPIRATORY ILLNESS IN CANADA, 2012-2015

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**Introduction** Respiratory syncytial virus (RSV) disease burden is under-characterized in older adults (OA). Understanding RSV-associated acute respiratory illness (ARI) hospitalizations among OA is critical for future immunization programs.
**Methods** The CIRN-SOS Network conducts active seasonal influenza surveillance among adults hospitalized with primary or underlying ARI. RSV burden was evaluated by testing the 2012-2015 nasopharyngeal swabs from patients ≥50 years using Seeplex RV15 PCR.
**Results** Of 7797 patients tested, 371 (4.8%) were RSV-positive. Overall, RSV, RSV-A, and RSV-B prevalence was 4.8%, 2.2%, and 2.6%, respectively. Mean age was 74.9y and 63.6% were female. RSV prevalence was 4.6% in non-frail, 5.0% in pre-frail, 4.4% in more frail, and 4.7% in most frail. Co-infection with another respiratory virus was observed in 12.9% (48/371), with FluA being the most common (5.1%). RSV presented with cough (87.1 %), difficulty breathing (78.2%), sputum production (52.6%), measured fever (≥38°C) (36.9%), wheezing (31.3%), and weakness (30.7%); 98.1% of cases had ≥1 comorbidity. Mean length of stay was 11.1d, 13.7% were admitted to intensive care unit, 7.0% required mechanical ventilation, and 7.0% died. Adults >75y are at higher risk of death (OR 3.71). Mean resource utilization and direct medical cost per case was CAD $13,315 [95% CI: $12,846; $13,785], ranging provincially from $12,093 to $24,830, and from $12,199 in ≥80y to $15,712 in 50-59y age groups.
**Conclusions** This study reports RSV hospitalizations among adults ≥50 years with ARI of 4.2% to 6.2% over three seasons, associated with considerable morbidity, mortality and cost. Understanding RSV burden better informs vaccine policy.

## USING MATHEMATICAL MODELLING TO UNDERSTAND THE IMPACT OF COVID-19 CONTROL MEASURES ON RSV IN WESTERN AUSTRALIA

Nicholas Everritt

**Background** Non-pharmaceutical interventions (NPIs) adopted in response to COVID-19 appear to have suppressed RSV in Western Australia (WA) during winter 2020. A large epidemic followed in summer 2020-21 after the lifting of NPIs, during which average patient age increased. The aim of this study was to assess the impact of COVID-19 NPIs on the transmission of RSV in WA.
**Methodology** A deterministic compartmental SEIRS transmission model previously parameterised for WA was adapted to allow for the impact of COVID-19 NPIs. Outputs were compared to RSV case data for WA to identify the most likely drivers of observed dynamics. A forecasting analysis was performed.
**Results** In the presence of reduced transmission due to COVID-19 NPIs the model replicated the suppression of RSV in WA in winter 2020. The dynamics of population immunity alone did not reproduce the summer 2020-21 epidemic or the increase in average patient age. By including several immunological factors in the model, namely waning maternal antibodies, waning cross-immunity and increased detection rates in older children, and reparameterising the model with higher transmission and lower seasonality parameters, the summer 2020-21 epidemic was broadly replicated. The size and timing of the epidemics produced by forecast scenarios were sensitive to model parameters, and they disagreed as to the size of epidemics expected in 2022 and 2023.



## THE EFFECT OF COMMUNITY DIFFERENCES IN GEOGRAPHIC MIXING AND POPULATION STRUCTURE ON THE SPATIO-TEMPORAL DYNAMICS OF RESPIRATORY SYNCYTIAL VIRUS (RSV) TRANSMISSION IN THE UNITED STATES

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**Introduction** To inform the optimal and equitable delivery of RSV prevention programs, including emerging vaccination strategies, a detailed understanding of the role spatial connectivity and regional socio-demographic variations play in RSV transmission dynamics will be crucial.
**Methods** We constructed a dynamic transmission model incorporating variations in age structure, density, rurality, and seasonality for the state of Connecticut (United States). To ensure the model results reflected empirical data, we fitted the model to RSV hospitalization data (1996-2013) for children in Connecticut aged <24 months using quasi-Bayesian Latin Hypercube Sampling approach.
**Results** Our age-structured, seasonally-forced "metapopulation" model accounted for 19 distinct geographic communities across Connecticut and considered RSV importation from neighbouring New York State. The model accurately captured the timing and magnitude of observed annual peaks in RSV-related hospitalizations, as well as variations in the peak timing of local seasonal epidemics, spanning a 4-week period between mid-January and mid-February. RSV incidence tended to peak earlier in regions with higher spatial connectivity with New York, greater population density, and more young children.
**General Impact** This ongoing research will fill critical gaps in our understanding of RSV transmission by realistically capturing variations in regional dynamics, which have historically been ignored. These results may inform the spatial targeting of population-based RSV interventions, e.g. modified start dates for seasonal prophylaxis or vaccination programs. As seen throughout the COVID-19 pandemic, "one-size-fits-all" approaches support neither equitable nor optimal population health outcomes. Similarly, RSV transmission dynamics are heterogeneous, requiring targeted prevention approaches.

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## SOCIO-DEMOGRAPHIC AND CLINICAL FACTORS PREDICTING POOR RESPIRATORY OUTCOMES FOLLOWING EARLY-LIFE RSV-INFECTIONS: A POPULATION-BASED COHORT STUDY

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**Background** Early-life Respiratory Syncytial Virus (RSV) infections have been associated with subsequent asthma and wheezing in children, but predictors and effect of age at first RSV are unclear. We aimed to identify factors for respiratory morbidity following laboratory-confirmed RSV.
**Methods** We used probabilistically linked perinatal, morbidity, and laboratory data of 262,493 children born in Western Australia, 2000-2009 with follow-up to 2012. Our primary cohort of interest was children with RSV-confirmed detections before age 2 years, and outcome was respiratory morbidity (hospitalisation or emergency department presentation for wheeze and asthma) after age 2 years. We used cox proportional hazard models to determine associations.
**Results** There were 5,579 early-life RSV- detections and 537 first respiratory morbidity episodes from 38,746.1 child-years of follow-up. During the whole follow-up period, the incidence of first asthma and wheeze episode was 13.8/1000 child-years. Children with their first RSV-exposure at 12-23 months had respiratory morbidity 2 times higher than those with first RSV at <3 months (20.2/1000 vs 10.3/1000 child-years). Maternal asthma (adjusted Hazard Ratio, aHR:1.5 [95% CI 1.2-1.9]), extreme prematurity (<28 weeks; aHR:2.1 [95% CI 1.4-3.4]), and low SES (aHR:1.9 [95%CI 1.1-3.2]) were among factors associated with respiratory morbidity. Compared to RSV <3 months, respiratory morbidity was higher with first RSV 6-11 months (aHR:1.4 [95% CI 1.1-1.8]) or 12-23 months (aHR:1.4 [95% CI 1.1-1.9]).
**Conclusions** Increased risk of subsequent respiratory morbidity alters with age of first RSV infection. The difference in risk suggests children aged 12-23 and preterm infants could be potential target groups for RSV prevention to reduce risk of subsequent morbidity.



## EXCESS MORTALITY FROM RESPIRATORY SYNCYTIAL VIRUS IN THE US, 1999-2018

Chelsea Hansen

The latest RSV excess mortality estimates in the US are from 2009. Updated burden estimates are needed to characterize RSV epidemiology to provide perspective on public health interventions contrasted with secular trends. We used linear regression models to attribute age-specific week-to-week fluctuations in underlying respiratory mortality to RSV, adjusting for Influenza. From 1999-2018 testing for RSV increased 8-fold, while the percentage of positive tests decreased from 14.9% to 8.5% ($p<0.003$). PCR testing accounted for 83.6% of all RSV tests in 2017/2018. Increased use of PCR testing may lead to underestimation of excess RSV-mortality in recent years. We estimate an annual average of 6,500 (95% CI 6,200 – 6,900) RSV-associated deaths, including 100 (95%CI 90-100) deaths in children <1 year. RSV mortality in infants has decreased since the 1990s but is still 5-fold higher than influenza mortality in this age group. The highest average RSV-associated mortality rate for all age-groups was in adults 65+ at 14.7 (95% CI 13.8-15.5) per 100,000 population. Mortality from RSV was higher than influenza mortality in this age group in seasons when the influenza A/H1 subtype predominated. HHS Region 6 had the highest RSV mortality among adults 65+. Despite differences in RSV seasonality in Florida, among seniors we did not find significantly more RSV mortality in HHS Region 4 compared to other regions. Including underlying circulatory deaths in the mortality outcome increased excess RSV mortality estimates in adults >50 years, but not in younger age groups. RSV contributes to substantial mortality in young children and older adults.

## RISK FACTORS AND MEDICAL RESOURCE UTILIZATION IN US ADULTS WITH RESPIRATORY SYNCYTIAL VIRUS OR INFLUENZA IN THE HOSPITALIZED ACUTE RESPIRATORY TRACT INFECTION (HARTI) STUDY

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**Background** An estimated 50,000 influenza-associated and 17,000 respiratory syncytial virus (RSV)-associated deaths occur annually in the United States (US). 1 Using data from the US cohort of the HARTI study2, we assessed risk factors for severe disease and medical resource utilization (MRU) during and post-hospitalization in US adults with influenza or RSV.
**Methods** HARTI was a prospective global epidemiological study in adults hospitalized with acute respiratory tract infection (12 countries, 40 centers). Patients with confirmed influenza, RSV, or human metapneumovirus were followed up to three months post-discharge. Baseline patient characteristics, prevalence of core risk factors for severe disease, and MRU in US patients with RSV or influenza were summarized descriptively.
**Results** The US cohort included 280 influenza-positive and 120 RSV-positive patients. RSV patients were older (mean: 63.1 vs 59.7 years) and a higher proportion had core risk factors (87.5% vs 81.4%). RSV patients more frequently experienced acute exacerbation of asthma or chronic obstructive pulmonary disease (33.3%), congestive heart failure (22.7%), and hypoxemia (34.7%) than influenza patients (24.4%, 16.5%, and 25.0%, respectively). RSV patients reported greater symptom severity, particularly among patients ≥60 years of age, and required longer hospital stays and higher MRU during and post-hospitalization than influenza patients (Table).
**Conclusions** RSV is an under-recognized pathogen associated with high morbidity and MRU in hospitalized patients in this study. Improved surveillance, diagnostics, and preventative efforts are needed for RSV.

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| | Influenza (N=178) | | RSV (N=112) | |
|---|---|---|---|---|
| | Presence of core risk factors (N=153) | No presence of core risk factors (N=25) | Presence of core risk factors (N=99) | No presence of core risk factors (N=13) |
| Length of hospital stay, mean (SD), days | 4.71 (3.03) | 4.80 (4.62) | 5.42 (3.07) | 6.69 (10.06) |
| Length of hospital stay, n (%) | | | | |
| ≤ 3 Days | 67 (43.8) | 13 (52.0) | 30 (30.3) | 7 (53.8) |
| > 3 Days | 86 (56.2) | 12 (48.0) | 69 (69.7) | 6 (46.2) |
| No mechanical ventilation given, n (%) | 150 (98.0) | 25 (100) | 99 (100) | 13 (100) |
| $O_2$ supplementation given, n (%) | 91 (59.5) | 13 (52.0) | 79 (79.8) | 7 (53.8) |
| $O_2$ supplementation duration, mean (SD), days | 4.54 (3.64) | 4.08 (4.33) | 4.16 (2.82) | 4.17 (4.58) |
| ICU stay during hospitalization, n (%) | 8 (5.2) | 1 (4.0) | 8 (8.1) | 1 (7.7) |
| ICU length of stay, mean (SD), days | 4.75 (1.28) | 3.00 (-) | 2.50 (1.00) | 4.00 (-) |
| Patient destination after hospital discharge, n (%) | | | | |
| Long-term care facility | 1 (0.7) | 0 | 8 (8.1) | 0 |
| Private residence | 131 (85.6) | 24 (96.0) | 84 (84.8) | 12 (92.3) |
| Rehabilitation unit | 6 (3.9) | 0 | 2 (2.0) | 1 (7.7) |
| Other | 12 (7.8) | 1 (4.0) | 4 (4.0) | 0 |
| Not reported | 3 (2.0) | 0 | 1 (1.0) | 0 |

ICU, intensive care unit; RSV, respiratory syncytial virus; SD, standard deviation.
[a] Core risk factors include patient age ≥65, chronic heart disease, chronic obstructive pulmonary disease, chronic kidney disease, and asthma.

## RESPIRATORY SYNCYTIAL VIRUS (RSV)-ASSOCIATED BURDEN OF DISEASE IN OLDER ADULTS IN EUROPE AND THE UNITED STATES

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**Background** The burden of RSV disease is insufficiently characterised in older adults (OA). We assessed the disease burden of RSV in OA in community dwelling (CD-OA) and long-term care facilities (LTCF-OA). **Methods** In this prospective, multi-country, cohort study covering 2 consecutive RSV-seasons (Oct2019- Mar2020 and Oct2020-Jun2021, season 1 results are shown), medically stable CD-OA aged ⩾50 years (Europe) or LTCF-OA ⩾65 years (Europe/US) were contacted every 2 weeks for acute respiratory infection (ARI) surveillance. Nasal and throat swabs collected during ARI episodes were tested for RSV by reverse transcription-polymerase chain reaction (RT-PCR). Blood samples were collected from ARI onset to outcome visits for serological diagnosis (ELISA) of RSV infection. Complications/ hospitalisations/ deaths/ co-infections were also evaluated for the positive (RT-PCR) RSV-ARI episodes.
**Results** 45.8% of CD-OA and 32.2% of LTCF-OA had ⩾1 ARI episode. RSV was detected in 4% (CD-OA) and 7% (LTCF-OA) of OA with ARI, leading to an RSV incidence proportion of 1.84% and 2.26%. In addition, RSV-ARI was identified by serology in 3 CD-OA and 3 LTCF-OA (Table). Complications, mostly respiratory, were more frequent among RSV-ARI vs non-RSV-ARI episodes (CD: 13.0% vs 2.4%; LTCF: 13.3% vs 7.8%). None of RSV-ARI episodes led to hospitalisation/death; no risk factors were identified. Co-infections were detected in 17.4% (4/23, CD) and 13.3% (2/15, LTCF) of RSV-ARI episodes.
**Conclusions** Despite the limited number of participants, this study showed that RSV causes disease burden in CD-OA and LTCF-OA. RSV-ARIs were more frequently associated with respiratory complications compared to non-RSV-ARIs.

**Funding** GlaxoSmithKline Biologicals SA

| | CD-OA (≥50 years of age) N=1251 | CD-OA (≥60 years of age) N=869 | LTCF-OA (≥65 years of age) N=664 |
|---|---|---|---|
| OA with ARI, % (n/N) | 45.8 (573/1251) | 44.4 (386/869) | 32.2 (214/664) |
| OA with RSV-ARI, % (n'/n) | 4.0 (23/573) | 3.9 (15/386) | 7.0 (15/214) |
| **RSV incidence proportion** | | | |
| RSV-ARI by RT-PCR, % (95% CI) | 1.84 (1.00–3.08) | 1.73 (0.82–3.18) | 2.26 (0.88–4.69) |
| RSV-ARI by ELISA*, % (95% CI) | 0.24 (0.03–0.84) | 0.0 (0.00–0.42) | 0.45 (0.09–1.32) |

*incidence proportion calculated for serologically positive (4-fold increase in RSV-F antibody titres) RSV-ARI episodes among RT-PCR negative RSV-ARI episodes; **RSV-ARI,** respiratory syncytial virus-associated acute respiratory infection; **CD-OA**, older adults (**OA**) living in community dwelling; **LTCF-OA**, OA living in long-term care facilities; **N**, number of followed-up participants; **n**, number of participants with ≥1 ARI episode; **n'**, number of participants with ≥1 RSV positive ARI result; **CI**, confidence interval; **RT-PCR**, reverse transcription-polymerase chain reaction; **ELISA**, enzyme-linked immunosorbent assay.
**ARI case definition:** ≥2 signs and/or symptoms: rhinorrhoea/nasal congestion, sore throat, cough (new or increasing), sputum production (new or increasing), shortness of breath or dyspnoea (new or increasing), wheezing (new or increasing), feverishness or fever (temperature ≥37.5°C).

## ESCALATIONS OF RESPIRATORY SUPPORT AMONG HOSPITALIZED ADULTS WITH HEALTHCARE-ASSOCIATED (HA) RESPIRATORY SYNCYTIAL VIRUS (RSV)

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**Background** Little is known about morbidity and mortality associated with HA-RSV in adults, including need for escalation of respiratory support.
**Methods** From 2017-2020, patients with HA-RSV were retrospectively identified. HA-RSV was defined as patients with new or worsening respiratory signs and symptoms who were RSV-positive by PCR assays after ≥4 days of hospitalization. Daily maximum respiratory support relative to RSV detection (Day 0) was used to assess escalation of respiratory support, defined as a new modality (e.g., room air (RA) escalated to mechanical ventilation) or increased support using the same modality (e.g., nasal cannula (NC) oxygen increased from 2L-5L), during Day -2 to Day +4. Characteristics and outcomes of HA-RSV cases with and without escalation of respiratory support were compared using Fisher's exact or t-test.
**Results** 84 HA-RSV cases were identified; 77 (92%) had adequate data to assess respiratory support escalation. 22 (29%) patients required escalation, most commonly RA to NC (11, 50%); two required ventilation. Most escalations (65%) occurred on Days 0 or +1 (median Day +1, IQR [0-1]). Patients with escalations were older (median: 73 vs. 62 years, $p<0.01$) and more likely to have lung comorbidities (50% vs. 18%, $p<0.01$) than those without escalations. After RSV detection, those requiring escalation had longer hospitalizations (median: 15 vs. 8 days, $p=0.03$), more ICU admissions within 7 days of RSV detection (28% vs. 7%, $p=0.03$), and higher in-hospital mortality (23% vs. 7%, $p=0.11$).
**Conclusions** HA-RSV requiring escalation of respiratory support was associated with increased morbidity, healthcare resource utilization, and mortality.



## THE ACUTE RESPIRATORY INFECTIONS GLOBAL OUTPATIENT STUDY (ARGOS): A PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS DISEASE BURDEN OF RESPIRATORY SYNCYTIAL VIRUS IN HIGH-RISK ADULTS

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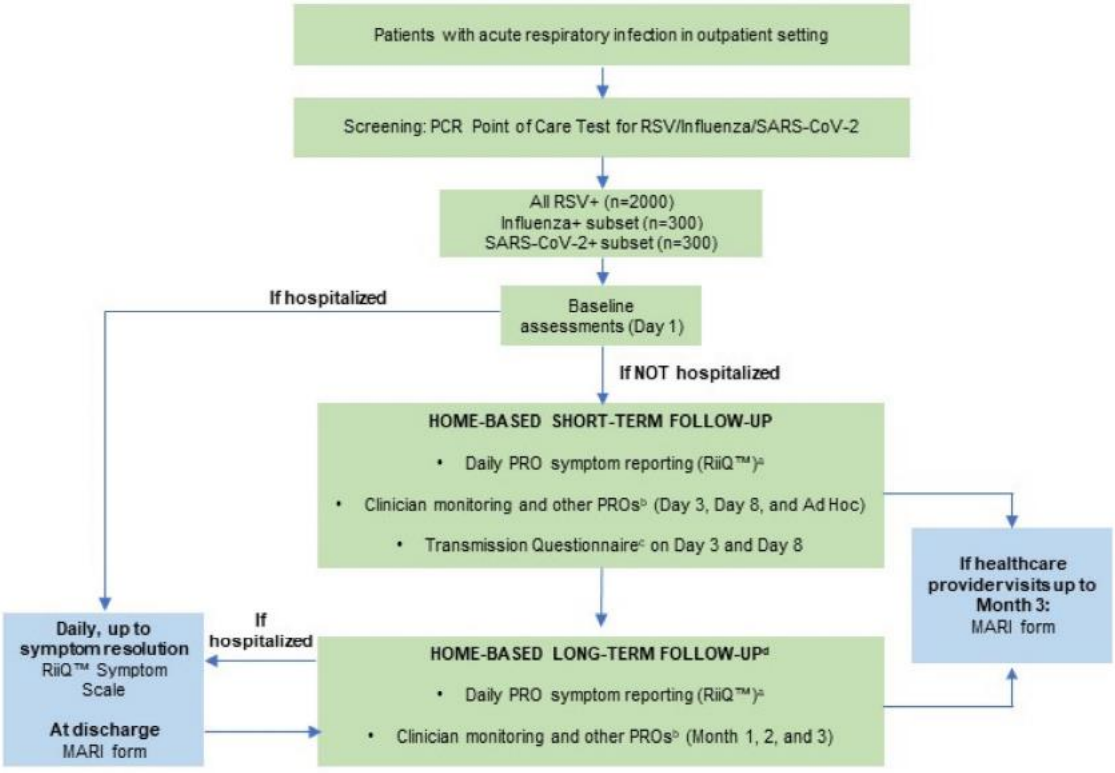
**Background** Human respiratory syncytial virus (RSV) is a contagious seasonal pathogen that causes 64 million acute respiratory infections (ARI) every year in adults and children globally, leading to significant morbidity and mortality. The burden of RSV-mediated disease in adults is poorly understood. Adults at highest risk for severe RSV infection are older, immunocompromised, and/or have comorbidities such as chronic heart or lung disease. The ARGOS study aims to assess the burden of RSV among adults who are at high risk for progression to severe respiratory disease.
**Methods** ARGOS is an ongoing global prospective study. Participants eligible for screening are patients with ARIs in outpatient settings aged ≥60 years with or without comorbidities or aged 18–59 years with ≥1 of the following comorbidities: chronic lung, cardiovascular, kidney, or liver disease; neurological disease; obesity; Type-2 diabetes; or are immunocompromised. A target of 18,000 patients will be screened to allow enrollment of ~2000 RSV-positive patients. Screening in healthcare settings is followed by home-based, short-term follow-up to Day 8 (±1 day), followed by a 3-month follow-up phase. Telemedicine and apps will optimize remote monitoring during home-based assessment.
**Primary outcomes** (1) PCR-based test positivity rate of RSV, influenza virus, and SARS-CoV-2 in patients presenting with ARIs in outpatient settings during the RSV/influenza season; (2) rates of lower respiratory tract disease and ARI-related hospitalization in RSV-positive patients. Study schedule and assessments are summarized in the **Figure**.

**Conclusions** ARGOS is the first global prospective study which aims to accurately characterize RSV disease burden in high-risk adult outpatients.




[a] Completed daily until resolution of ARI symptoms.
[b] PROs include Patient Global Impression questions, Days Missed from Work Questionnaire, EQ-5D-5L, and MRU questionnaire.
[c] The Transmission Questionnaire includes questions on the number, age, and ARI symptoms of household and external proximity contacts.
[d] Contact can be by telemedicine, phone call, or home nurse visit. Clinician assessments continue only for patients with ongoing symptoms.
ARI, acute respiratory infection; MARI: medically attended respiratory infections; MRU, medical resource utilization; PRO: patient-reported outcome; RiiQ™: Respiratory Infection Intensity and Impact Questionnaire, RSV: respiratory syncytial virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

## Evolution & Epidemiology E&E-26

### BURDEN OF HOSPITAL ACQUIRED ACUTE VIRAL RESPIRATORY TRACT INFECTIONS IN A TERTIARY CARE HOSPITAL, SRI LANKA

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**Introduction** Hospital acquired infections (HAI) are associated with a great deal of burden. It is troublesome to spot the prevalence of any of nosocomial viral infection. In this study we have assessed the risk factors for occurrence of nosocomial and community acquired viral acute respiratory tract infections (ARTIs) in children 1 month to 3 years of age.
**Methods** We have assessed the risk factors for occurrence of HA and community acquired (CA) viral ARTIs in children. Children who were having ARTI on admission (CA) and develops ARTI following 48 hours after admission or 3 days of discharge (HA) was included. Indirect immunofluorescence assay (IFA) was performed and multivariable analyses were done to determine the risk factors for the development of viral CA and HA-ARTI.
**Results** Total of 418 with ARTIs, 108 (26%) RSV cases were detected. Out of 108, 40 (37%) HA-RSV cases were detected. CA-viral-ARTI was significantly high ($p < 0.05$). Compared to CA-RSV-ARTI immunodeficiency, seizures, trisomy-21 and congenital heart disease (CHD) was having 3.3, 3.4, 2.8- and 2.4-times risk for acquiring HA-RSV respectively. Number of deaths were significantly high following HA-RSV. Associated burden was significant following HA-RSV and it was 429.77 disability adjusted life years.
**Discussion** RSV was predominantly associated with nosocomial ARTIs. Children who died from HA- RSV had chronic diseases (Down's syndrome and CHD). Adherence to meticulous infection control practices will be helpful to minimize the HA-viral ARTIs in great.

*nosocomial: viral acute respiratory tract infections; Respiratory syncytial virus and risk factors*

## SYSTEMATIC REVIEW AND META-ANALYSIS OF THE PREVALENCE OF COMMON RESPIRATORY VIRUSES IN CHILDREN < 2 YEARS WITH BRONCHIOLITIS IN THE PRE-COVID-19 PANDEMIC ERA LANKA

Kenmoe, Sebastien

**Introduction** The advent of genome amplification assays has allowed description of new respiratory viruses and to reconsider the role played by certain respiratory viruses in bronchiolitis. This systematic review and meta-analysis was initiated to clarify the prevalence of respiratory viruses in children with bronchiolitis in the pre-COVID-19 pandemic era.
**Methods** We performed an electronic search through Pubmed and Global Index Medicus databases. We included observational studies reporting the detection rate of common respiratory viruses in children with bronchiolitis using molecular assays. Data was extracted and the quality of the included articles was assessed. We conducted sensitivity, subgroups, publication bias, and heterogeneity analyses using a random effect model.
**Results** The final meta-analysis included 51 studies. Human respiratory syncytial virus (HRSV) was largely the most commonly detected virus 59.2%; 95% CI [54.7; 63.6]). The second predominant virus was Rhinovirus (RV) 19.3%; 95% CI [16.7; 22.0]) followed by Human bocavirus (HBoV) 8.2%; 95% CI [5.7; 11.2]). Other reported viruses included Human Adenovirus (HAdV) 6.1%; 95% CI [4.4; 8.0]), Human Metapneumovirus (HMPV) 5.4%; 95% CI [4.4; 6.4]), Human Parainfluenzavirus (HPIV) 5.4%; 95% CI [3.8; 7.3]), Influenza 3.2%; 95% CI [2.2; 4.3], Human Coronavirus (HCoV) 2.9%; 95% CI [2.0; 4.0]), and Enterovirus (EV) 2.9%; 95% CI [1.6; 4.5]).
**Conclusions**: The present study has shown that HRSV is the main cause of bronchiolitis in children, we lso have Rhinovirus, and Bocavirus which also play a significant role. Data on the role played by SARS-CoV-2 in children with acute bronchiolitis is needed.

**Acknowledgements** None



## ESTIMATING THE PROPORTION OF ALRI HOSPITALIZATIONS ATTRIBUTABLE TO RSV IN THE FIRST YEAR OF LIFE

John Kubale[1], Irena Chen[2], Zhenke Wu[2], Eric A.F. Simões[3,4], Ilham Abu Khader[5], Danielle R. Hunt[6], Silvia Bino[7], Basima I. Marar[8], Lionel Gresh[9], Joanne N. de Jesus[10], William Campbell[6], Iris Hasibra[7], Enkeleda Duka[7], Mahmoud Al-Gazo[5], Samir Faouri[5], Felix Sanchez[11], Marilla G. Lucero[10], Veronica L. Tallo[10], Artan Simaku[7] ,Aubree Gordon[1] on behalf of the IRIS Network.

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**Background** Recent studies have demonstrated that RSV is a substantial driver of the global burden of pneumonia hospitalizations among children aged <5. However, the etiology of broader acute lower respiratory tract infections (ALRI) remains less clear, particularly within narrower age ranges like the first year of life.
**Methods** Using data from a multi-country study (Albania, Jordan, Nicaragua, and the Philippines) of hospitalized infants and non-ill community controls between 2015-2017, we assessed the proportion of ALRI-hospitalizations attributable to 21 respiratory viruses including RSV (i.e. population aetiologic fractions [PAF]). Viruses were identified via multiplex real time RT-PCR using Fast Track Diagnostics Respiratory 21 panel. We estimated PAF by fitting Bayesian partially latent class models using the baker R package.
**Results** A total of 3631 hospitalized infants and 1068 non-ill community controls participated in the study and were tested for the panel of viruses. Among hospitalized infants in the sample, 1743 (48.0%) were diagnosed with ALRI. The proportion of ALRI hospitalizations attributable to RSV across sites decreased as age increased, peaking at 36.1% (95% Credible Interval [CrI]: 32.6, 39.8) among infants aged <3 months, before decreasing to 25.2% (95% CrI: 20.2, 30.3) and 22.4% (95% CrI: 17.8, 26.9) among infants aged 3-5 months and 6-11 months respectively. RSV's PAF was the highest across all age groups.
**Conclusions** RSV was a substantial source of ALRI hospitalizations in the study, particularly in infants aged <3 months. As such, development of maternal vaccines or long-acting monoclonal antibodies could substantially reduce ALRI hospitalizations among infants.

## RESPIRATORY SYNCYTIAL VIRUS SEASONALITY AND PREVENTION STRATEGY PLANNING FOR PASSIVE IMMUNISATION OF INFANTS IN LOW-INCOME AND MIDDLE-INCOME COUNTRIES: A MODELLING STUDY

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**Objective** We aimed to assess the potential effect of different approaches for passive RSV immunisation of infants in LMICs.
**Methods** We developed a mathematical model to compare the effect of different RSV passive immunisation approaches (seasonal approaches vs a year-round approach). We calculated the expected annual proportion of RSV incidence among infants younger than 6 months averted (effectiveness) and the ratio of per-dose cases averted between that approach and the year-round approach (relative efficiency).
**Findings** 39 (75%) of 52 LMICs included in the study had clear RSV seasonality. In these countries with clear RSV seasonality, the seasonal approach in which monoclonal antibody (mAb) administration began 3 months before RSV season onset was only a median of 16% (IQR 13–18) less effective in averting RSV-associated acute lower respiratory infection (ALRI) hospital admissions than a year-round approach, but was a median of 70% (50–97) more efficient in reducing RSV-ALRI hospital admissions per dose. The seasonal approach that delivered maternal vaccination 1 month before the season onset was a median of 27% (25–33) less effective in averting RSV-ALRI hospital admissions than a year-round approach, but was a median of 126% (87–177) more efficient at averting these hospital admissions per dose.
**Interpretation** In LMICs with clear RSV seasonality, seasonal approaches to mAb and maternal vaccine administration might optimise disease prevention by dose given compared with year-round administration. More data are needed to clarify if seasonal administration of RSV mAb or maternal immunisation is programmatically suitable and cost effective in LMICs.

**Table.** Effectiveness and relative efficiency results for each candidate approach among countries with ≤5 epidemic months

| Approach | Dose months | RSV-ALRI | | | RSV-ALRI hospitalisation | | |
|---|---|---|---|---|---|---|---|
| | | Effectiveness | Effectiveness ratio* | Relative efficiency | Effectiveness | Effectiveness ratio* | Relative efficiency |
| **Monoclonal antibody** | | | | | | | |
| **Seasonal A** | 4 (3–5) | 18·1 (14·5–21·9) | 0.39 (0.32–0.46) | 1.19 (1.09–1.30) | 25.8 (20.3–30.7) | 0.45 (0.37–0.53) | 1.36 (1.24–1.54) |
| **Seasonal B** | 4 (3–5) | 22.3 (19.3–28.0) | 0.48 (0.40–0.59) | 1.55 (1.46–1.70) | 33.0 (28.2–39.0) | 0.58 (0.51–0.65) | 1.83 (1.65–2.10) |
| **Seasonal C** | 5 (4–6) | 32.1 (26.9–36.2) | 0.68 (0.60–0.73) | 1.69 (1.52–1.80) | 42.4 (36.4–48.0) | 0.75 (0.70–0.78) | 1.82 (1.60–2.09) |
| **Seasonal D** | 6 (5–7) | 38.6 (34.7–42.9) | 0.82 (0.79–0.84) | 1.65 (1.46–1.89) | 49.4 (44.3–53.8) | 0.84 (0.82–0.87) | 1.70 (1.50–1.97) |
| **Year-round** | 12 (12–12) | 49.1 (42.2–52.5) | 1 (Reference) | 1 (Reference) | 59.9 (51.5–64.1) | 1 (Reference) | 1 (Reference) |
| **Maternal vaccine** | | | | | | | |
| **Seasonal A** | 4 (3–5) | 6.8 (5.2–7.7) | 0.66 (0.59–0.70) | 2.03 (1.79–2.40) | 11.1 (7.8–13.7) | 0.60 (0.51–0.67) | 1.82 (1.69–2.07) |
| **Seasonal B** | 4 (3–5) | 7.1 (5.3–8.2) | 0.7 (0.64–0.75) | 2.22 (1.85–2.69) | 13.7 (10.6–15.8) | 0.73 (0.67–0.75) | 2.26 (1.87–2.77) |
| **Year-round** | 12 (12–12) | 10.4 (8.8–11.2) | 1 (Reference) | 1 (Reference) | 19.6 (16.4–21.0) | 1 (Reference) | 1 (Reference) |

*Effectiveness ratio is calculated by the ratio between the effectiveness of seasonal approach and that of the year-round approach. Results are presented as median (IQR) among the included countries.

## ESTIMATING GLOBAL RSV BURDEN AT INTENSIVE CARE UNITS IN CAMEROON USING MOLECULAR POINT-OF-CARE DIAGNOSTICS: THE RSV GOLD-III STUDY

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**Background** Respiratory syncytial virus (RSV) infection is an important cause of hospitalization and death in young children. Most deaths (99%) occur in low- and lower-middle-income countries (LMICs). Vaccines against RSV infection are expected to become available in the next 5-10 years. LMICs require support from Gavi, the Vaccine Alliance, to obtain access to future RSV vaccines. However, there is a lack of individual patient data in LMICs, of patients with life-threatening RSV infection. The RSV GOLD III – ICU Network study aims to define clinical, demographic and socioeconomic characteristics of children with life-threatening RSV infection in Cameroon.
**Methods** The current study is embedded in the RSV GOLD study. GOLD-III is an international, prospective, observational multicenter study and will be conducted in Cameroon and other 9 Gavi-eligible countries at pediatric intensive care units/high-dependency units (PICUs/HDUs) during 2 local respiratory seasons. Children younger than 2 years with respiratory symptoms according to the WHO extended severe acute respiratory infection (SARI) case definition will be tested for RSV using a molecular point-of-care (POC) diagnostic device. Patient characteristics will be collected through a questionnaire. Mortality rates of children admitted to the PICU/HDU will be calculated.
**Expected Impact**: This multicenter descriptive study will provide a better understanding of the characteristics and mortality rates of children younger than 2 years with RSV infection admitted to the PICU in Cameroon. These results will contribute to knowledge on global disease burden and awareness of RSV and will directly inform decision makers on the impact of future RSV prevention strategies.

*Respiratory syncytial virus, Children, Pediatric intensive care unit, Study design, Lower-middle-income countries, Burden, Awareness*



## RSV GOLD III – SARI DISEASE BURDEN AT MUHIMBILI NATIONAL HOSPITAL DAR ES SALAAM, TANZANIA

Marc Mazur

RSV infection is an important cause of hospitalization and death in young children. Limited patient data are available from lower-middle-income countries, where RSV burden is highest. To assess the feasibility of calculating disease burden, we performed a retrospective pilot study to calculate the incidence and mortality of severe acute respiratory infection (SARI)-related admissions in children younger than 2 years within the catchment area of the pediatric ICU of Muhimbili National Hospital. The numerator for this sentinel site was assessed by collecting retrospective anonymized patient data of children <2 years admitted to the pediatric ICU with SARI between March 2019 — March 2021. The WHO SARI case definition was used to identify cases. Admission diagnoses related to respiratory illness or respiratory infection were included but cases of aspiration pneumonia were excluded. The denominator was calculated using the Tanzanian National Bureau of Statistics Populations Projections report provided Population data for the number of children <2 living in the catchment area during the study period. The catchment area – where <80% of cases reside – was found to be Dar Es Salaam region. 218 children <2 years with SARI-related symptoms were admitted between March 2019 and March 2021. The calculated SARI-related incidence rate per 100,000 children <2 years is 35.7 and 32.8 and mortality was 25.9 and 23.5 for 2019-2020 and 2020-2021 respectively. SARI incidence is higher for male children in both years. Special thanks to Dr. Yasser, Dr. Karim, Dr. Lowensteyn and the Muhimbili nurses and doctors.

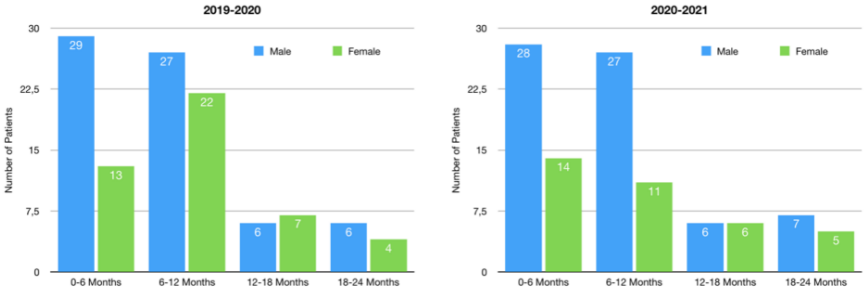


**Figure 1.** *SARI cases admitted to PICU March 2019 — March 2020 and March 2020 — March 2021 stratified by age group.*

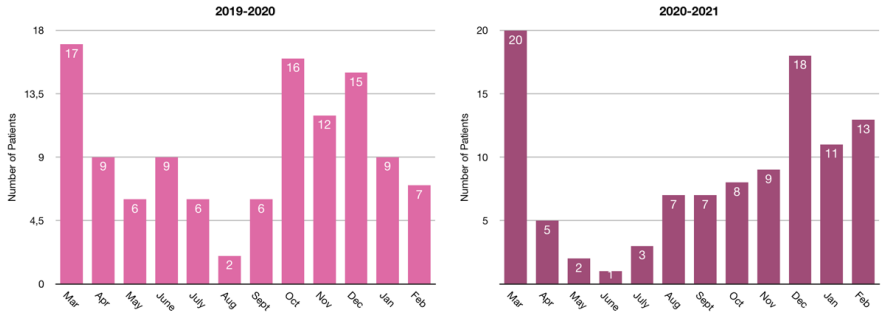


**Figure 2.** *SARI cases admitted to PICU March 2019 — March 2020 and March 2020 — March 2021 stratified by month of admission.*

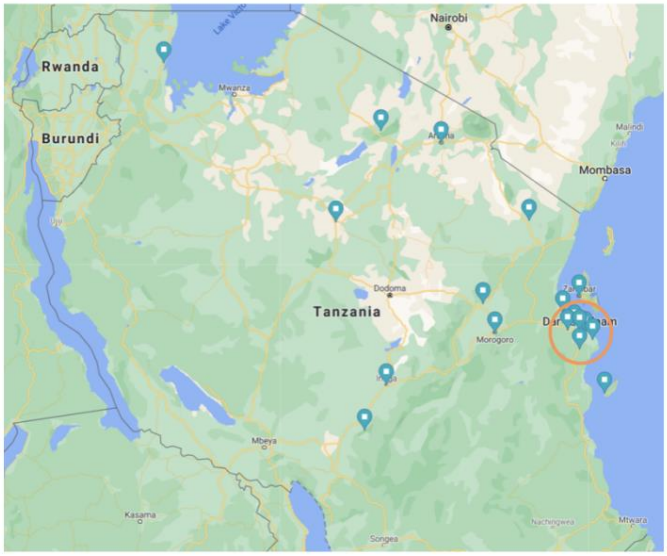


***Figure 3.*** *Spotmap displaying the residence area of SARI cases admitted to MNH PICU Mar 2019 — Mar 2021. Orange circle represents an approximation of the catchment area where 80% of the patient population resides (Table 3).*

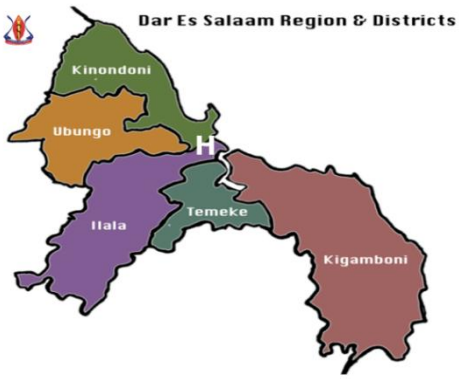


**Figure 4.** *Districts within the Dar es Salaam region.*

## Evolution & Epidemiology E&E-32

### ASSESSING THE IMPACT OF MULTIMORBIDITY AND VIRAL CHARACTERISTICS ON RESPIRATORY SYNCYTIAL VIRUS ILLNESS IN AN AMBULATORY CLINIC COHORT

Katherine Miller

**Background** Detailed information on adults impacted by Respiratory Syncytial Virus (RSV) illness would inform development of targeted treatments and vaccines. Multimorbidity, the coexistence of multiple chronic conditions, is associated with worse health outcomes and is difficult to meaningfully quantify with traditional measures of morbidity, such as the Charlson Comorbidity Index. The Multimorbidity-Weighted Index (MWI-ICD10), a comprehensive, patient-centric measure, generates individual scores by weighting the impact of various chronic conditions on physical functioning. Our study assessed relationships between multimorbidity and clinical outcomes as well as virologic characteristics of RSV.

**Methods** Data was obtained from the Michigan Henry Ford Influenza Vaccine Effectiveness (MFIVE) study (2017-2020) a prospective, ambulatory-care study spanning twelve sites. Using the MWI-ICD10, we classify adults with a non-zero MWI-ICD10 score as those with multimorbidity and those with an MWI-ICD10 equal to zero to be without. We use multivariable, firth-adjusted logistic regression to test associations between multimorbidity and illness outcomes.

**Results** Among 2,681 enrolled adults, 7.7% (n=207) had RSV detected. RSV prevalence was 9.0% among adults with multimorbidity and 5.9% among adults without multimorbidity. 34.5% (n=49) of RSV-positive adults with multimorbidity and 35.4% (n=23) without multimorbidity experienced extended illness (⩾7 days). Those with RSV-B had significantly higher odds of having a high quantitated viral load (copies/mL) detected compared to those with RSV-A [OR=1.74 (95%CI:1.11-2.73), p-value=0.02].

**Conclusions** A considerable proportion of adults in this population seeking ambulatory care for ARI were infected with RSV. Testing for RSV in vulnerable adult populations presenting with ARI symptoms is crucial to providing appropriate care.

## CONTENT VALIDITY OF FLU-PRO TO MEASURE RESPIRATORY SYNCYTIAL VIRUS SYMPTOMS IN ADULTS: A QUALITATIVE STUDY

Desmond Curran[1], Benjamin Bracke[1,a], Eliazar Sabater Cabrera[1], Kimberly Raymond[2], April M Foster[2], Cindy Umanzor[2], Daniel Molnar[1], Philibert Goulet[1,b], John H. Powers III[3]

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**Background** It is important to understand symptoms of respiratory syncytial virus (RSV) in older populations as the risk of severe disease increases with age. A patient-reported outcome measure, the InFLUenza Patient-Reported Outcome (FLU-PRO), assesses symptoms of viral respiratory illness in adults.
**Objectives** To assess the content validity of the FLU-PRO as a tool for capturing symptoms of RSV illness in older adults in the United States.
**Methods** This qualitative cross-sectional study included hybrid concept elicitation and cognitive debriefing interviews with adults aged ⩾50 years with a confirmed RSV diagnosis within six months of screening to capture both acute and long-term symptoms. Webcam/telephone interviews were conducted by researchers using a semi-structured interview guide. Data were analyzed using NVivo and Microsoft Excel to identify important symptoms of RSV illness and summarize participants' feedback on the understandability and relevance of FLU-PRO items, response options, recall period and instructions.
**Results** Thirty interviews were conducted in three age groups: 50-64 years (n=15), 65-79 years (n=12) and ⩾80 years (n=3). Eighteen participants had co-morbidities including asthma and/or chronic obstructive pulmonary disease. Symptoms reported generally align with those listed in FLU-PRO. All participants reported the FLU-PRO as easy to understand and the 24-hour recall period as suitable. Of the 32 symptoms in the FLU-PRO, all were reported as relevant with 29 symptoms reported by ⩾50% of participants.
**Conclusions** This qualitative study supports the content validity of the FLU-PRO instrument suggesting that it is appropriate to measure RSV symptoms in adults aged ⩾50 years.

**Acknowledgement** Business & Decision Life Sciences; **Funding** GSK (Study #: 213364)

**Conflict of interest** Desmond Curran, Eliazar Sabater Cabrera and Daniel Molnar are employed by and hold shares in the GSK group of companies. Benjamin Bracke was employed by the GSK group of companies during much of the study conduct and holds shares in the GSK group of companies. Benjamin Bracke is employed by and holds shares in AstraZeneca. Philibert Goulet was an employee of the GSK group of companies during much of the study conduct and holds shares in the GSK group of companies. Philibert Goulet is an employee of and holds shares in Incyte Corporation. John H. Powers III declares having received consulting fees from Arrevus, Celularity, Corbus, DaVolterra, Eicos, Eli Lilly, Evofem, Eyecheck, Fuji, Gilead, the GSK group of companies, Johnson & Johnson, Microbion, Mustang, OPKO, Otsuka, Romark, Shiniogi, SpineBioPharma, Vir. Kimberly Raymond, April M. Foster, and Cindy Umanzor are employees of QualityMetric who received funding to conduct the study from the GSK group of companies. The authors declare no other financial and non-financial relationships and activities.

## SUPPRESSION AND RESURGENCE OF RSV AND ALRI-ADMISSIONS IN 2020 FOLLOWING SHORT-TERM COVID-19 RELATED NON-PHARMACEUTICAL INTERVENTIONS IN WESTERN AUSTRALIA

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**Background** Comparative with other jurisdictions, Western Australia experienced a short period of COVID-19-associated non-pharmaceutical interventions (NPI) in 2020. We quantified the changes in paediatric hospitalisations in 2020 with the preceding five years for acute lower respiratory infections (ALRI) in the context of all-cause admissions and compared patterns to RSV detections with the preceding eight years.
**Methods** We assessed anonymised hospitalisation data from Perth Children's Hospital (Jan 2015-Dec 2020) for all-cause admissions and ALRI. We evaluated the weekly change in admissions from interrupted time-series models according to NPI introduction and easing across five periods. We aligned these patterns to RSV detections from routine laboratory surveillance in the Perth metropolitan area.
**Results** Following strict NPIs, ALRI admissions in children <5 years declined by 89%, which was sustained throughout the gradual easing of NPI until an increase of 579% (997% in those aged <3 months) following NPI cessation that saw the return of interstate travel. This followed the pattern of RSV detections with a 98% reduction in the 2020 winter compared to epidemic curves from 8 pre-pandemic seasons, followed by a 2.5-fold increase in spring/summer. In comparison to ALRI, all-cause admissions initially declined by 35%, recovered to pre-pandemic levels, then increased by 24% following NPI cessation.
**Conclusion** NPIs had significant unintended consequences in ALRI-related health service utilisation, especially for infants <3 months, largely driven by the suppression and subsequent resurgence of RSV activity. This has prompted the need to understand viral transmission dynamics, particularly in young children to plan effective control measures.



## RISK FACTORS FOR RESPIRATORY SYNCYTIAL VIRUS ASSOCIATED COMMUNITY DEATHS IN ZAMBIAN INFANTS

Caitriona Murphy

**Background** Respiratory syncytial virus (RSV) is a major cause of infant mortality. Its epidemiology in low-middle-income countries is poorly understood. Risk factors associated with infant RSV deaths that occur in community settings are incompletely known.
**Methods** Community deaths for infants aged 4 days to 6 months were identified during a 3-year post-mortem RSV prevalence study at the main city morgue in Lusaka, Zambia where 80% of deaths are registered. This analysis focuses on the subset of deaths where an abbreviated verbal autopsy was available and intended to sort deaths into respiratory or non-respiratory causes by clinical adjudication. Posterior nasopharyngeal swabs were collected within 48 hours of death and tested for RSV using quantitative RT-PCR. Associations between potential risk factors were determined as relative risks with 95% confidence intervals.
**Results** We prospectively enrolled 798 community infant deaths with verbal autopsies and an RSV lab result, of which 62 were positive. The mean age was 10 weeks and 41.4% were male. Out of all deaths 44% were attributed to respiratory causes. RSV was detected in 7.8% of the community infants and was significantly associated with respiratory deaths (RR 4.0 95%CI: 2.2, 7.1). Infants aged 0 to 8 weeks had a 2.83 (95%CI: 1.30, 6.15) increased risk of dying with RSV compared to older infants. The risk of RSV for the 0 to 8-week age group increased to 5.24 (1.56, 33.14) with adjustment for demographics, parental education and geography. RSV deaths were increased with domiciliary overcrowding and were concentrated in poor and dense neighbourhoods in Lusaka (RR 2.00, 95%CI: 1.22, 3.27).
**Conclusion** RSV is a significant contributor to community respiratory deaths in this population, particularly in the first 3 months of life and in the more poor and dense parts of Lusaka.

## BURDEN OF RESPIRATORY SYNCYTIAL VIRUS INFECTION IN OLDER AND HIGH-RISK ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE EVIDENCE FROM DEVELOPED COUNTRIES

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**Background** Respiratory syncytial virus (RSV) infection has a significant health impact in older adults and adults with comorbidities (high-risk adults). We aimed to synthesise the evidence on the burden of RSV infection and RSV-related healthcare utilisation in these two populations.
**Methods** We searched Embase and Medline for papers published between 2000-2019 reporting the burden and clinical presentation of symptomatic RSV infection and the associated healthcare utilisation in developed countries among adults ⩾60 years old or adults ⩾18 years at high-risk. We calculated pooled estimates using a random-effects, inverse variance-weighted meta-analysis.
**Results** 103 out of 3429 articles met the inclusion criteria. Among older adults, an estimated 4.66% (95% confidence intervals (CI), 3.34-6.48) of symptomatic respiratory infections were caused by RSV in annual studies and 7.80% (95% CI, 5.77-10.45) in seasonal studies; with RSV related case fatality proportion (CFP) estimated at 8.18 (95% CI, 5.54-11.94). Among high-risk adults, mostly patients with immunodeficiency or cardiopulmonary disease, an estimated 7.03% (95% CI, 5.18-9.48) of symptomatic respiratory infections were caused by RSV in annual studies, and 7.69% (95% CI, 6.23-9.46) in seasonal studies, with CFP estimated at 9.88% (95% CI, 6.66-14.43). There were insufficient data to calculate pooled estimates on clinical presentation and healthcare-related utilisation.
**Conclusions** Older and high-risk adults frequently experience symptomatic RSV infection with appreciable mortality; however, detailed data on the disease burden of RSV is lacking. Improved surveillance and more research are both needed to quantify population-based disease burden and facilitate the development of RSV treatments and vaccines.



## PLANS TO CREATE AND PUBLISH A FORTNIGHTLY ELECTRONIC BULLETIN ON RSV ACTIVITY IN EUROPE AND THE ESTABLISHMENT OF A EUROPEAN LABORATORY NETWORK FOR RSV

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**Background** RSV epidemics can pose a huge burden to healthcare systems and several vaccines are currently in Phase 3 trials. Due to a lack of harmonised surveillance data, knowledge and monitoring of RSV is currently limited to sparse reporting in the European Union.
**Methods** Building on the outcomes of the RESCEU project, a consortium of European public health institutes are planning to gather expertise, data and resources to: a) develop a robust surveillance platform; b) initiate the collection of age-specific data; and c) publish a Fortnightly Electronic Bulletin on RSV activity. In addition, a Network of Laboratories is planned which aims to strengthen and harmonise RSV testing and surveillance in Europe.
**Results** These different activities will be implemented in 2022 and 2023. In 2022, we will identify a number of core participating countries, develop data upload templates and develop a format for the Fortnightly Electronic Bulletin. In 2023, we will publish the Bulletin. The European Laboratory Network for RSV will have a number of objectives, including: 1) promote the harmonisation of methods used for the detection and reporting of RSV data; 2) support the reporting of sequencing data to GISAID-RSV; and 3) create a library of Standard Operating Procedures.
**Conclusion** Under the umbrella of a European project, we plan to upgrade the quality of RSV surveillance in Europe in the coming years. This work will be done in close collaboration with ECDC, WHO Euro, the global reference laboratory in London, and national reference laboratories for RSV.

## UNRAVELING CIRCULATION DYNAMICS OF RSV BASED ON 10 YEARS OF ARI SURVEILLANCE IN MADAGASCAR (2011 – 2021)

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**Background** RSV is among the major threats of acute respiratory infection (ARI) in Malagasy under 5 years old children (CU5). Its annual incidence is estimated at 11299 hospitalizations in CU5. In Madagascar, seasonal epidemic occurs each year. We aim to understand factors that drive circulation dynamics of RSV in the country.
**Materials & Methods** A total of 266 partial sequences of RSV G gene detected from ARI surveillance in Madagascar were analyzed. Worldwide sequences including those closest to Madagascar was added. Spatial phylodynamic analyses were conducted using BEAST. Driver factors for repetitive circulation were determined by correlating meteorological factors with RSV cases using GAM and GLM.
**Preliminary Results** For RSV type A, a circulation pattern characterized by local evolution and possible multiple new introductions during the same epidemic was observed while for type B multiple introductions during the same epidemic occurred: circulating strains in 2014 originated from France and China, those spreading in 2017 came from Spain. Meanwhile, a significant positive effect on rainfall, humidity and temperature in RSV repetitive circulation ($p<0.001$) were observed.
**Conclusions**: This study demonstrates how the pattern of connectivity of Madagascar with the rest of the world can potentially affect the epidemiology of infectious diseases in the country. Knowing factors responsible for local introduction and dissemination of RSV may be helpful for clinicians in predicting epidemic occurrence to rapidly manage patients and reduce the number of hospitalizations and will be a key control for both classic and new emerging epidemic viruses and to adapt vaccine strategies.



## EPIDEMIOLOGICAL AND BIOLOGICAL ASPECTS OF RSV BASED ON 11 YEARS-SURVEILLANCE OF SARI IN MADAGASCAR

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**Background** In Madagascar, the incidence of RSV-associated hospitalization in children younger than 5 years is estimated at 11 299 annually. This study reports RSV results obtained through 11 years of well-functioning SARI surveillance.
**Methodology** The biological SARI surveillance is functional since 2011 in the country. Briefly, NP samples and clinical data were collected from suspected cases that consult 3 sentinel hospitals. RSV detection was routinely performed based on real-time PCR. Results were shared to local and international stakeholders.
**Results** From 2011 to 2021, 2324 nasopharyngeal samples from all age groups were tested. The rate of RSV detection was 37% with a significant risk of infection for children ⩽ 6 months (OR=4.4). Cough, dyspnea, rhinorrhea, and intercostal recession seemed to predict RSV infection. RSV detection occurred during the first semester of the year with a peak between February and March. BA and ON1 genotypes predominated during this period. In comparison to influenza, despite health control measures RSV continued to circulate during COVID-19 outbreak even if the intensity was lower than previous years.
**Conclusion** These results will be part of baseline information to evaluate vaccine effectiveness. Indeed, these data will inform and alert decision-makers to the impact of RSV diseases and its related complications that should be considered as a significant public health concern.

## ASSOCIATION BETWEEN RESPIRATORY SYNCYTIAL VIRAL INFECTION (RSV) AND ASTHMA OR WHEEZING IN CHILDHOOD: A DANISH REGISTER-BASED CASE-CONTROL STUDY

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**Background** In Denmark, RSV is associated with ~2,500 hospitalizations of children aged <5 years annually. Literature suggests that RSV infection in young children is associated with increased risk of respiratory disorders in later life. This study further evaluates the association between RSV infection in early life and later development of asthma or wheezing in Denmark.
**Methods** This is a nationwide nested case-control study. The source population generated two case populations: 1) children aged 6-17 years diagnosed with asthma (or ≥2 prescriptions for obstructive airway disease within 12 months); 2) children aged ≤6 years diagnosed with recurrent wheezing (≥3 episodes). Cases were age- and gender-matched to a random sample of children without asthma or wheezing (controls). Adjusted odds ratios for the association between RSV infection and asthma or wheezing were calculated using multiple logistic regression mutually adjusted for high risk factors, family history of atopic disease, number of gestational weeks, and birth weight.
**Results** The case population comprised 63,502 children with asthma and 1,695 with wheezing; controls comprised 254,008 and 6,780 children, respectively. Children with RSV infection had a 2.5-times (95% CI: 2.3, 2.6) greater risk of asthma and 6.4-times (95% CI: 5.0, 8.1) greater risk of recurrent wheezing vs controls (both P<0.001). Presence of high-risk factors and parental history of atopic disease were also significantly associated with diagnosis of asthma or wheezing.
**Conclusions** This study provides further evidence that documented RSV infection in early life is significantly associated with the later diagnosis of asthma and recurrent wheezing in Denmark.



## PHYLOGENETIC ANALYSIS OF HUMAN RESPIRATORY SYNCYTIAL VIRUS F PROTEIN IN CHILDREN UNDER 2 YEARS OF AGE WITH ACUTE RESPIRATORY INFECTION DURING 2015 AND 2016

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**Background and Aim** Human Respiratory Sensual Virus (HRSV) is the leading cause of acute lower respiratory tract infection in children (ALRTI) worldwide. Given the role of HRSV fusion surface protein (F) in pathogenesis, the development of immune responses, and prevention strategies, little is known about F molecular evolution. The present study was designed based on virus genotype determination based on complete F gene sequence, investigation of nucleotide changes in Palivizumab region, and phylogenetic analysis.
**Methods** In this study, RT-PCR test was performed on 180 respiratory samples of children under 2 years of age with acute respiratory symptoms to confirm the HRSV virus in the samples. The complete sequence of the F gene was performed on positive samples with three pairs of specific primers. Then, the complete sequence of the F gene was determined by bidirectional sequencing. Sequences were genotyped using the reference strain and nucleotide changes in the Palivizumab region were examined.
**Results** Out of 180 respiratory samples tested, 83 (46.1%) samples were HRSV positive. Of these, 27 samples were completely sequenced for the F gene. Phylogenetic analysis showed that all positive samples belonging to ON-1 genotype belonged to subgroup A and we did not have any mutations at the binding site of Palivizumab monoclonal antibody.
**Conclusion** Further studies in the HRSV outbreak season in different geographical regions of Iran are proposed to investigate the distribution of HRSV genotypes to better understand the epidemiology.

## CIRCULATION OF RESPIRATORY SYNCYTIAL VIRUS AMONG SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 INFECTION SUSPECTED PATIENTS DURING THE ONGOING COVID-19 PANDEMIC IN CENTRAL PROVINCE OF SRI LANKA

Shiyamalee Arunasalam

Respiratory syncytial virus (RSV) is one of the most common viruses infecting children worldwide and increasingly recognized as an important pathogen in elderly. During the COVID-19 pandemic, diagnosis is only focused on detecting SARS-CoV-2.Thus knowing the epidemiological patterns of other respiratory viruses including RSV is valuable to improve diagnostic efficacy in COVID-19 suspected patients.

A total of 223 respiratory samples from COVID-19 suspected patients with symptoms of ARTI received to National Hospital, Kandy, Sri Lanka were simultaneously tested using real time RT-PCR for 18 other respiratory viruses including RSV from 1st of January to 30th of June 2021.

Only 6% patients were eventually confirmed to have SARS-CoV-2 infection. Overall detection rate of other respiratory pathogens was 51% (113/223). Of the 113 virus positive patients, 18% were diagnosed with RSV infection. Human coronavirus (C229E,NL63), rhino/ enterovirus, parainfluenza virus, adeno virus, boca virus and influenza virus were 24%, 22%, 19%, 13%, 3% and 1%, respectively. Of the RSV infected patients, single infection with RSV A and RSV B was noted in 35% and 18%, respectively and mixed infection with RSV A and B was present in 47%. Age of RSV infected patients ranged from 47 days to 53 years and the majority were children (82%). All the RSV infected patients had fever and cough. Sore throat, crepitus, rhonchi and dyspnoea were noted in less than 50% of patients.

The current findings highlight the importance of diagnosing the other respiratory viruses including RSV and their clinical impact during the ongoing COVID-19 pandemic.



## RISK FACTORS FOR RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS HOSPITALIZATIONS IN CHILDREN WITH CHRONIC DISEASES

Einat Shmueli

**Background** Respiratory syncytial virus (RSV) bronchiolitis is the most common lower respiratory tract disorder causing hospitalization in infants. Due to decreased hospitalization rates of premature infants following Palivizumab immune prophylaxis, the proportion of infants with chronic diseases not eligible for Palivizumab has increased.
**Aim** To characterize infants hospitalized during 2014-2018 with RSV bronchiolitis, to compare between those with and without chronic conditions, and to identify risk factors for severe disease.
**Methods** This retrospective study analyzed demographic and clinical data of patients younger than two years admitted with bronchiolitis during four consecutive RSV seasons.
**Results** Of 1124 hospitalizations due to RSV bronchiolitis, 244 (22%) were in infants with chronic diseases. Although 20/1124 qualified for RSV prophylaxis, only eight received immune prophylaxis. Compared to otherwise healthy infants, children with chronic diseases had longer hospitalizations, median 4.8 days (interquartile range (IQR) 3.4-8.3) vs 3.7 days (2.7-5.1), p<0.001; and higher pediatric intensive care unit (PICU) and readmission rates (9% vs 4.5%, p=0.007 and 3% vs 1%, p=0.055, respectively). Children with Down's syndrome comprised 2% of all hospitalizations, but 8% of PICU admissions; their median length of hospitalization was 10.7 days (IQR 6.6-17.6). Respiratory tract malformations were present in 2% of hospitalizations, and comprised 4% of PICU admissions.
**Conclusion** Among infants admitted with RSV bronchiolitis, those with chronic diseases had longer hospitalizations and higher rates of transfer to the PICU. Children with multiple comorbidities, and especially those with Down's syndrome, are at particularly high risk for severe hospitalization and may benefit from RSV immune prophylaxis.

| Characteristic | Chronic morbidities n=244 (%) | Healthy n=880 (%) | p-value |
|---|---|---|---|
| **Fever ≥ 38°C** | 147 (60.2%) | 455 (51.7%) | 0.018 |
| **CRP ≥ 2mg/dl[a]** | 91 (55.2%) | 253 (50.5%) | 0.32 |
| **O2 saturation < 90%** | 169 (69.5%) | 553 (63.0%) | 0.059 |
| **Co-infection[b]** | 88[c] | 300[c] | 0.45 |
| **Adeno, n=383** | 86 (35.2%) | 296 (33.6%) | |
| **Influenza, n=13** | 4 (1.6%) | 9 (1.0%) | |
| **LOS, median (IQR)** | 4.8 (3.4-8.3) | 3.7 (2.7-5.1) | <0.001 |
| **PICU admission, n=62** | 22 (9.0%) | 40 (4.5%) | 0.007[d] |
| **Age <2m** | 6 | 28 | |
| **2m-1 y** | 13 | 11 | |
| **>1y** | 3 | 1 | |
| **Readmission, n=16** | 7 (2.8%) | 9 (1.0%) | 0.055 |

RSV= Respiratory syncytial virus; CRP=C-reactive protein; O2=Oxygen; LOS=length of stay; IQR=interquartile range; PICU= pediatric intensive care unit; m=month; y=year

[a]Out of 666 tested for CRP- 165 with chronic morbidities and 501 healthy infants

[b]Out of 1062 tested for adenovirus (225 with chronic morbidities, 837 healthy) and 227 tested for influenza virus (44 with chronic morbidities, 183 healthy)

[c]4/88 and 5/300 tested positive for both Adeno and Influenza viruses

[d] comparing all age groups combined

## ASSESSING RESPIRATORY SYNCYTIAL VIRUS INCIDENCE AND SEVERITY IN A COMMUNITY-BASED PROSPECTIVE COHORT OF CHILDREN AGED 0-14 YEARS IN MANAGUA, NICARAGUA

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**Background** Respiratory syncytial virus (RSV) is a substantial source of severe illness like acute lower respiratory infections (ALRI), particularly in children.
**Methods** Using a community-based prospective cohort we assessed the burden and severity of symptomatic RSV among Nicaraguan children aged 0-14 years. RSV was detected and subtyped using real-time RT-PCR. ALRI was defined as physician diagnosis of pneumonia, bronchiolitis, bronchitis, or bronchial hyperreactivity.
**Results** Between 2011-2016, 2575 children participated in the cohort. Of these, 630 (24.5%) had at least one episode of symptomatic RSV and 194 (7.5%) had multiple episodes. Subtype was identified in 610 (74.0%) episodes: 442 (72.5%) RSV-A, 162 (26.5%) RSV-B, and 6 (1%) testing positive for both. Children under two years displayed the highest incidence of RSV, 269.3 per 1000 person-years (95% Confidence Interval [CI]: 242.1, 299.5). In older age groups, RSV incidence decreased rapidly, specifically 145.6 (95% CI: 129.9, 163.1), 37.9 (95% CI: 31.9, 45.0), 19.3 (95%CI:14.9, 25.0) per 1000 person-years among children aged 2-4, 5-9, and 10-14 years respectively. Participants aged <2 also had the highest rates of RSV-ALRI (12.3 per 1000 person-years, 95% CI: 10.2, 14.8), which was 2.1, 9.5, and 17.3 times that of participants aged 2-4, 5-9, and 10-14 years respectively. Those <2 years had 24 RSV-hospitalizations, while children over 2 had only 8.
**Conclusions** A substantial burden of symptomatic and severe RSV exists among children in Managua, Nicaragua. While older children did present with RSV, the rates of symptomatic and severe RSV decreased by as much as 95% beyond age two.



## SEASONALITY METHODS USED TO DETERMINE THE TIMING OF RSV EPIDEMICS: A SYSTEMATIC AND COMPARATIVE REVIEW

Lisa Staadegaard

**Background** Understanding the timing of Respiratory Syncytial Virus (RSV) epidemics is important to effectively implement time sensitive prevention and control measures (e.g. Palivizumab). Several analytical methods exist to define seasonality, but no clear overview as well as guidance on their application currently exists. We aimed to characterize methods used to estimate RSV seasonality.
**Methods** We performed a systematic literature review in PubMed and included articles published between 2016 and 2021 that used estimation techniques to determine the start and end of a RSV season. Full text articles were searched for other relevant publications. For each included publication, study characteristics were extracted as well as details on data collection and seasonality estimation method(s) used.
**Results** We identified 1,145 peer-reviewed articles of which 30 met the inclusion criteria. After "snowballing", a total of 40 articles was included. As some articles included multiple estimation methods we identified a total of 57 estimations, of which the methods could be put into 10 broad categories (Table 1).
**Conclusion** A wide variety of methods have been developed to define RSV seasonality. The choice of a method is restricted by the availability of data, the timing (real-time or retrospective analysis) and is complicated by the type of RSV epidemics in the region (e.g. less clearly defined epidemics are seen in the tropics). We will initiate an analysis using global surveillance data from the GERi project to identify the most appropriate method to define RSV seasonality in different contexts.

Table 1: categorization and description of seasonality estimation methods.

| Data availability | Timing framework | Method | Definition |
|---|---|---|---|
| Numerator and Denominator | Real-time (potential) | % positivity threshold | First till last of two consecutive weeks where % positivity is above threshold |
| | | Moving Epidemic Method (MEM) | First till last week when curve exceeds the epidemic threshold |
| | Retrospective | Mean threshold | Various |
| Numerator only | Real-time (potential) | # of cases | Various |
| | | MEM | First till last week when curve exceeds the epidemic threshold |
| | | Change point analysis | No formal definition, modelled via change point analysis |
| | Retrospective | 1.2% threshold | First till last week when RSV detections exceed 1.2% of total RSV positive specimens |
| | | 60% threshold | First till last week when the number of RSV cases identified is above 60% from the average weekly identifications for that year |
| | | Mean threshold | Above the average monthly/weekly number of cases |
| | | Average Annual Percentage | First till last month of the longest consecutive months to be included in the sorted AAP 75% |
| | | Search index | Total number of weeks where the minimum percentile rank was greater than the percentile value. |



## OUTSMART-RSV MOLECULAR SURVEILLANCE IN THE UNITED STATES OVER THE 2015-2021 RSV SEASONS

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**Background** Nirsevimab is an extended half-life monoclonal antibody that targets the prefusion RSV F protein (AA 62-69 and 196-212 within site ∅) in Phase 3 clinical development to prevent lower respiratory tract infections caused by RSV in all infants. OUTSMART-RSV is a multi-year molecular surveillance study to monitor prevalence and distribution of United States RSV strains and track the emergence of RSV F variants and their susceptibility to nirsevimab neutralization.
**Methods** RSV-positive nasal samples collected from participating hospitals each RSV season were sequenced. Identified RSV F variants were engineered and tested for nirsevimab neutralization.
**Results** Across 6 RSV seasons (2015–2021), 3921 RSV G HVR2–F sequences (RSV A: N=1954; RSV B: N=1967) were obtained from 4879 RSV-positive samples. RSV A ON1 (2015–2016, 2019–2021) and RSV B BA9 (2016–2019) cocirculated with fluctuating predominance. Most RSV were from infants 99% conserved. Variations in all 6 RSV F protein antigenic sites were intermittently observed; emergent polymorphisms at site ∅ (I206M:Q209R) and site V (L172Q:S173L:K191R) progressed to 95–100% among RSV B strains. Nirsevimab retained neutralization activity against nearly all recombinant RSV viruses tested. RSV B F variants that conferred significant reduced susceptibility to nirsevimab: (N201S: 127-fold; N201T: >406-fold) were rare (<0.5%) and did not increase in prevalence.
**Conclusions** As RSV continues to evolve, ongoing molecular epidemiology and surveillance of circulating strains is necessary to track potential neutralization escape variants that may impact the effectiveness of nirsevimab.

## OUT-OF-SEASON CIRCULATION OF SEASONAL RESPIRATORY VIRUSES IN THE NETHERLANDS DURING THE COVID-19 PANDEMIC

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**Background** With an aim to reduce the circulation of SARS-CoV-2, non-pharmaceutical interventions (NPIs), were introduced in the Netherlands during a large part of 2020 and 2021. These measures did not only impact the circulation of SARS-CoV-2, but also of other respiratory pathogens.
**Methods** We monitored the weekly circulation of respiratory pathogens in the Netherlands. Samples of patients with acute respiratory infections were obtained by the general practitioner (GP) sentinel surveillance and tested for respiratory viruses. In addition, the national virological laboratory surveillance system includes weekly data on the number of positive test results for respiratory pathogens originating mainly from hospitalized patients.
**Results** During the 2020/21 winter, circulation of several respiratory viruses was highly diminished, resulting in hardly any detections of influenza virus, RSV, and other seasonal respiratory viruses. However, after measures were eased and schools reopened, a surge of infections appeared for several respiratory viruses. All viruses seemed to follow a distinct pattern. We observed an exceptional high out-of-season peak for RSV detections during summer.
**Conclusion** The NPI's that were introduced during the COVID-19 pandemic have caused a disruption in the circulation of several respiratory viruses in the Netherlands, leading to an alteration of the usual patterns of circulation. It is important for surveillance systems in the Netherlands, Europe and elsewhere to monitor patients with acute respiratory infections with integrated virological testing to better understand the impact of these different viruses on society and the effect of the 'reset' of 2020/2021 on the patterns of circulation of several pathogens.



## RSV INCIDENCE AMONG PRIVATELY INSURED U.S. CHILDREN UNDER 5 YEARS OF AGE

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**Background** Respiratory syncytial virus (RSV) is a major contributor to lower respiratory tract infections (LRTIs) in infants. Epidemiologic data on milder RSV infections requiring only outpatient care and among children ≥2 years are limited. Approaches to define unique RSV episodes have varied.
**Methods** Using IBM® MarketScan® Commercial Claims Databases 2011-2019, we estimated seasonal incidence rates among children <5 years between November-February. Three approaches were used to consider multiple encounters possibly representing one episode. For each outcome (LRTIs, RSV-ARIs [upper and lower respiratory infections], and RSV-LRTIs), episodes were defined by requiring a 30-day gap between encounters (Approach 1) or by allowing 1 infection per setting (in- or outpatient) per season (Approach 2). Approach 3 counted each medical encounter.
**Results** Approach 1 and 2 resulted in similar estimates: 230 and 217 LRTIs, 42 and 41 RSV-ARIs, and 34 and 33 RSV-LRTI (in- and outpatient episodes combined) per 10,000 children-months. Approach 3 found approximately one-third more: 300 LRTI, 68 RSV-ARI, and 55 RSV-LRTI encounters per 10,000 children-month. The number of inpatient encounters and episodes was similar with 9 inpatient encounters for LRTIs, 5 for RSV-ARIs, and 5 for RSV-LRTIs per 10,000 children-month. RSV-LRTI incidences were stable across seasons, varied across regions (outpatient 20-80; inpatient 3-6 encounters), and decreased rapidly with each year of increasing age (0-4 years): 164/64/23/9/4 for outpatient and 16/5/2/1/0.4 for inpatient encounters.
**Conclusions** Outpatient RSV episodes added appreciable disease burden regardless of approaches. Most identified RSV episodes were RSV-LRTI, with proportionally higher contribution to inpatient LRTIs and among infants.

## MEASURING THE CLINICAL AND SOCIO-ECONOMIC DISEASE BURDEN OF RSV INFECTIONS IN YOUNG CHILDREN IN PRIMARY CARE IN 5 EUROPEAN COUNTRIES: THE RSV COMNET STUDY

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**Background** RSV burden of disease studies have mostly focused on morbidity and mortality rates, with relatively few studies investigating the clinical and socio-economic burden, especially in primary care. The aim of the RSV ComNet study is to measure the clinical and socio-economic disease burden in young children with RSV in primary care.
**Methods** The study has a prospective cohort design with a follow-up of 30 days and is based on a protocol that was developed and evaluated in Italy and the Netherlands during the winter of 2019/20. Data will be collected in 5 countries in 2021/22: Italy, the United Kingdom, Spain, Belgium and the Netherlands. Children, aged <5 years, consulting a primary care physician i.e. pediatrician or general practitioner, with symptoms of an acute respiratory infection (ARI), and a laboratory confirmed diagnosis of RSV will be eligible to participate. At the day of swabbing physicians will complete a short questionnaire on clinical symptoms and medical history of the child. After approximately 14 and 30 days, parents will complete a questionnaire regarding the health care use, days of illness, socio-economic impact, current health status, and quality of life of the child and guardian. In the second parental questionnaire complications related to the RSV infection (e.g. pneumonia) will also be collected.
**Discussion** The RSV ComNet study will contribute to knowledge regarding the disease burden of RSV infections in young children in primary care. This knowledge is relevant for many purposes, including modelling studies used to evaluate the cost-effectiveness of future RSV interventions.

## TIME-VARYING ASSOCIATION BETWEEN SEVERE RESPIRATORY SYNCYTIAL VIRUS INFECTIONS AND SUBSEQUENT SEVERE ASTHMA AND WHEEZE, AND INFLUENCES OF AGE AT THE INFECTION

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**Background** This study aimed to assess the time-varying association between RSV and subsequent asthma and wheeze admission, and explore how the association was affected by the age at RSV infection.
**Methods** We retrospectively followed up a cohort of 23,365 children for a median of 6.9 years using Scottish health databases. Children who were born between 2001 and 2013 and had RSV-associated respiratory tract infection (RTI) admissions under 2 years were in the exposed group; those with unintentional accident admissions under 2 years comprised the control group. The Cox proportional-hazards model was used to report adjusted hazard ratios (HR) of RSV admissions on subsequent asthma and wheeze admissions. We did subgroup analyses by follow-up years. We also explored how this association was affected by the age at first RSV admission.
**Results** The association persisted for 6 years in children whose first RSV-RTI admission occurred at 6-23 months of age, with an adjusted HR (95% CI) of 3.9 (3.1-4.9) for the first 2 years, 2.3 (1.6-3.2) for 2-< 4 years, and 1.9 (1.2-2.9) for 4-<6 years of follow up. In contrast, the association was only significant for the first 2 years after first RSV-RTI admissions occurring at 0-5 months.
**Discussions** We found a more persistent association for subsequent severe asthma and wheeze in children whose first severe RSV infection occurred at 6-23 months compared to those whose first severe RSV infection occurred at 0-6 months. This provides new evidence for further assessment of the association and for RSV intervention programmes.

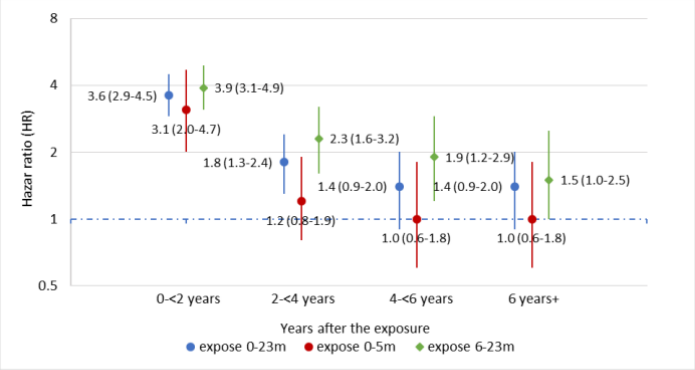


Figure 1. Hazard ratios (HR) of first asthma and wheeze admission in children with RSV-RTI admission at 0-23 months, 0-5 months, and 6-23 months of age.

X-axis marks follow-up years after the exposure (i.e. the first RSV-RTI admission; the first accident admission). Blue colours show the HR estimates for children who were exposed at 0-23 months of age. Red colours show the HR estimates for those who were exposed at 0-5 months of age. Green colours show the HR estimates for those who were exposed at 6-23 months of age. M: months. RSV-RTI: respiratory syncytial virus associated respiratory tract infection.

## RSV-ASSOCIATED HOSPITALIZATION BURDEN ACROSS AGE AND SOCIOECONOMIC GROUPS

Zhe Zheng

**Background** Surveillance for Respiratory Syncytial Virus (RSV) likely captures just a fraction of the burden of disease. Understanding the burden of severe disease and disparities between populations can help to inform upcoming RSV vaccine programs and to improve surveillance.
**Methods** We obtained monthly age-, ZIP code- and cause-specific hospitalizations in New York, New Jersey, and Washington from the US State Inpatient Databases (2005-2014). We estimated the incidence of respiratory hospitalizations attributable to RSV by age and by socioeconomic status using Negative Binomial regression models with identity link. This model quantified the association between RSV activity and all-cause respiratory hospitalization while controlling for temporal trend and seasonality. We compared the estimated RSV hospitalizations with the reported RSV hospitalizations to estimate the underreporting rate in the different sub-populations.
**Results** The estimated RSV respiratory hospitalization rates were much higher in low socioeconomic status groups in young children. Reported rates of RSV hospitalization represent a significant undercount, particularly in adults. among children age <1 year 68 – 72% of the estimated burden of RSV was captured in the reported statistics; while < 3% of the estimated RSV cases were recorded as such in the elderly.
**Conclusions** RSV causes a considerable hospitalization burden in young children and the elderly in the U.S. To substantially reduce the burden of RSV hospitalizations, vaccination strategies should not only target young children but also the elderly. RSV incidence in the elderly is very much underreported. A better RSV surveillance system for the elderly group is needed.



## SO BIG AND STILL UNDERPOWERED? ACCOUNTING FOR YEAR-TO-YEAR VARIATION IN ATTACK RATES IN SAMPLE SIZE CALCULATIONS FOR RSV VACCINE EFFICACY TRIALS

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**Background** Planning phase 3 vaccine trials is a major challenge. Year-to-year variation in attack rates of seasonal infectious diseases adds to this challenge. We aimed to illustrate the impact of year-to-year variation in attack rates on the likelihood of demonstrating efficacy against respiratory viruses.
**Methods** We used maternal RSV vaccine efficacy trials against RSV-associated hospitalizations as an example. The power to show VE for varying attack rates but constant VE and sample size was calculated from the expected number of events with Fisher's exact test. Attack rates were selected to reflect realistic relative year-to-year variations using observational studies identified through literature review. Eight scenarios including varying number of countries and seasons were developed to assess the influence of these trial parameters.
**Results** Including up to three seasons decreased the width of the interquartile range for power. As statistical power was centered closer around 80%, least powered trials had higher statistical power to show VE when up to three seasons were included. In all scenarios, at least half of the trials had< 80% power target. For three-season trials, increasing sample size by 10% was sufficient to reduce the proportion of underpowered trials (<80% power target) to less than one-quarter of trials.
**Conclusions** Year-to-year variation in attack rates should be accounted for during trial design. Mitigation strategies include recruiting over more seasons, adding subjects to account for the uncertainty, or adapting the sample size or the selection of site according to the results of interim analyses during the trial.

## SAFETY AND IMMUNOGENICITY OF MRNA-1345, AN MRNA-BASED VACCINE AGAINST RESPIRATORY SYNCYTIAL VIRUS IN ADULTS

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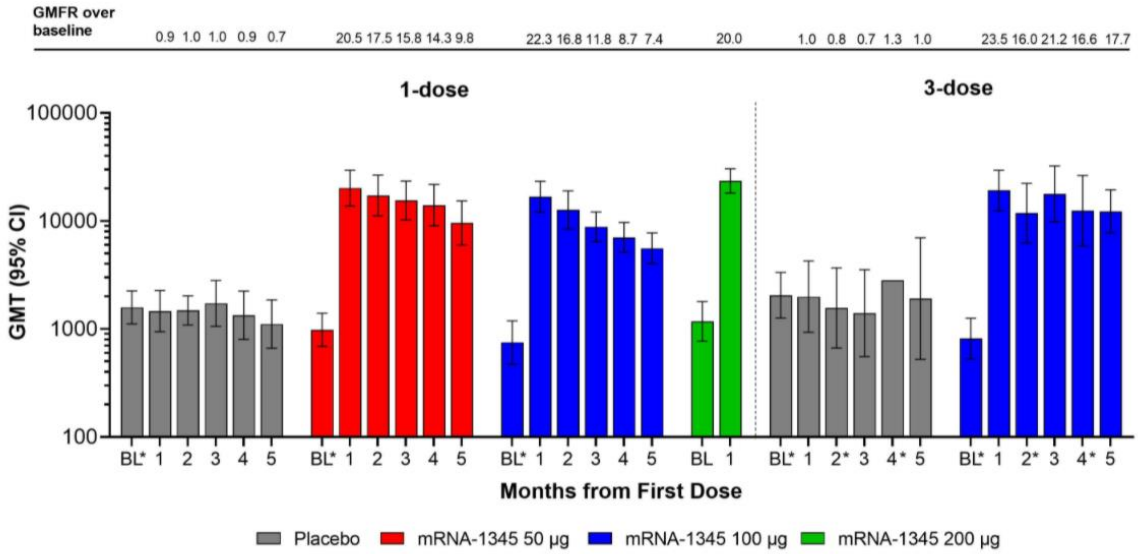
**Background** RSV is a global health concern for which no vaccine is available. A lipid nanoparticle-encapsulated mRNA-based RSV vaccine (mRNA-1345) is under clinical investigation.
**Methods** This phase 1, randomized, observer-blind, placebo-controlled, dose-ranging study assessed safety and immunogenicity of mRNA-1345 in adults and children (NCT04528719). Participants were randomized to receive mRNA-1345 or placebo; cohorts included healthy younger adults (18-49 years; 1 dose mRNA-1345 50, 100, or 200µg or 3 doses mRNA-1345 100µg 56 days apart; n=100), older adults (65-79 years; 2 doses of mRNA-1345 12.5, 25, 50, 100, or 200µg 12 months apart; n=300), women of childbearing potential (18-40 years; 1 dose of mRNA-1345 12.5, 25, or 50µg; n=180), and healthy RSV-seropositive children (12-59 months; 3 doses of mRNA-1345 30 or 100µg 56 days apart; n=40).
**Results** mRNA-1345 was well-tolerated in younger adults at all dose levels. At month 1, a single injection of mRNA-1345 increased RSV-A (Figure) and RSV-B neutralizing titers at all dose levels (geometric mean fold rise [GMFR]: RSV-A, ⩾20.0; RSV-B, ⩾11.7), with no dose response observed. The GMFR at month 5 was >7.4. In the 3-dose mRNA-1345 100-µg group, doses 2 and 3 did not further increase neutralizing antibody titers but helped maintain peak titers through month 5 relative to dose 1 of mRNA-1345 (Figure). Analyses for all other populations are ongoing.
**Conclusion** Overall, mRNA-1345 is well-tolerated as an RSV vaccine in younger adults and induces a functional and persistent immune response, supporting its continued development as an RSV vaccine.

**Figure. Serum neutralizing antibody titers for RSV-A in younger adults**




BL, baseline; CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer; RSV, respiratory syncytial virus.
CIs are only plotted when n >2.
*Vaccine dosing timepoints.

## OPTIMIZATION OF ALUM-FORMULATION FOR DELIVERY OF RSV G CENTRAL CONSERVED REGION PEPTIDE IMPROVES VACCINE IMMUNOGENICITY AND EFFICACY AGAINST VIRAL INFECTION

Xi Chen

Respiratory syncytial virus (RSV) is a leading cause of severe lower respiratory tract illness in both infants and elderly, and an RSV vaccine remains a critical unmet public health need. The RSV virion has two major surface glycoproteins, F and G, both of which are targets for neutralizing antibody responses. Although the most potently neutralizing antibodies target the F protein, it is also known that the central conserved region of G (Gcc) can elicit protective responses that complement and augment F-specific immunity. To elicit robust Gcc-specific immunity, we utilized prior findings demonstrating that improved coupling of antigens to alum can increase their immunogenicity. We found that a Gcc peptide with phosphorylated serine residues at the C terminus (pSerGcc) had improved binding to alum, with increased complex stability in serum as compared to conventional alum-adsorbed Gcc. The improved binding to alum mediated by pSerGcc translated to superior Gcc-specific antibody responses in both mice and non-human primates , as well as improved protection against viral challenge in the mouse model. Through this work, we have extended a previously published approach to eliciting robust peptide-specific antibody responses using a well characterized and safe adjuvant. This approach not only resulted in the identification of a promising RSV vaccine candidate, but also may represent a platform that can be applied more broadly to other vaccine antigens.



## METHANOL LEAF EXTRACT OF ASPILIA AFRICANA INHIBIT RSV REPLICATION INVITRO

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**Background** Respiratory syncytial virus (RSV) on a global scale remains the most common cause of viral lower respiratory tract infection in infants and children, while also having a substantial impact on the elderly. There is currently no approved vaccination or safe and specific antiviral drug that can be used to combat the virus. Medicinal plants have already been identified as a possible source for the development of anti-RSV therapies.
**Methods** In this present study, the anti-RSV and cell cytotoxicity effects of methanol extract of A. africana were tested in Hep-2 and Vero cells of human origin, using viral plaque reduction and corresponding cell viability techniques. The related set-up for studies of A. africana extract on cell viability was performed using the standard method of thiazolyl blue tetrazolium bromide (MTT) reduction in Hep-2 cells.
**Results** The results of the evaluation of the extract of A. africana showed anti-RSV activities with inhibition of RSV at IC50, 42.5 ± 8.89 µg/ml, while the cell cytotoxic effect in Hep2 cells recorded was TC50, 121.4. ± 7.21 µg/ml.
**Conclusion** As a result, our findings reveal that the methanol extract of A. africana exhibits anti-RSV activity and has a moderate influence on recipient host cell viability, implying that target chemical compounds against RSV can be develop from the extract.

*RSV, antiviral, cytotoxicity*

## PROTECTIVE EFFICACY INDUCED AGAINST RSV BY AN INACTIVATED FORMULATED VACCINE AFTER MUCOSAL APPLICATION

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Asthma is under the most widespread chronic diseases among children, with severe impacts on their life quality. Currently available treatments can lead to significant side effects in longtime-use, so alternative treatments are urgently needed. It has been shown that children are more likely to develop asthma, after repeated infections with respiratory syncytial virus (RSV) in infancy or early childhood. We investigate whether a vaccination against RSV can protect from repeated infections and thus prevent asthma. Currently no vaccine is approved to protect against RSV infections.

Three vaccine candidates are tested side-by-side in an RSV-infection-mouse-model. We included a candidate based on killed RSV via low-energy electron beam inactivation. To enhance the uptake, this is formulated with nanoparticular liposomes or lipoplexes. Furthermore, we tested a new vector-delivery-platform based on non-human-papillomavirus-capsids (nhPV) for transfer of RSV-F encoding plasmid-DNA to the airway mucosa.

The vaccines were tested in a homologous prime-boost regimen with 4weeks interval in BALB/c mice via intranasal route. One month after boost mice were challenged with 1x106 ffu RSV and scored for 5days. We analyzed protective efficacy by the viral load in lungs of challenged animals and immunogenicity by RSV-binding and -neutralizing antibodies in serum samples.

Surprisingly DNA delivery by nhPV-vector system showed only slight protection in the challenged animals. However, the formulated inactivated virus-composition showed promising effects with a 171-fold reduction of the virus load in lungs.

In conclusion, we found a promising inactivated vaccine candidate for a mucosal application against RSV. After optimization we will translate the mucosal inactivated vaccine delivery into clinical trials to evaluate safety and efficacy against RSV in human challenge experiments



## EFFICACY, SAFETY, AND IMMUNOGENICITY OF AD26.RSV.PREF-BASED VACCINE IN ADULTS AGED ≥65 YEARS WITH OR WITHOUT ADDITIONAL RISK FACTORS FOR RSV-MEDIATED LOWER RESPIRATORY TRACT DISEASE

Ann R. Falsey[1], Kristi Williams[2], Efi Gymnopoulou[3], Stephan Bart[4], John Ervin[5], Arangassery Rosemary Bastian[6], Joris Menten[3], Els De Paepe[3], Hilde de Boer[7], Sjouke Vandenberghe[3], Eric Chan[8], Jerald Sadoff[6], Macaya Douoguih[6], Benoit Callendret[6], Christy A. Comeaux[6], Esther Heijnen[6], on behalf of the CYPRESS Investigators

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**Background** Respiratory syncytial virus (RSV) can cause serious lower respiratory tract disease (LRTD) in older adults. We evaluated efficacy, safety, and immunogenicity of an Ad26.RSV.preF-based vaccine for prevention of RSV-mediated LRTD in adults aged ≥65 years with or without additional risk factors for severe disease.
**Methods** CYPRESS (NCT03982199) is a randomized, double-blind, placebo-controlled Phase 2b proof-of-concept trial. Before the RSV season, adults aged ≥65 years were randomized 1:1 to Ad26.RSV.preF-based vaccine or placebo. The primary endpoint was the first occurrence of RT-PCR-confirmed RSV-mediated LRTD according to any of 3 case definitions: (CD1) ≥3 symptoms of lower respiratory tract infection (LRTI), (CD2) ≥2 LRTI symptoms, or (CD3) ≥2 LRTI symptoms or ≥1 LRTI + ≥1 systemic symptom. Vaccine efficacy, safety, and immunogenicity were evaluated by subgroup indicating presence of additional risk factors for severe disease defined as chronic cardiopulmonary disease or a broader definition including chronic kidney disease and diabetes.
**Results** Among 5782 participants, additional risk factors were present in 25.4% (cardiopulmonary disease) or 40.1% (broader definition). Using CD1, vaccine efficacy was 80.0% (94.2% CI: 52.2-92.9%) in the overall study population, 60.3% (95% CI: −142.2-96.2%)/68.3% (−27.1-94.5%) in participants with additional risk factors by cardiopulmonary/broad definition, and 83.9% (53.4-95.9%)/85.2% (50.3-97.2%) in those without additional risk factors. Ad26.RSV.preF was safe, well tolerated, and elicited similar robust humoral and cellular immune responses in participants with or without additional risk factors.
**Conclusions** Ad26.RSV.preF-based vaccine was safe, immunogenic, and effective against RSV-mediated LRTD in older adults with or without additional risk factors for severe disease.

## SAFETY AND TOLERABILITY OF AN AD26.RSV.PRE–F-BASED VACCINE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2B STUDY IN ADULTS AGED ≥65 YEARS

Ann R. Falsey[1], Kristi Williams[2], Efi Gymnopoulou[3], Stephan Bart[4], John Ervin[5], Arangassery Rosemary Bastian[6], Joris Menten[3], Els De Paepe[3], Hilde de Boer[7], Sjouke Vandenberghe[3], Eric Chan[8], Jerald Sadoff[6], Macaya Douoguih[6], Benoit Callendret[6], Esther Heijnen[6], Christy A. Comeaux[6], on behalf of the CYPRESS Investigators

1. University of Rochester School of Medicine, Rochester, NY, USA; 2. Janssen Research and Development, Spring House, PA, USA; 3. Janssen Infectious Diseases, Beerse, Belgium; 4. Optimal Research, LLC/Synexus Clinical Research/AES, Woodstock, MD, USA; 5. AMR Kansas City, Kansas City, MO, USA; 6. Janssen Vaccines & Prevention BV, Leiden, The Netherlands; 7. Janssen-Cilag, Breda, The Netherlands; 8Janssen Global Services, LLC, Raritan, NJ, USA.

**Background** Respiratory syncytial virus (RSV) can cause severe lower respiratory tract disease in older adults; there is currently no approved vaccine. We assessed the safety and reactogenicity of an Ad26.RSV.preF-based vaccine in a Phase 2b proof-of-concept trial in adults aged ≥65 years.
**Methods** CYPRESS (NCT03982199) is a randomized, double-blind, placebo-controlled Phase 2b trial. Adults aged ≥65 years were randomized 1:1 before the RSV season to receive Ad26.RSV.preF-based vaccine or placebo. Solicited adverse events (AEs; fatigue, headache, nausea, myalgia, fever, injection site reactions) and unsolicited AEs were assessed at vaccination (Day 1) to Day 8 and Day 29, respectively, in a subset of 695 participants (vaccine, n=348; placebo, n=347). All participants were followed for serious AEs (SAEs) until the end of the RSV season or 6 months after vaccination, whichever occurred later.
**Results** A total of 5728 participants were randomized and received vaccine or placebo (n=2891 in each group). The frequency of solicited AEs and Grade ≥3 solicited AEs was 51.4% and 3.2% in the vaccine group and 20.2% and 0.6% in the placebo group, respectively. The most frequent solicited AEs in the vaccine group were fatigue, myalgia, headache, and injection site pain/tenderness. The rate of unsolicited AEs and Grade ≥3 unsolicited AEs were similar between the vaccine (16.7% and 1.7%) and placebo (14.4% and 1.4%) groups. The rate of SAEs was similar between groups (vaccine, 4.6%; placebo, 4.7%); none were considered to be related to the vaccine.
**Conclusions** Ad26.RSV.preF-based vaccine was safe and well tolerated in adults aged ≥65 years.



## AN IMMUNOINFORMATICS-BASED APPROACH TO DESIGN A POPULATION-SPECIFIC VACCINE AGAINST RSV

Carla Goldin, Sofia Balestra, Sebastián Esperante, Fernando Polack, Damian Alvarez-Paggi

Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory infections (ALRI) in young children around the world. Although the development of an effective vaccine has been a priority for the past 50 years, an effective and safe formulation is not yet available.

We are currently employing state-of-the-art immunoinformatics techniques to design a new multiepitope-based vaccine with the aim of conferring cellular and humoral protection against RSV, analyzing the viral proteome for potential T and B epitopes which are specifically immunogenic for populations living in South America, Africa and South Asia, considering population-level distribution of Human Leukocyte Antigen (HLA) genes. To achieve this, we are investigating the vaccine target populations such as sub-Saharan African and Indian populations, to determine their most prevalent HLAs. We are using this information to predict the strongest binding epitopes of RSV proteome to HLA I and HLA II molecules, using NetMHCpan-4.1 and NetMHCIIpan-4.0, respectively. We will select the peptides for the final formulation in order to ensure optimal HLA population coverage. Furthermore, we predict linear epitopes for RSV membrane proteins (using Bepipred). Finally, we will test the best arrangements for the polytope, with the aim of avoiding the formation of new epitopes, anticipating side effects. These results will enable the inclusion of multiple epitopes onto a novel modular platform currently under development by our research group.

In conclusion, we are confident this computational approach enables a rational design of a potentially effective vaccine prototype.

## IMPACT OF RILEMATOVIR ON PATIENT-REPORTED OUTCOMES IN ADULTS INFECTED WITH RESPIRATORY SYNCYTIAL VIRUS: RESULTS FROM A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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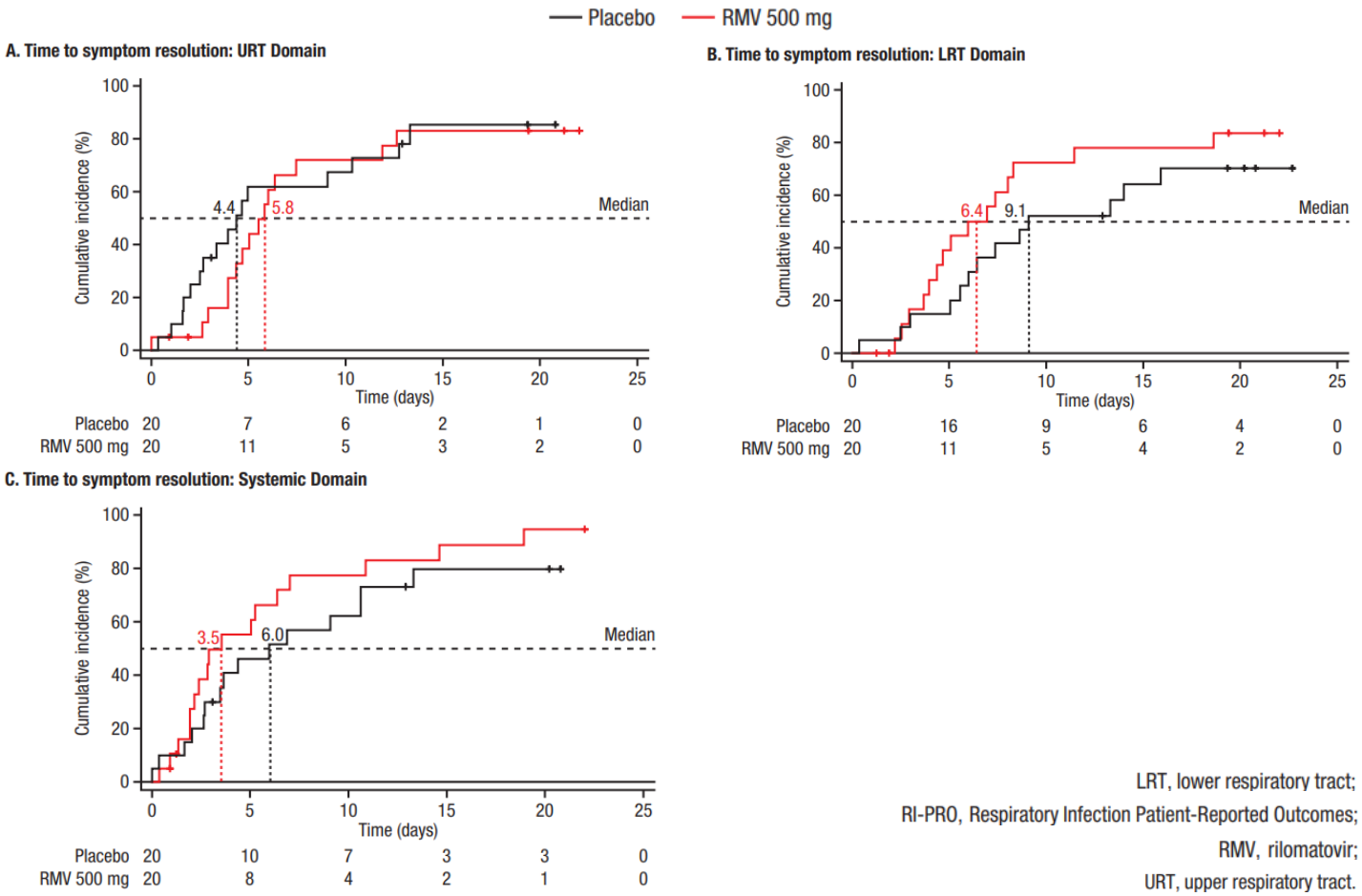
**Background** Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract disease (LRTD) in older and high-risk adults. Rilematovir (RMV; JNJ-53718678) is an investigational RSV-specific fusion inhibitor for the treatment of RSV infection.
**Methods** In this Phase 2a, randomized, double-blind, placebo-controlled study, non-hospitalized adults aged ⩾18 years with laboratory-confirmed RSV infection ⩽5 days from symptom onset were randomized 1:1:1 to RMV (80 mg or 500 mg) or placebo once daily for 7 days, with follow-up through Day 28. Clinical outcomes were assessed by Kaplan-Meier estimates of median time to resolution (TTR) of symptoms in the 4 RSV-relevant domains of the Respiratory Infection-Patient Reported Outcomes (RI-PRO) questionnaire: nose and throat (upper respiratory tract [URT]), chest/respiratory (lower respiratory tract [LRT]), and systemic symptoms. The association between RSV symptom severity and health-related quality of life (HRQoL) was evaluated using Spearman correlation between EQ-5D-5L valuation index and visual analogue scale (VAS) scores and RI-PRO domain scores.
**Results** Sixty-six RSV-positive patients were included in the analysis. Baseline demographics and characteristics were similar among treatment groups. Median TTR of LRT and systemic symptoms was shorter for RMV 500 mg vs placebo (Figure); findings were similar for RMV 80 mg. EQ-5D-5L valuation index and VAS scores were negatively correlated with RI-PRO domain scores (Spearman's rho, valuation index: URT, −0.58; LRT, −0.65; systemic, −0.75; VAS: URT, −0.69; LRT, −0.72; systemic, −0.69).
**Conclusions** Adult outpatients with RSV treated with RMV experienced earlier symptom resolution than those receiving placebo. Improvement of RSV symptoms is associated with improved HRQoL.




LRT, lower respiratory tract;
RI-PRO, Respiratory Infection Patient-Reported Outcomes;
RMV, rilomatovir;
URT, upper respiratory tract.

## ANTIVIRAL ACTIVITY AND SYMPTOM RESOLUTION WITH RILEMATOVIR IN NON-HOSPITALIZED ADULTS INFECTED WITH RESPIRATORY SYNCYTIAL VIRUS (RSV): A PILOT PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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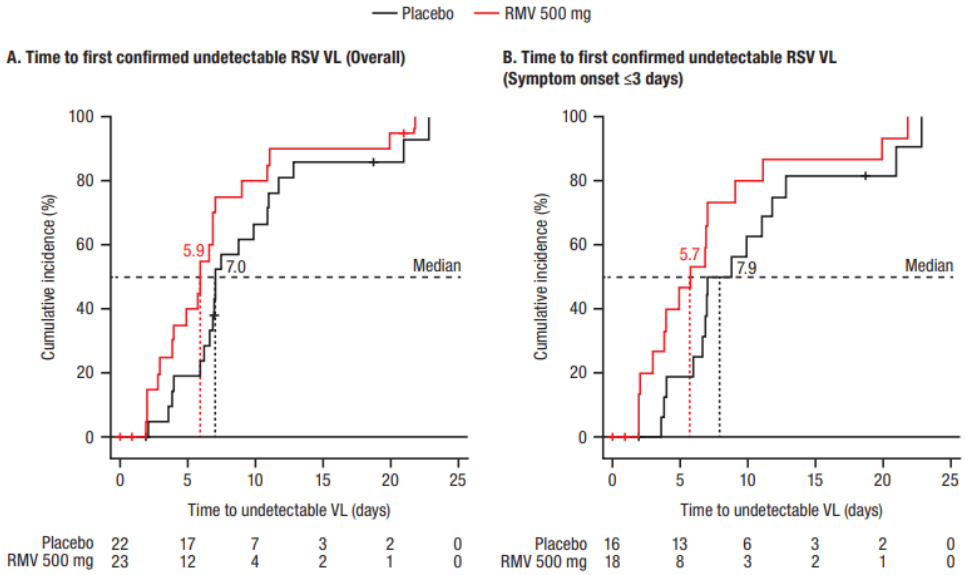
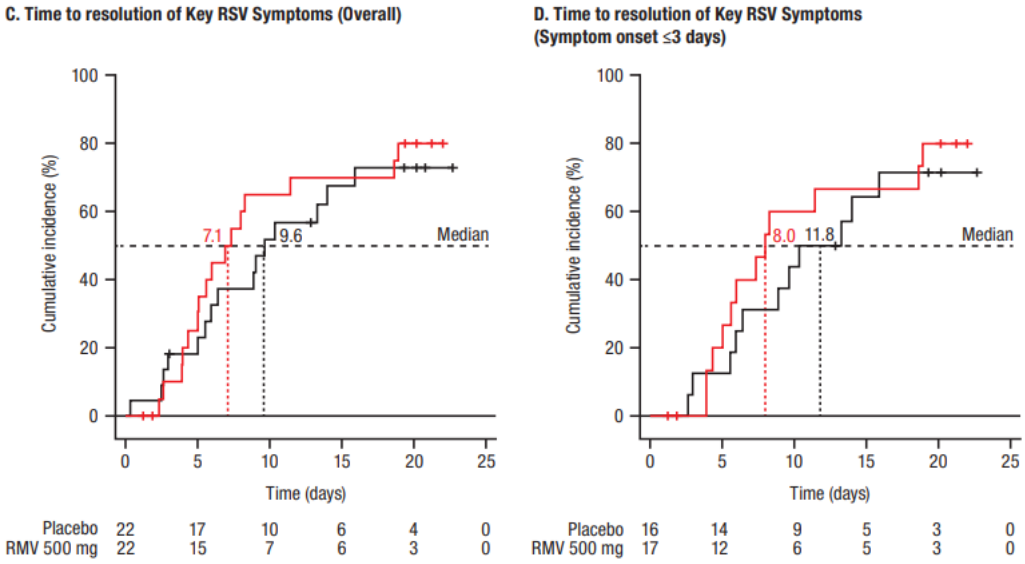
**Background** RSV may cause serious illness in some adults, with no approved treatment available. Rilematovir (RMV; JNJ-53718678) is an experimental RSV-specific fusion inhibitor for the treatment of RSV infection.

**Methods** In this Phase 2a, randomized, double-blind, placebo-controlled study, non-hospitalized adults aged ⩾18 years with confirmed RSV infection ⩽5 days from symptom onset were randomized 1:1:1 to receive once-daily RMV 80 mg, RMV 500 mg, or placebo for 7 days and followed until Day 28. We assessed antiviral effect (primary endpoint: RSV viral load [VL], qRT-PCR) and time to resolution (TTR) of Key RSV symptoms (RI-PRO/RiiQ) using median Kaplan-Meier estimates.

**Results** Sixty-six volunteers with laboratory-confirmed RSV infection (50% female, 84.8% white, median age 52.5 years) were randomized and received RMV 80 mg (n=21), RMV 500 mg (n=23), or placebo (n=22). Although there was no clear effect of RMV on VL change from baseline or area under the curve, median time to first confirmed undetectable RSV VL was shorter with RMV 500 mg than placebo (overall, 5.9 vs 7.0 days; symptom onset ⩽3 days, 5.7 vs 7.9 days; Fig.1A/1B). Median TTR of Key RSV symptoms occurred earlier with RMV 500 mg than placebo (overall, 7.1 vs 9.6 days; symptom onset ⩽3 days, 8.0 vs 11.8 days; Fig.1C/1D). RMV was generally safe and well-tolerated.

**Conclusions** This is the first dataset to show trends for antiviral and clinical effect of an RSV antiviral in RSV-infected adult outpatients. These data support further investigations of RMV as treatment for RSV infection in adults.






ITT-i, intent-to-treat infected; LLOQ, lower limit of quantification; LOD, limit of detection; RiiQ, Respiratory Infection Intensity and Impact Questionnaire; RI-PRO, Respiratory Infection-Patient-Reported Outcomes; RSV, respiratory syncytial virus; VL, viral load.
[1]Time to first post-baseline time point with undetectable RSV RNA (confirmed by one undetectable assessment).
[2]RSV-A VL LLOQ=3.00 $\log_{10}$ copies/mL, LOD=2.79 $\log_{10}$ copies/mL. RSV-B VL LLOQ=2.40 $\log_{10}$ copies/mL, LOD=1.90 $\log_{10}$ copies/mL. Results <LLOQ and >LOD (target detected) imputed with 2.90 (RSV-A) or 2.15 $\log_{10}$ copies/mL (RSV-B). Results <LOD (target not detected) imputed with 0 $\log_{10}$ copies/mL.
[3]Key symptoms included nasal congestion, sore throat, wheezing, dyspnea, productive cough, and fatigue. Resolution defined as score of 0 or 1 (scale, 0-4) for ≥24h.



## DESIGN AND EVALUATION OF NOVEL VIRAL ENTRY INHIBITORS AGAINST RESPIRATORY SYNCYTIAL VIRUS

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Human respiratory syncytial virus (RSV) infection of host cell is initiated by the attachment to host cell receptors, followed by RSV-F glycoprotein mediated fusion of viral and host cell membrane. The newly identified neutralizing epitopes on the prefusion conformation of the RSV-F protein offer attractive target sites for anti-RSV agents.

Our project entails design and preclinical evaluation of peptide-based inhibitors derived from the complementarity determining region (CDR) of a neutralizing antibody directed against the prefusion form of the RSV-F trimeric glycoprotein.

By analyzing several CDR-derived truncated peptide variants, we identified a 14-amino-acid peptide as a minimal sequence required for antiviral activity against RSV. Furthermore, we performed an alanine scanning mutagenesis analysis and determined amino acids that are critical for RSV inhibition. To enhance the stability of designed peptides, non-canonical amino acids were incorporated at different positions. Intranasal delivery of the two most potent peptide candidates led to a 100-fold reduction of viral load in the lungs of infected mice.

Furthermore, the identified peptide inhibitors were conjugated to DNA-structures to form trimeric tweezer-like scaffolds that carries three peptide inhibitor arms targeting the prefusion conformation of RSV-F and leading to increased antiviral activity in comparison to the monomeric peptides.

Overall, we identified novel peptide inhibitors that target the prefusion RSV-F trimer leading to inhibition of RSV infection in vitro and in vivo. The trivalent presentation of peptide inhibitors on DNA scaffolds can significantly increase their antiviral potency. The designed inhibitors could serve as promising candidates for interventions against RSV infections.

## EVALUATION OF RSV G CENTRAL CONSERVED DOMAIN VACCINE ADMINISTERED ALONE OR WITH PRE-F

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A safe and effective vaccine against the human Respiratory Syncytial Virus (RSV) remains an important unmet public health need. Vaccine and therapeutics development efforts have largely focused on the RSV fusion (F) protein. Recently, the RSV attachment (G) glycoprotein reemerged as a vaccine target due to its ability to elicit potent neutralizing antibodies and ameliorate disease in animal models. We designed three constructs to display the G central conserved domain (Gcc) focused on inducing broad and potent neutralizing antibodies and tested them in mice and in MIMIC® , a pre-immune human in vitro model. One construct displaying Gcc from both RSV subgroups trimerized via a C-terminal foldon (Gcc-Foldon) was highly immunogenic in both mice and MIMIC® . To explore an optimal RSV vaccine, we then combined the Gcc-Foldon antigen (Ag) with pre-F nanoparticles (pre-F-NP) as a bivalent vaccine and detected no antigenic interference between the two Ags in the MIMIC® model. This bivalent vaccine provided effective protection against RSV challenge in mice. This bivalent approach could potentially provide enhanced protective efficacy in humans and warrants further clinical evaluation.



## THE EFFICACY, IMPACT AND SAFETY OF NIRSEVIMAB FOR THE PREVENTION OF RSV MEDICALLY ATTENDED LOWER RESPIRATORY TRACT INFECTION IN HEALTHY LATE PRETERM AND TERM INFANTS

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Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection (LRTI) in infants. Nirsevimab, a monoclonal antibody with extended half-life, was shown to protect preterm infants 29 to <35 weeks gestation (wGA) against RSV LRTI. The phase 3 MELODY trial (NCT03979313) investigated the efficacy and safety of nirsevimab in late preterm and term infants.

Infants (≥35 wGA) entering their first RSV season were randomized 2:1 to receive nirsevimab (50 mg for infants <5 kg, 100 mg for infants ≥5 kg) or placebo. The primary endpoint was the incidence of medically attended (MA) RSV LRTI through 150 days postdose. Cases were confirmed using real-time reverse-transcriptase PCR. Safety was evaluated through 360 days postdose.

Overall, 1490 infants were included in the intent-to-treat population. Incidence of MA RSV LRTI was 1.2% in nirsevimab and 5.0% in placebo recipients (efficacy 74.5%; 95% confidence interval [CI], 49.6, 87.1; p<0.0001). Incidence of hospitalization due to RSV LRTI was 0.6% in nirsevimab and 1.6% in placebo recipients (efficacy 62.1%; 95% CI, −8.6, 86.8; p=0.0708). Nirsevimab was well tolerated; adverse events (87.4% nirsevimab; 86.8% placebo) and serious adverse events (6.8% nirsevimab; 7.3% placebo) were similar across groups.

A single dose of nirsevimab administered prior to the RSV season protected healthy late preterm and term infants from MA RSV LRTI and had a favourable safety profile. Nirsevimab has the potential to be an important intervention to reduce the burden of RSV LRTI in healthy infants.

## FORWARD AND REVERSE TRANSLATIONAL APPROACHES TO PREDICT EFFICACY OF THE NEUTRALIZING RESPIRATORY SYNCYTIAL VIRUS (RSV) ANTIBODY MK-1654

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**Background**: MK-1654 is an RSV F glycoprotein neutralizing monoclonal antibody (mAb) with an extended half-life in late development to prevent RSV infection in infants. Neutralizing mAbs, like MK-1654, have great potential for prophylaxis against viral infection. However, well-validated approaches for clinical dose and efficacy predictions are lacking.
**Methods**: Five decades of clinical trial literature were leveraged to build a model-based meta-analysis (MBMA) describing the relationship between RSV serum neutralizing activity (SNA) and clinical endpoints. The MBMA was validated by backward translation to animal challenge experiments and forward translation to predict phase 3 efficacy results against RSV A for REGN-2222. MBMA predictions were evaluated against a human trial of 70 participants who received either placebo or one of four dose-levels of MK-1654 and were challenged with RSV [NCT04086472]. The MBMA was used to perform clinical trial simulations and predict efficacy of MK-1654 in the infant target population.
**Results**: The MBMA established a quantitative relationship between RSV SNA and clinical endpoints. This relationship was quantitatively consistent with animal model challenge experiments and results of a recently published clinical trial. Additionally, SNA elicited by increasing doses of MK-1654 in humans reduced RSV symptomatic infection rates with a quantitative relationship that approximated the MBMA. The MBMA indicated a high probability that a single dose of ⩾75 mg of MK-1654 will result in prophylactic efficacy (>75% for 5 months) in infants.
**Conclusion**: MBMA-based efficacy predictions support continued development of the MK-1654 antibody for the prevention of RSV in infants.



## NIRSEVIMAB FOR THE PREVENTION OF RESPIRATORY SYNCYTIAL VIRUS: SAFETY IN INFANTS WITH CONGENITAL HEART DISEASE, CHRONIC LUNG DISEASE OR PREMATURITY

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We report the primary safety analysis of the double-blind Phase 2/3 MEDLEY trial (NCT03959488) evaluating nirsevimab vs palivizumab for the prevention of medically attended (MA) respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) in infants with congenital heart disease (CHD), chronic lung disease of prematurity (CLD) or prematurity.

Infants with CHD, CLD (CHD/CLD cohort) or preterm infants ⩽35 weeks gestational age (preterm cohort) were randomized 2:1 to receive nirsevimab (a single intramuscular [IM] dose, [<5 kg, 50 mg; ⩾5 kg 100 mg], followed by 4 once-monthly placebo doses) or palivizumab (5 monthly IM doses [15 mg/kg]). Safety was assessed through Day 361. Anti-drug antibodies (ADA) were reported at Day 151.

The CHD/CLD cohort comprised 310 infants and the preterm cohort comprised 615 infants. Adverse event (AE) incidence was similar across nirsevimab and palivizumab arms and cohorts (preterm: nirsevimab 66.0%, palivizumab 65.0%; CHD/CLD: nirsevimab 71.2%, palivizumab 73.5%). Two AEs of special interest were reported in nirsevimab recipients (0.3%). Six fatal events occurred (nirsevimab: 0.8%; palivizumab: 0.3%); all were judged unrelated to treatment; these infants had serious, complex underlying medical conditions

at baseline. Seven episodes of MA RSV LRTI were recorded (nirsevimab: 0.6%; palivizumab: 1.0%), with 2 hospitalizations in each arm. ADA occurrence on Day 151 was low (nirsevimab: 0.4%; palivizumab: 3.7%).

Nirsevimab had a similar safety and tolerability profile to palivizumab (the current standard of care) in infants with CHD, CLD or those born preterm. The single-dose regimen provides important advantages for these infants, their families and many healthcare stakeholders.

## Vaccines, Therapies & Treatments VT&T-67

### INTRANASAL PALIVIZUMAB ADMINISTRATION

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**Background** Proof of concept exists that local administration of antibodies inhibits infection for respiratory syncytial virus (RSV) and SARS-CoV2. RSV is the second cause of death in the infant period. However, not a single vaccine candidate targets the developing world market of fourteen late stage candidates. Prohibitive costs of approved RSV prevention with palivizumab restrict access to high-risk infants in high income countries. We hypothesize that local intranasal administration blocks RSV at the port of entry and avoids massive product waste of systemic administration.
**Objective** We investigated whether intranasal administration of palivizumab caused local or systemic adverse events in healthy adults.
**Methods** We conducted a double-blinded, randomized placebo-controlled cross-over phase I trial (NTR7378) in 20 healthy adult volunteers between 18-60 years of age. One drop of drug or placebo was administered for 7 days in the right nostril with a 14 day washout period in between trial arms. The main study outcome was local safety measured by self-reported symptoms and SAEs. When possible, symptoms were objectified by study staff and a nasal swab was taken for viral PCR.
**Results** One subject was excluded before any study medication was administered. Airway patency after 10 minutes was 100% in both the intervention (10/10) and placebo (9/9) group. There were no SAEs in either trial arm, 4 AEs in the placebo group and 6 AEs in the intervention group. No SAEs or AEs were considered to be treatment-related.
**Conclusions** Intranasal palivizumab was safe in a phase I trial in healthy adults and may provide an affordable and child-friendly route of administration for a proven effective drug. Future studies will test safety and efficacy in relevant populations, including infants and older adults. This study supports further clinical development of locally administered monoclonal antibodies against a non-human target to inhibit infection at the site of viral entry.

## Vaccines, Therapies & Treatments VT&T-68

### MEMBRANE MICRODOMAINS AS THERAPEUTIC TARGETS TO CONTROL RESPIRATORY SYNCYTIAL VIRUS

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**Background** Therapeutics targeting respiratory syncytial virus (RSV) remain limited. Our previous studies have shown that a naturally occurring phosphatidylserine species, SAPS, perturbs membrane microdomains (MM) and the associated proinflammatory response to rhinovirus. A role for MM in the adsorption of RSV and productive infection of airway epithelial cells has been reported. We therefore hypothesise that MM disruption by SAPS will modulate the attachment, replication and egress of RSV in airway epithelial cells, and the resultant inflammatory response to RSV.
**Methods** Lifespan extended human bronchial epithelial cells (HBEC3-KT), and normal human bronchial epithelial (NHBE) cells were infected with RSV and simultaneously incubated with SAPS or the comparative liposome PAPC for 2h. Unbound virus was removed and SAPS/PAPC re-added for the remaining incubation period. After 24 and 48h, cell-free supernatant and RNA were collected to determine cytokine production (ELISA) and viral replication (qPCR) respectively. Infectivity of cells was quantified after 24h using a viral plaque assay. Cell viability was measured using CellTiter-Glo®.
**Results** RSV infected HBEC3-KT and NHBE cells co-incubated with SAPS exhibited significantly decreased viral replication and release of CXCL8, CCL5 at both 24 and 48h when compared to untreated cells alone or RSV infected cells co-incubated with PAPC. Of note, SAPS treatment had no detrimental effects on cell viability. Furthermore, NHBE cells that were infected with RSV in the presence of SAPS had significantly reduced numbers of infected cells at 24h in comparison to controls. These data support the potential therapeutic value of SAPS as an effective anti-viral agent.

## DEVELOMPENT OF AN ORAL RESPIRATORY SYNCYTIAL VIRUS VACCINE BASED ON VIRUS LIKE PARTICLES BEARING GIARDIA LAMBLIA'S SURFACE PROTEINS

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Mucosal vaccines elicit immune responses, secretory IgA and mucosally imprinted lymphocytes that provide protection at the first line of defence of the organism where the majority of pathogens enter. But, to achieve proper bioavailability mucosal vaccines must avoid antigen degradation by proteases.

We have recently developed a vaccine platform that leverages the properties of Giardia lamblia's variant-specific surface proteins (VSPs) to allow oral immunization of subunit vaccines. VSPs cover the entire surface of this parasite that inhabits the upper gastrointestinal tract where digestive enzymes have their highest concentration. Since VSPs are resistant to proteolysis, we engineered them to accommodate at a virus like particle (VLP), and demonstrated that they could confer protection to a viral antigen displayed on the particle. As a proof of concept, mice were orally immunized with VLPs containing glycoproteins of influenza virus and VSP1267. Immunized mice generated an efficient humoral and cellular, mucosal and systemic immune response that protected them from infection with the virus and from tumours expressing viral antigens. These exciting results prompted us to study the application of this platform as a potential respiratory syncytial virus vaccine. The fusion and attachment glycoprotein sequences have been cloned in expression vectors and the production and validation of VLPs are currently being evaluated. Next, we plan to administer these particles to mice and analyse the immune response and the protection from infection.

The results obtained will shed light on the mechanisms of VLP-VSP vaccines and provide information on the attractive oral vaccination strategy for RSV prevention.



## COMBINATION OF SUBUNIT AND ADENOVIRAL VECTOR-BASED RSV PREFUSION F VACCINES IN ONE INJECTION INDUCES SUPERIOR IMMUNE RESPONSES AND PROTECTIVE EFFICACY IN PRE-CLINICAL ANIMAL MODELS

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Respiratory Syncytial Virus (RSV) is a leading cause of severe respiratory disease for which no licensed vaccine is available. The RSV Fusion protein (F) is an important vaccine target and prefusion (preF) conformation stabilized antigens have been shown in animals to provide superior immunogenicity and efficacy compared to the wild type F protein. We have demonstrated that an RSV preF subunit vaccine and an adenoviral vector vaccine encoding preF protein (Ad26.RSV.preF) are immunogenic and protective in animal models, respectively. While the subunit vaccine may induce superior humoral responses, Ad26.RSV.preF elicits stronger cellular responses. Here we study the combination of the two components in one injection with the aim to combine advantages of each one. In naïve mice, prime-boost immunization with the mix induced significantly higher virus neutralization titers (VNT) compared with Ad26.RSV.preF alone while maintaining the CD8+ T cell responses induced by the adenoviral vector. In 18-month-old, RSV pre-exposed mice, one dose regimen of the mix induced both strong humoral and cellular immune responses. Mice immunized with the mix showed significantly higher VNT and preF IgG ELISA titer compared with mice immunized with Ad26.RSV.preF alone. High level of cellular immune responses was measured in splenocytes by IFNγ ELISPOT and intracellular cytokine staining irrespective if dosed with the mix or Ad26.RSV.preF alone. Immunization with the mix induced better protection against RSV challenge in cotton rats than with either vaccine component alone. These results demonstrate the advantage of a combination vaccine comprised of Ad26.RSV.preF and the preF protein for further clinical development.

## HIGH RESPIRATORY SYNCYTIAL VIRUS VACCINE EFFICACY AGAINST HUMAN CHALLENGE

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**Background** Human respiratory syncytial virus (RSV) is an important cause of morbidity and mortality in older adults. Yet, there is no licensed RSV vaccine. This phase 2a study evaluated a bivalent prefusion F vaccine (RSVpreF) protection from human experimental RSV challenge.
**Methods** Healthy adults 18–50 years of age were randomized 1:1 to receive RSVpreF or placebo. Approximately 28 days after vaccination, participants were challenged with RSV A Memphis 37b and observed for 12 days. Outcomes included symptomatic RSV infection, total symptom scores, area under the viral load-time curve, immunogenicity, and safety.
**Results** After challenge, symptomatic infections associated with quantifiable virus detection occurred in 0% of RSVpreF (n=31) and 41.9% of placebo participants (n=31), corresponding to a vaccine efficacy of 100% (95% CI: 72.8%, 100%). Median area under the viral load-time curve by qRT-PCR was 0.0 hours for RSVpreF (IQR: 0.0, 19.0 × $\log_{10}$ copies/mL; $P$ <0.001) and 96.7 hours for placebo (IQR: 0.0, 675.3 hours). Compared with baseline, geometric mean fold-rise in RSV A neutralizing titers 28 days after vaccination were 20.5 (95% CI: 16.6, 25.3) for RSVpreF and 1.1 (95% CI: 0.9, 1.3) for placebo. RSVpreF was well-tolerated, with no vaccine-related serious adverse events.
**Conclusion** The well-tolerated RSVpreF vaccine was highly effective against RSV associated mild-to-moderate illness and viral shedding. These findings support further study of RSVpreF in a phase 3 study.



## RESPIRATORY SYNCYTIAL VIRUS PREFUSION F-BASED POLYANHYDRIDE NANOVACCINE INDUCES LONG-LASTING PROTECTION AND HUMORAL IMMUNITY IN A GENETICALLY DIVERSE MOUSE MODEL

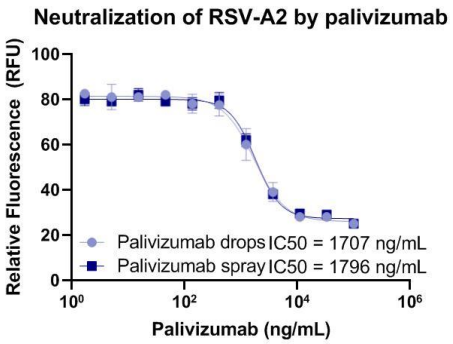
Laura Stephens

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections in children, accounting for 7% of deaths in those less than one year of age. Repeated infections throughout an individual's lifespan induce only partial protection, and there are currently no licensed vaccines to prevent RSV infection. We developed a vaccine, termed RSVNanoVax, composed of polyanhydride nanoparticles encapsulating the RSV prefusion F protein and a CpG1668 oligodeoxynucleotide adjuvant. Wildtype BALB/c mice that received a prime-boost vaccination with RSVNanoVax were protected from RSV-induced disease and exhibited enhanced viral clearance compared to unvaccinated animals out to at least 6 months post-vaccination. To assess the efficacy of RSVNanoVax in an outbred population, the vaccine was administered intranasally to Swiss Webster mice. A prime-boost vaccination induced robust titers of RSV F-specific IgG serum antibodies. High antibody titers were detected out to at least 6 months post-vaccination. Vaccination also induced RSV F-specific IgA within the lung tissue, suggesting that RSVNanoVax induces both systemic and mucosal antibody responses in outbred mice. In addition, serum antibodies generated by RSVNanoVax maintained long-lasting neutralizing activity against both RSV A and B virus strains. Following RSV challenge, vaccinated mice exhibited complete viral clearance in the lungs as early as day 2 post-infection. This protection was partially mediated by serum antibodies, as demonstrated by serum transfers from vaccinated animals. Based on the robust humoral immune response and the high level of protection observed in an outbred population, our prefusion RSV F nanoparticle formulation represents a promising RSV vaccine candidate.

## CHARACTERIZATION AND STABILITY OF PALIVIZUMAB DELIVERED VIA NASAL SPRAY: THE NEXT STEP IN AFFORDABLE RSV PREVENTION?

Jonne Terstappen

**Background** Nearly all children contract respiratory syncytial virus (RSV) infection in the first two years of life and 99% of the yearly 118 200 deaths occur in lower-middle income countries (LMICs).[1–3] Prophylaxis with intramuscular palivizumab is unavailable in LMICs due to high costs but intranasal administration could reduce the costs by minimally 90% and protect preterm neonates worldwide from RSV.
**Aim** We aim to (1) investigate the stability (integrity, concentration, and function) of palivizumab under shear force delivered by nasal sprays and (2) characterize the delivered dose (droplet size, dosage mass, plume geometry) of the spray.
**Methods** Concentration and integrity of palivizumab undergoing the shear force of the spray in comparison to palivizumab nasal drops were determined using ELISA and high-performance size-exclusion chromatography. Function was determined by comparing IC50 titers (half maximum inhibitory capacity) on an RSV-A2 neutralization assay.[4,5] Desired product characteristics include dosing uniformity, droplet size distribution measured by laser diffraction and plume geometry of palivizumab nasal spray.[6–8]
**Findings** We observed no fragmentation or aggregation of palivizumab. The concentration and neutralizing capacity remained within the acceptance criteria for palivizumab delivered via spray compared to nasal drops. Sprayed formulation with a lower viscosity had a 35% reduction in neutralizing capacity.
**Interpretation** Palivizumab is stable when delivered via nasal spray, which may also open the door to affordable intranasal administration of other monoclonal antibodies. Deposition patterns of the spray compared to nasal drops and the acceptability of a daily nasal spray for infants need further testing before clinical implementation.






## METHANOL LEAF FRACTIONS OF ALCHORNEA FLORIBUNDA AND ALCHORNEA CORDIFOLIA POSSESS ANTI-RSV ACTIVITIES

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**Background** Respiratory syncytial virus (RSV) viral infection is a global burden affecting the lower respiratory tract of infants and children, and requires urgent effective therapy for its control and eradication. At present, there are no available vaccines or suitable antiviral drugs against it. Products from natural sources possess promising prospects for the discovery of anti-RSV agents.
**Methods** In this study the anti-RSV activities of Alchornea floribunda (AF) and Alchornea cordifolia (AC) were assessed. The antiviral activities of the methanol leaf fractions of AC and AF were evaluated by a modified viral plaque reduction assay. Cytotoxicity studies on the leaf fractions were performed on HEp-2 cells using the 3-(4, 5-dimethylthiazolyl-2)-2, 5- diphenyltetrazolium bromide (MTT) reduction assays. Furthermore, time-of-addition assay was conducted to determine the mechanism of the anti-RSV action of the leaf fractions.
**Results** AF and AC leaf fractions showed anti-RSV activities with IC50 values of 75.62 ± 3.38 and 5.64 ± 1.16 µg/ml respectively, while the cell cytotoxic effect of leaf fractions were TC50 = 333.82 ± 6.32, and 103.14 ± 3.98 µg/ml, respectively. Results from the time-of-addition assay suggest that AF and AC interfere with viral replication at a viral post-entry step.
**Conclusion** The AF and AC leaf fractions demonstrated profound anti-RSV activities and holds potential for further development for clinical application in anti-RSV therapy.

## ASSAY DEVELOPMENT TO DETECT HUMAN MILK ISOTYPE-SPECIFIC ANTIBODIES

Arthur van Stigt, Maaike Nederend, Gaby Smits, Marjan Kuijer, Rutger Schepp, Pieter van Gageldonk, Anneke Hellinga, Rob van Binnendijk, Louis Bont, Belinda van 't Land, Gerco den Hartog, Jeanette Leusen

Humans have nine different antibody isotypes (i.e. IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4 and IgM, determined by the immunoglobulin heavy chain, that are paired to either kappa or lambda light chains) of which IgG1 and IgG2 are the most extensively studied. IgG1 and IgG2 are the most abundant isotypes in human serum and most frequently used subclass for clinical monoclonal antibodies is IgG1, e.g. palivizumab. However, IgA1 and IgA2 are the most prevalent isotypes in human mucosa, indicating a role for other isotypes in the protection of mucosal surfaces, in particular gastrointestinal and respiratory infections. Here, we aim to develop assays to measure natural and vaccine-induced antibody isotypes against respiratory pathogens including RSV. Moreover, specific isotypes have already been linked to the outcome of SARS-CoV2 infections. We developed an isotype-specific ELISA to quantify all nine different human isotypes in human serum and cord blood. Since infants mostly rely on maternal antibodies, derived from either cord blood or human milk. Here we show that our assay is specific for all human antibody isotypes and is able to detect both kappa and lambda antibodies. Currently we are translating the ELISA assay into a bead-based Multiplex Immunofluorescence assay to enable screening of larger quantities of samples.



## AIRWAY ORGANOIDS AS A HUMAN EX-VIVO MODEL TO EVALUATE RSV THERAPEUTICS

Ashley Weaver, Anubama Rajan, Gina Aloisio, Vasanthi Avadhanula, Pedro Piedra

Respiratory syncytial virus (RSV) remains the leading cause of acute lower respiratory infections and hospital admissions in infants. To date, the only approved preventative therapy is the monoclonal antibody – palivizumab (Synagis®). Discovery and evaluation of new therapeutics can be improved with pre-clinical human model systems. The development of physiologically relevant, Airway Organoids (AOs) represent a promising model system with the ability to mimic human physiology and disease response. We hypothesize that an AO model system could mimic the human immunoprophylactic response using a known preventative therapy. In this study, AOs derived from human bronchoalveolar lavage (lung) and mid-turbinate swab with nasal wash (nose) were used to generate 3-dimensional epithelium in transwell AO-air liquid interface (AO-ALI) cultures mirroring the respiratory environment. Unlike traditional in vitro models where the monoclonal antibody is incubated with the virus to evaluate the therapeutic effect, we added palivizumab in the basolateral compartment mimicking systemic circulation. After palivizumab administration, RSV was inoculated on the apical side. A single palivizumab dose or a two-dose regimen with the second dose at 4 days post-inoculation was administered at various concentrations. Viral kinetics over 8 days were determined using real-time PCR and a quantitative plaque assay. Results showed that a single dose of palivizumab delayed viral replication while a second dose completely inhibited RSV replication. However, replication of palivizumab resistant RSV was uninhibited. This study provides proof-of-concept for the use of AO-ALIs as a pre-clinical human model to evaluate RSV therapeutics.

## EFFICACY, SAFETY AND IMMUNOGENICITY OF THE RECOMBINANT MVA-BN-RSV VACCINE AGAINST RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTION IN A HUMAN CHALLENGE TRIAL (HCT) IN HEALTHY ADULT PARTICIPANTS

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**Background** RSV can cause severe respiratory tract infection leading to high disease burden in infants, older adults and other vulnerable populations. Bavarian Nordic has developed a multi-valent MVA-BN vector-based vaccine encoding surface and internal RSV proteins (G (A and B), N, M2, in addition to F). A broad humoral and cellular immune response elicited by MVA-BN-RSV and a favorable safety profile have been demonstrated in Phase 1 and 2 trials.
**Methods** In a double-blinded, placebo-controlled, HCT (EudraCT no. 2020-004814-36) subjects were randomly vaccinated with MVA-BN-RSV or placebo, intranasally challenged with RSV-A (Memphis-37b strain) after 28 days and quarantined for 12 days. Viral load (VL) by RT-PCR and quantitative culture was determined in nasal washes twice daily. The primary objective was to assess the effect of MVA-BN-RSV in reducing RSV VL after challenge compared to placebo. Secondary endpoints included area under the curve (AUC) by cell culture and disease severity by total symptom score over time.
**Results** 61 subjects (30 MVA-BN-RSV and 31 placebo) were evaluable. The AUC for RSV VL by RT-PCR was significantly lower for MVA-BN-RSV vaccinated subjects as compared to placebo (P=0.017), meeting the primary endpoint. The median VL AUC for RSV in the vaccine group was 0.0 (log10 copies*h/mL) compared to 49.05 for placebo. The vaccine efficacy defined by combining infection (RT-PCR) and moderate symptoms (⩾1 symptom ⩾ Grade 2) was 79.3%.
**Conclusion** MVA-BN-RSV was highly efficacious in the HCT, meeting the primary endpoint, and demonstrated a vaccine efficacy of 79.3% in preventing moderately symptomatic RSV infection.



## PEDIATRIC REAL-TIME RSV-RELATED ILLNESS AT THE INTENSIVE CARE UNIT OF JAFAR IBN AUF SPECIALIZED HOSPITAL IN KHARTOUM, SUDAN

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**Background** Respiratory Syncytial Virus (RSV) is the main viral cause of SARI leading to hospitalization among children. Thus, RSV has been prioritized for vaccine development by the Global Alliance for Vaccines and Immunizations (GAVI). However, in many of the countries eligible for GAVI support, individual patient data is lacking. This information is required to specify target populations for RSV interventions when these interventions become available in the next 5-10 years. As part of the RSV GOLD III study, we aimed to obtain clinical and socioeconomic characteristics of RSV-positive children admitted to the Intensive Care Unit (ICU) or High Dependency Unit (HDU) at Jafar Ibn Auf pediatrics Specialized Hospital in Sudan.
**Materials and Methods** Children <2 years of age admitted to the ICU or HDU meeting the WHO extended SARI case definition were tested for RSV using a point-of-care (POC) ID NOW test. The test results were confirmed in Central Laboratory by real-time PCR.
**Results** From April to May 2021, a total of 29 children were eligible for participation. Of these 29 patients, 8 patients tested positive for RSV. Socioeconomic and clinical data show a median age less than one year of age. The concordance between POC testing and real-time PCR was 93% (2/22 samples were RSV negative according to POC testing and RSV positive according to PCR).
**Expectations** Study's next season expected to be from October to December 2021, when cold weather is exist and more cases are expected to be found in Jafar Ibn Auf Hospital.

## DURABILITY OF ADULT MEMORY T CELL RESPONSES TO RESPIRATORY SYNCYTIAL VIRUS FUSION PROTEIN FOLLOWING NATURAL INFECTION

Brittani Blunck

To evaluate the durability of the adaptive immune response to RSV, we prospectively enrolled healthy adult subjects (n=19) and collected serum and peripheral blood mononuclear cells (PBMCs) during the 2018–2019 RSV season. Previously, we described their RSV-specific antibody responses and identified three distinct antibody kinetic profiles associated with infection status: uninfected, acutely infected, and recently infected. Here, we evaluated the longevity of their RSV-specific memory T-cell responses to the fusion protein in the presence or absence of natural RSV re-infection. We stimulated PBMCs with overlapping fusion protein peptide libraries, and found that memory T-cell response profiles mimic the antibody response profiles for all three groups. The uninfected group had stable, robust memory T-cell responses and polyfunctionality. The acutely infected group had reduced polyfunctionality of their memory T-cell response at enrollment compared to the uninfected group, but these returned to comparable levels by end-of-season. The recently infected group, who could not maintain high levels of RSV-specific antibody following infection, also had decreases in their memory T-cell responses and polyfunctionality by end-of-season. We observed subtype-specific differences in memory T-cell responses and polyfunctionality, with RSV/A stimulating stronger memory T-cell responses with higher polyfunctionality, though RSV/B was the dominant subtype in circulation. In conclusion, we identified a subset of individuals who have an overall deficiency in the generation of a durable RSV-specific adaptive immune response and that higher memory T-cell polyfunctionality is associated with protection against re-infection. Further studies investigating the mechanisms underlying these observations will provide important insight into vaccine development efforts.



## PREFUSION F-BASED RESPIRATORY SYNCYTIAL VIRUS IMMUNIZATION IN PREGNANCY

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1. University of Colorado School of Medicine, Aurora, CO, USA and Children's Hospital Colorado, Aurora, CO; 2. Vaccine Research and Development, Pfizer, New York, NY; 3. Iowa Clinic, Des Moines, IA; 4. Ventavia Research Group, Plano, TX.

**Background** Respiratory syncytial virus (RSV) is a major cause of infant morbidity and mortality worldwide and could be preventable by vaccination in pregnancy.
**Methods** We are conducting a randomized, placebo-controlled phase 2b trial evaluating safety, immunogenicity, and potential efficacy of a bivalent RSV prefusion F vaccine (RSVpreF) in pregnant women and their infants. Participants were randomized between 24- and 36-weeks gestation to receive 120 or 240 µg RSVpreF, with or without aluminum hydroxide, or placebo.
**Results** This interim analysis includes 406 women and 403 infants; 327 (80.5%) women received RSVpreF. Postvaccination reactions, most commonly injection site pain, fatigue, and myalgia, were generally mild-to-moderate. Adverse events (AE) in the month following vaccination were mostly anticipated events in pregnancy and similar between vaccine and placebo groups. AEs in the first month of life were similar between infants of mothers who received RSVpreF or placebo.
The 50% neutralizing titer geometric mean ratios between vaccine and placebo recipients' infants were 9.7-11.7 for RSV A and 13.6-16.8 for RSV B. Transplacental transfer ratios were 1.41 to 2.10. Infants of women immunized across the range of assessed gestational ages had similar cord blood titers and transplacental transfer ratios. Observed efficacy (95% CI) against medically attended infant RSV lower respiratory tract illness (LRTI) in an exploratory analysis was 84.7% (21.6%, 97.6%).
**Conclusions** RSVpreF was well tolerated in pregnant women, elicited robust neutralizing responses with efficient transplacental transfer, and has the potential to prevent infant RSV LRTI.

**Funded** by Pfizer. ClinicalTrials.gov, NCT04032093)

## A COMPARISON OF RSV AND HMPV ASSOCIATED ARTI IN CHILDREN LESS THAN 5 YEARS ADMITTED TO A GENERAL HOSPITAL IN SRI LANKA

Maduja Divarathna

Introduction Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) are major viral pathogens associated with acute respiratory tract infections (ARTIs) in children. hMPV has been the second most prevalent virus after RSV in pediatric populations from many countries. Clinical characteristics of RSV and hMPV associated ARTIs are indistinguishable. Materials and methods A total of 500 nasopharyngeal aspirates (NPA) were collected from children <5 years hospitalized at the District General Hospital, Kegalle between May 2016 and July 2018. Antigen detection for seven respiratory viruses including RSV was carried out using an immunofluorescence assay (IFA). hMPV was detected by a conventional reverse transcription PCR (RT-PCR) followed by the nucleic acid extraction from NPA. Results In the study sample, 300 (60%, 300/500) children were tested positive for respiratory viruses – RSV, influenza-A (Inf-A), Inf-B, parainfluenza virus-1 (PIV-1), PIV-2, PIV-3, adenovirus and hMPV. The most predominant virus identified in the study sample was RSV (20.6%; 103/500). hMPV was identified as the second dominant virus after RSV (11.8%; 59/500). Highest number of co-infections in children was detected between RSV and hMPV (n=36). The clinical presentation associated with RSV and hMPV associated ARTIs were similar. Both viruses caused severe disease in children <5 years as breathing difficulties were experienced by children infected with RSV and hMPV. RSV peaks overlapped the hMPV peaks sometimes coinciding and other times appearing before the hMPV peaks. Conclusions RSV was identified as the most predominant respiratory virus affecting children <5 years in Sri Lanka and hMPV was only second to RSV in children <5 years of age. The clinical characteristics and seasonality of RSV and hMPV infections were similar in the study sample.



## SEVERE RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTION IS ASSOCIATED WITH DECREASED INTERFERON (IFN) GENE EXPRESSION IN THE NASAL MUCOSA

Rebecca Glowinski, Zhaohui Xu, PhD, Santiago Lopez, MD, Sara Mertz, BS, Fang Ye, PhD, Octavio Ramilo, MD Asuncion Mejias, MD, PhD

**Background** RSV is a leading cause of infectious respiratory morbidity and mortality in infants and young children. Most infants requiring hospitalization for RSV infection are previously healthy with no known risk factor for increased disease severity.
**Objectives and Methods** We analyzed nasal mucosal immune transcriptional response in children <2 years of age hospitalized with RSV bronchiolitis (n=81), and healthy controls (n=8), using Illumina Chips. RSV viral loads (VL) were quantified using real-time PCR targeting the N gene. RSV patients were classified as non-severe or severe disease based on the requirement for supplemental oxygen and PICU admission, and as having high or low VL based on median VL. Transcriptional profiles were analyzed using modular analysis that clusters genes based on biological function.
**Results** Of the children enrolled, 49 had severe disease (median age 2.53 months), while 32 had non-severe disease (median age 3.19 months). Transcriptional profiles in children with severe RSV (median VL: 6.93 log10 copies/mL) had decreased over-expression of IFN genes, and higher over-expression of inflammation genes, compared those with non-severe disease (median VL: 7.39 log10 copies/mL). In addition, children with high VLs had increased over-expression of IFN-related genes and decreased over-expression of inflammation genes, compared to those with lower VL.
**Conclusion** These data highlight the importance of mucosal IFN responses in RSV infection and suggest a role for VL in inducing a robust IFN response. Differences in immune responses between severe and non-severe disease suggests impaired innate mucosal responses as a potential mechanism for enhanced disease severity.

## TOWARDS DISSECTION OF IMMUNOGENIC AND IMMUNOMODULATORY PROPERTIES OF RSV SURFACE GLYCOPROTEIN

Juan Gutman, Alana Byrne, Julian de Luca, Carla Goldin, Sebastián Esperante, Fernando Polack, Damian Alvarez-Paggi

The attachment (G) protein is one of the three envelope proteins of RSV and it is, undoubtedly, the most intriguing one. It's evolutionary origin is still unknown: it shows no sequence similarity with the envelope proteins of the other paramyxoviruses. Efforts to obtain it's molecular structure have been sterile (except for the cysteine noose in the central conserved region), since most of the protein exhibits great flexibility and extensive glycosylation. In addition, G has an alternative initiation codon that synthetizes a truncated version which is secreted. On top of this, G has been shown to be extremely relevant in two manners: immunogenicity and immunomodulation. G epitopes account for half of the neutralizing antibodies after exposition to RSV, with all these epitopes focalized in the central conserved region. Regarding the immune modulating effects: secreted G has been shown to act as a antigen decoy reducing the efficacy of neutralizing antibodies; to have a chemotactic effect via mimicking a relevant cytokine (fractalkine); to down-regulate Toll like receptors, among other effects.This work in progress aims to make a molecular dissection of these two properties (immunogenicity and modulation). With this knowledge, we aim to design a recombinant virus carriying single-residue substitutions that conserve the immune epitopes, while it's immune modulating properties are disrupted. By achieving this, the immune response generated would be robust and well directed, providing a promising vaccine prototype.



## PREVALENCE OF RESPIRATORY SYNCYTIAL VIRUS (RSV) IN PATIENTS WITH ACUTE RESPIRATORY INFECTION DURING THE COVID-19 PANDEMIC IN BULGARIA, 2020-2021

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RSV is a major respiratory pathogen, associated with significant morbidity, exibiting the greatest disease burden in infants and young children. The objective of this study was to investigate the prevalence and circulation pattern of RSV during the COVID-19 pandemic in Bulgaria. Clinical, epidemiological data, and nasopharyngeal swabs were prospectively collected from patients of all ages presenting with acute respiratory infections from November 2020 to July 2021. Real Time PCR for 12 respiratory viruses was performed. In total, 780 patients were examined: 230 SARS-CoV-2 positive and 550 SARS-CoV-2 negative. Of them, 154 (19.7%) were positive for at least one viral respiratory pathogen other than SARS-CoV-2; 23 (2.9%) patients were coinfected with two viruses, and 1 (0.1%) was coinfected with 3 viruses. No influenza viruses were identified in this period. Among the non SARS-CoV-2 viruses, RSV was the most commonly detected (7.4%), followed by rhinoviruses (5.5%), bocaviruses (2.8%), human metapneumovirus (2.7%), parainfluenza viruses type 3 (2.7%) and adenoviruses (2.4%). The incidence rate of RSV was highest among children 0-4 years (17.6%). Five cases of coinfections of RSV and SARS-CoV-2 were identified: three in chidren 0-4 years and two in pateints 65+. The incidence of RSV was very low in the months with a high COVID-19 morbidity and increased significantly in June and July 2021, when the prevalence of SARS-CoV-2 decreased sharply. The study showed the leading role of RSV as causative agents of serious respiratory diseases in early childhood.

## CONFORMATIONAL SHIFT IN THE RESPIRATORY SYNCYTIAL VIRUS FUSION GLYCOPROTEIN BY A SINGLE AMINO ACID SWITCH CAUSES GLOBAL NEUTRALIZING ANTIBODY EVASION

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**Background** Respiratory syncytial virus (RSV) is the most common cause of infant hospitalizations worldwide. RSV consists of two subtypes, A and B, that share greater than 95 % sequence identity. These subtypes have different phenotypes and often alternate in seasons where they predominate, or they can coexist as infections in the same locale or even as coinfections in the same patient in a given 'flu season.' We find that these viruses tend to have different growth and serum neutralization profiles depending on their subtype. Given the high level of amino acid identity between subtypes A and B we asked how these subtypes diverged from the parent virus and how they remain distinct subtypes.
**Methods** We characterized the antibody and serum neutralization profiles of RSV types A and B clinical isolates against autologous and heterologous patient sera. From this we identified a single amino acid mutation in the RSV-F gene. We cloned this mutation into the rgRSV reverse genetics system where the growth kinetics, antibody and serum neutralization profiles of the recombinant virus were studied. Patient RSV isolates and rgRSV were grown in the presence of patient sera and polymerase inhibitors, and whole genome sequenced by NGS after 20 passages. The WT and recombinant RSV-F proteins were modelled from previously crystallized RSV-F protein by molecular dynamics simulations.
**Results** Here, we show how a single amino acid mutation at amino acid position 305 in the RSV fusion glycoprotein (RSV-F) causes global shape-shift in RSV-F and escape from patient serum neutralization. Viral passage experiments in the presence of selective pressure forced this amino acid mutation to occur at evolutionary bottlenecks.
**Conclusions** We postulate that this event was a significant determinant in the divergence of RSV-type B from type-A. These findings reveal a mechanism of virus immune evasion that led to the evolution of a new virus called subtype-B and provides insight into vaccine and therapeutic efficacy.



## CIRCULATION PATTERNS AND RISK FACTORS TO SEVEREACUTE RESPIRATORY INFECTION ASSOCIATED WITH RSV IN CHILDREN UNDER 2 YEARS OF AGE IN MAPUTO, MOZAMBIQUE IN 2017-2018

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**Introduction** Respiratory Syncytial Virus (RSV) represents the main cause of lower respiratory tract infections and hospitalization in infants and young children worldwide. However, data on the circulation patterns and risk factors for Severe-acute-respiratory-infection (SARI) associated to RSV in low-middle income countries are scarce. This study aimed to evaluate the circulation patterns and risk factors for SARI associated to RSV in children < 2 years of age in Maputo, south-Mozambique.
**Methodology** Nasopharyngeal swabs(NPS) and data of 608 children recruited in 2017 and 2018 at three sentinel hospitals in Maputo City were retrospectively analysed. RNA of NPS swabs were collected to extract and perform RT-PCR. RSV-Positive samples were typed to RSV A/B and the whole genome of 34 amples were sequenced using next generation sequencing.
**Results** One hundred and eleven children 18.3%(111/608) were RSV positive of whom 23.1%(109/472) had SARI. Regarding the age 42.2%(46/109) of SARI children were aged 12-<24 months. In children with SARI, dyspnoea was observed in 88.1%(96/109), and bronchopneumonia in 63.3%(69/109). Seventy and five RSV positive children (68.8%) with SARI were detected in the rain season. In 2017, RSV were detected between January and April, and 81.3%(13/16) were RSV B. In 2018, the virus was detected between February and August, and 65.9%(56/85) were RSV A. The RSV Sequences from 2017 and 2018 either A or B type clustered together, and some were like RSV from outside Africa.
**Conclusions** RSV A and B were detected in first semester of 2017 and 2018 in Maputo city and children between 12-<24 months had severe respiratory disease. Keys Words: RSV, Children, SARI and ILI.

## SIMULATING RSV GENE EXPRESSION WITH A PROBABILISTIC MODEL INCLUDING SCANNING AND COLLIDING POLYMERASES

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**Background** RSV gene expression is thought to follow a gradient, but multiple studies show non-gradient mRNA levels.
**Objective** To determine if non-gradient mRNA levels can be fit using a stochastic discrete mechanistic model incorporating multiple scanning and colliding polymerases. Methods: A model was written in Python that divides the RSV genome into discrete chunks. Each of a variable number of pols starts a random walk at the 3' of the genome until encountering a gene start (GS) signal where transcription is initiated with defined probability. If transcription is initiated, the pol switches from random walk to unidirectional motion until encountering a gene end (GE) signal and either terminating transcription or reading through with defined probability. Collisions between scanning pols are reflective while a collision between a transcribing and scanning pol results in ejection of the scanning pol and its rebinding at the 3' end of the genome.
**Results** An initial scan of major parameter values showed both that the model behaved as designed and generated a range of nearly gradient and non-gradient patterns of RSV gene expression. Simulations with data-derived transcription termination and data-constrained transcription initiation probabilities are in progress.
**Conclusion** We predict that ejective collisions between transcribing and scanning pols underlie transcriptional attenuation in RSV, and that both 1) the ratio of transcription speed to pol scanning speed and 2) variable transcription initiation probabilities from both known GS signal sequence differences and differences in GS signal N-phase play a major role in shaping RSV gene expression.



## THE EFFICIENCY OF P27 PEPTIDE CLEAVAGE DURING IN VITRO RSV INFECTION IS SUBTYPE DEPENDENT

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**Background** Enzymatic cleavage of the Respiratory Syncytial Virus (RSV) F protein precursor yields two subunits (F1 and F2) and releases a 27 amino acid peptide (p27), whereas partial cleavage retains p27 in the mature F protein. For virus-cell fusion to occur, the F protein precursor undergoes a dramatic conformational change from a metastable pre-F to a stable post-F state, and p27 must be cleaved entirely.
**Objective** To determine the amounts of p27 on RSV subtypes, and if its detection depends on F protein conformation.
**Methods** Western Blot, ELISA, and HEp-2 cell-based ELISA were used to detect p27 epitope, and antigenic sites II and Ø in RSV/A subtype (GA1 and Ontario genotype) and RSV/B subtype (GB1 and BA genotype) in sucrose purified RSV (spRSV) and infected cells.
**Results** Sucrose purified RSV/A and RSV/B subtypes showed uncleaved p27, with RSV/A having higher amounts (22% vs 11%); these results were also observed in RSV-infected cells. Surface-exposed p27 on spRSV/A was conformation dependent; post-F had ~1.5-fold higher p27 compared to pre-F. In contrast, spRSV/B p27 levels were not conformation-dependent.
**Conclusions** Amounts of partially cleaved p27 on infectious RSV and on the surface of infected cells were subtype dependent and mostly predominant on post-F conformation. This suggests that during synthesis of RSV F protein efficiency of p27 enzymatic cleavage varies by RSV subtype.

## EVALUATING THE DIAGNOSTIC CAPACITY OF THE ID NOW RSV POC TEST AFTER THE EXPIRATION DATE

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**Context** The ID NOW RSV point of care (POC) test manufactured by Abbott™ uses isothermal nucleic acid amplification as the basis for molecular diagnostics. Since the POC test has a sensitive molecular underlying mechanism, there is a presumption that the tests will still perform well beyond their expiration date of one year.
**Aim** To test the validity of the Abbott ID NOW RSV test after the manufacturers' expiration date has passed.
**Methodology** We first defined the limit of detection (LOD) as the lowest concentration RSV that can still be detected 2 out of 3 times by the ID NOW RSV test device before the expiration date. The LOD was determined by testing different concentrations of RSV, starting with the lowest concentration of $1x103\ TCID50/mL$. After assessing the LOD, we determined the diagnostic capacity of the ID NOW RSV test using a concentration 100 times the LOD at t=1, t=6, t=8, t=12, t=18 and t=24 months after the expiration date.
**Results** The LOD was determined at $1x103\ TCID50/mL$. RSV was detected 2/3 times for t=1, t=6, and t=8 months.
**Conclusion** The ID NOW RSV POC test gives valid RSV test results at least 8 months after the expiration date.