WHO RSV Meeting March 23-24, 2015

RESPIRATORY Syncytial Virus Epidemiology and Vaccine Development/Immunization Strategies: Critical Gaps

Janet A. Englund, M.D.
Professor of Pediatrics
Seattle Children’s Hospital, University of Washington
Fred Hutchinson Cancer Research Center
FINANCIAL DISCLOSURES AND CONFLICTS OF INTEREST

My institution has received research support for clinical studies from Roche, Gilead, GSK, and Chimerix.

I have served as a consultant for Gilead.

I have served and am serving on US government and medical society committees.
Global causes of child deaths*

How much is RSV??


Location of 36 Study Sites for Global Burden of Disease

ALRI- Ass’d Outpt, Inpt, and RSV Mortality in Indonesia
1. RSV Seasonality
2. RSV Incidence – infection, disease, severe disease
   - Children
   - Women of child-bearing age; pregnant women
3. Risk factors in children
4. Surveillance study results vary widely:
   - Prospective vs retrospective, passive vs. active
   - Laboratory surveillance vs geographic area vs specific age group
   - Hospital, clinic, community, or home visits
5. Correlates of Protection – Antibody data
1. RSV Seasonality

**Seasonality:**

- Laboratory detection: Increasing data available worldwide; earlier studies relying on culture likely underestimate.
- Annual midwinter epidemics in temperate areas.
- Longer seasonality in tropical regions (and arctic regions).
- Burden of disease varies; better descriptions of incidence rates in developed countries.
- Rates of hospitalization, emergency department visits, outpatient clinics in developing countries not well described with studies not generalizable within/across countries.
RSV Seasonality: Turkey, Northern Hemisphere

TURKEY*: RSV Season: Jan-May

FIGURE 2.
Monthly distribution of respiratory viruses from June 2008 to May 2010. Total patients represent the number of patients enrolled in each month.
RSV Hospitalizations, YK Delta, Alaska Occur Year-Round (Courtesy R. Singleton)
RSV Season in Nepali Children < 3 Years of Age Varies By Year*
RSV SEASONALITY:
Temperate vs Tropical, North vs South

- Northern temperate regions: N. America/Europe: Nov-February
- Northern tropical areas: India, Nepal: Aug-Nov
- Equatorial: Singapore: Year round
- Southern Temperate: S. Africa, Australia: Mar-July

PROBABLY NOT CRITICAL DATA GAP
2. RSV Incidence in various populations

- Hospital-based rates of RSV infection in children is more widely known worldwide as nucleic-acid-based technologies are becoming more widely available (and RSV studies are piggy-backed onto influenza surveillance).

- HOWEVER: The incidence of RSV infection, disease, severe disease, and mortality based on active, prospective, population-based, sensitive laboratory testing in young children < 6 months is limited in developing countries.
Pediatric RSV Hospitalization Rates, Duration Vary Tremendously In Developed Countries

Table 2: Duration of hospitalization among infants and young children with RSV LRI by country (n = 1,563)

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of centers</th>
<th>Number of cases</th>
<th>Median days in hospital</th>
<th>Interquartile range (days) 5th-95th percentile range (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>4</td>
<td>250</td>
<td>4</td>
<td>3-6</td>
</tr>
<tr>
<td>Finland</td>
<td>1</td>
<td>100</td>
<td>4</td>
<td>3-6.5</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>4</td>
<td>195</td>
<td>4</td>
<td>3-7</td>
</tr>
<tr>
<td>United States</td>
<td>4</td>
<td>305</td>
<td>4</td>
<td>3-6</td>
</tr>
<tr>
<td>Belgium</td>
<td>5</td>
<td>131</td>
<td>8</td>
<td>6-12</td>
</tr>
<tr>
<td>France</td>
<td>7</td>
<td>199</td>
<td>8</td>
<td>6-11</td>
</tr>
<tr>
<td>Germany</td>
<td>7</td>
<td>149</td>
<td>9</td>
<td>6-14</td>
</tr>
<tr>
<td>Italy</td>
<td>4</td>
<td>72</td>
<td>9</td>
<td>6-11</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>5</td>
<td>162</td>
<td>8</td>
<td>6-11</td>
</tr>
<tr>
<td>Total sample</td>
<td>41</td>
<td>1,563</td>
<td>6</td>
<td>4-9</td>
</tr>
</tbody>
</table>

*a Interquartile range is the range between the 25th and 75th percentiles

Table 3: Factors influencing duration of hospitalization among infants and young children with RSV LRI (n = 1,555)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Effect estimate</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with no risk factors</td>
<td>3.059</td>
<td>2.905–3.221</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hospitalization in continental Europe</td>
<td>1.802</td>
<td>1.685–1.928</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diagnosis of bacterial pneumonia</td>
<td>1.482</td>
<td>1.314–1.671</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diagnosis of gastroenteritis</td>
<td>1.397</td>
<td>1.290–1.514</td>
<td>0.0001</td>
</tr>
<tr>
<td>Multiple congenital anomalies</td>
<td>1.394</td>
<td>1.233–1.575</td>
<td>0.0001</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1.127</td>
<td>1.042–1.218</td>
<td>0.0028</td>
</tr>
<tr>
<td>Respiratory rate above 70/min</td>
<td>1.127</td>
<td>1.035–1.226</td>
<td>0.0057</td>
</tr>
<tr>
<td>Radiographic evidence of RSV</td>
<td>1.119</td>
<td>1.062–1.178</td>
<td>0.0001</td>
</tr>
<tr>
<td>Per every week premature</td>
<td>1.051</td>
<td>1.038–1.064</td>
<td>0.0001</td>
</tr>
<tr>
<td>Per every week short of 13 weeks old</td>
<td>1.034</td>
<td>1.024–1.044</td>
<td>0.0001</td>
</tr>
<tr>
<td>Per every 1% deficit in oxygen saturation</td>
<td>1.010</td>
<td>1.006–1.013</td>
<td>0.0097</td>
</tr>
<tr>
<td>Interaction between prematurity and age less than 13 weeks</td>
<td>1.006</td>
<td>1.001–1.010</td>
<td>0.0007</td>
</tr>
<tr>
<td>Interaction between continental Europe and age less than 13 weeks</td>
<td>0.978</td>
<td>0.966–0.991</td>
<td>0.0013</td>
</tr>
<tr>
<td>Interaction between prematurity and congenital anomalies</td>
<td>0.954</td>
<td>0.927–0.983</td>
<td>0.0018</td>
</tr>
<tr>
<td>Interaction between continental Europe and bacterial pneumonia</td>
<td>0.858</td>
<td>0.743–0.991</td>
<td>0.0377</td>
</tr>
</tbody>
</table>
Incidence and severity of respiratory syncytial virus pneumonia in rural Kenyan children identified through hospital surveillance

DJ Nokes*,1,2, MJ Ngama1, A Bett1, J Abwao1, P Munywoki1, M English1,3, JAG Scott1,4, PA Cane5, and GF Medley2

1Kenya Medical Research Institute (KEMRI), Centre for Geographic Medicine Research-Coast, Kilifi, Kenya

Clin Infect Dis. 2009 November 1; 49(9): 1341–1349.

Fig. 2. Geographical variation within the Kilifi Health and Demographic in the incidence of RSV associated severe or very severe pneumonia in <5 yr old admissions to Kilifi District Hospital. Represented is the rate of hospitalization per 100,000 per year) for the 5 year period May 2002-April 2007.

[Higher incidence = darker color]
Population-based Surveillance

Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa

Susan E. Robertson, Anna Roca, Pedro Alonso, Eric A.F. Simoes, Cissy B. Kartasasmita, David O. Olaleye, Georgina N. Odaibo, Mark Collinson, Marietjie Venter, Yuwei Zhu, & Peter F. Wright

- Studies 1987-2001; 600-2000 samples/site in Indonesia, Mozambique, Nigeria, South Africa:
  - RSV LRI rates 6/1000-14/1000 but varied in each country by age group studied, home visits vs clinic vs hospital, rates of HIV
  - Higher rates in < 1 year vs < 5 years
RSV Studies in Developing Countries Prior to 2000*

*Robertson et al 2004

Table 1. Incidence of respiratory syncytial virus-associated lower respiratory infections in studies from developing countries

<table>
<thead>
<tr>
<th>Country (study site)</th>
<th>Dates</th>
<th>Method of case ascertainment</th>
<th>Denominator (age group)</th>
<th>Diagnostic tests</th>
<th>Incidence of all LRIs³ (age group)</th>
<th>Incidence of RSV-associated² LRIs (age group)</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil (Rio de Janeiro)</td>
<td>January 1987–December 1989</td>
<td>Weekly home visits</td>
<td>n = 262 (&lt; 5 years)</td>
<td>IFA, culture</td>
<td>64/1000 child-years (&lt; 5 years)</td>
<td>14/1000 child-years (&lt; 5 years)</td>
<td>2</td>
</tr>
<tr>
<td>Colombia (Cali)</td>
<td>February 1977–February 1979</td>
<td>Passive surveillance at 5 primary health-care clinics</td>
<td>n = 8 748 (&lt; 15 years)</td>
<td>Culture, serology</td>
<td>70/1000 child-years (&lt; 15 years)</td>
<td>6/1000 child-years (&lt; 15 years)</td>
<td>6</td>
</tr>
<tr>
<td>Colombia (Cali)</td>
<td>October 1986–April 1988</td>
<td>Weekly home visits</td>
<td>n = 340 (birth cohort)</td>
<td>IFA, culture</td>
<td>1710/1000 child-years (&lt; 1.5 years)</td>
<td>198/1000 child-years (&lt; 1.5 years)</td>
<td>3</td>
</tr>
<tr>
<td>Gambia (Western Region)</td>
<td>January 1994–December 1996</td>
<td>Passive surveillance of admissions to 3 hospitals</td>
<td>n = 20 338 (&lt; 1 year)</td>
<td>IFA, serology</td>
<td>96/1000 child-years (0–11 months)</td>
<td>8/1000 child-years (&lt; 1 year)</td>
<td>7</td>
</tr>
<tr>
<td>Indonesia (Lombok Island, 83 villages)</td>
<td>January 2000–December 2001</td>
<td>Passive surveillance of admissions to 5 hospitals</td>
<td>n = 30 000 (&lt;2 years)</td>
<td>ELISA⁴</td>
<td>60/1000 child-years (&lt; 2 years)</td>
<td>10/1000 child-years (&lt; 2 years)</td>
<td>8</td>
</tr>
<tr>
<td>Israel (Negev Region)</td>
<td>1 January 1987–15 April 1987</td>
<td>Passive surveillance of admissions to 1 hospital</td>
<td>n = 8 323 (&lt; 1 year)</td>
<td>ELISA, culture, serology</td>
<td>Not reported</td>
<td>10/1000 child-years (&lt; 1 year)</td>
<td>9</td>
</tr>
</tbody>
</table>
Deaths from acute lower respiratory illness and RSV detections, Dhaka, among children under 5 years, 2004 - 2008
2. RSV Incidence: What is the critical gap?

- RSV hospitalization rates becoming available but are NOT the best data for evaluating the disease burden of RSV in young children.
- RSV mortality data alone not widely available but also probably not best marker of RSV disease burden.
- Burden of illness in moderate to severe disease is most critical gap: data on true mortality (including home deaths), clinic/practitioner visits, emergency care, unnecessary antibiotics, short and long term pulmonary sequelae, impact on growth not available.
3. RSV Risk Factors

Risk factors from developed countries also apply to developing countries:

- Age
- Male sex
- Prematurity, ? SGA
- Multiple births
- Underlying pulmonary and cardiac conditions
- Congenital or acquired immunodeficiency
- Congenital anomalies or syndromes (Down, neuromuscular)
- Crowded home, large families,
- School age siblings
- Air pollution/wood smoke
- Cigarette smoking during pregnancy, in home
- Familial atopy

The Burden of Respiratory Syncytial Virus Infection in Young Children

Hall et al

Figure 2. Odds Ratios for Potential Risk Factors in Patients with and Those without Respiratory Syncytial Virus (RSV) Infection, According to Treatment Site.

According to multiple logistic-regression analyses, the only risk factors associated with RSV illness requiring hospitalization were an age of less than 2 years (especially under 6 months) and a history of prematurity. For age groups, the reference group is patients between the ages of 24 months and 59 months. Horizontal lines indicate 95% confidence intervals.
OTHER RSV RISK FACTORS

- Delivery by Caesarean section (Denmark) (Kristensen et al. PIDJ 2015)
- Gestational age 32-35 weeks at RSV season (MARI rates of 25/1000) (Ambrose PIDJ 2014)
- Malnutrition (poor growth) (Paynter et al. PIDJ 2014)
- HIV Infection (Madhi group, South Africa)
- Running water inside home (Bulkow et al. Pediatrics 2012)
- Wood stove for heat (Bulkow et al. Pediatrics 2012)

QUESTION: Is more research needed on risk factors, or can evaluation of risk factors be incorporated into clinical trials and studied further in a PROBE design?
3. RISK FACTORS: Spread of RSV*

- At least one RSV infection was observed in children attending 7/13 separate classrooms.

- In rooms with 5-15 children enrolled, the rate of RSV infection rapidly increases:
  - After first case: 50% of children in the same room are have symptomatic RSV with identical virus within 6 days.

*Chu et al J Clin Vir 2013
URBAN vs Small Town: RSV Predominant Cause of Community-Acquired Pneumonia in Nepal

RNA Viruses in Young Nepalese Children Hospitalized With Severe Pneumonia

Maria Mathisen, PhD,*† Sudha Basnet, MD,‡ Arun Sharma, MD,‡ Prakash S. Shrestha, MD,‡ Biswa N. Sharma, MSc,*§ Palle Valentin-Branth, PhD,‖ Halvor Sommerfelt, PhD,*¶ and Tor A. Strand, PhD,*++

RNA viruses in community-acquired childhood pneumonia in semi-urban Nepal; a cross-sectional study

Maria Mathisen*¹, Tor A Strand¹,², Biswa N Sharma³, Ram K Chandyo¹, Palle Valentin-Branth⁵, Sudha Basnet⁶, Ramesh K Adhikari⁴, Dag Hvidsten⁶, Prakash S Shrestha⁴ and Halvor Sommerfelt¹,⁷

BMC Medicine 2009, 7:35

Figure 1. Monthly number of cases with community-acquired severe pneumonia and cases testing positive for the different viruses among 627 children 2 to 35 months old admitted in Kanti Children’s Hospital, Kathmandu, Nepal, from January 2006 to June 2008. Parainfluenza type 2 was not included in the graph because of less detections.
4. INCIDENCE OF RSV LRI VARIES WIDELY IN REPORTS FROM DEVELOPED COUNTRIES: WHY?

- Variability also reported in USA/Europe, with widest variation in smaller subpopulations such as aboriginal
- Target population under surveillance
- Accuracy of population estimates
- Surveillance method
- Laboratory method
- Year –to–year and even local variability of RSV season
- RSV subtype
- Other outbreaks – pandemic influenza, Ebola
CONCLUSION: WHAT ARE IMPORTANT GAPS IN DEVELOPING COUNTRIES?

- Seasonality, risk factors are not most important knowledge gaps
- Specifics regarding disease incidence is important gap and is reflected in varying or unknown results of surveillance
  - LRTI rates due to RSV in infants < 6 months of age
  - Non-hospital rates of severe and moderately severe LRTI in infants in diverse settings
  - Prospective and active surveillance for community-based evaluation of mortality, especially in youngest infants
- Potentially protective RSV antibody levels in infants
- Short and longer term sequelae of RSV infection during infancy in terms of growth, development, and pulmonary function/airway disease
Important issues to consider in future vaccine studies

- Populations: Where? What ages?
  - Infants: how is gestational age determined
  - Issue of preterm vs SGA in developing countries
- Study locations – need for diversity
- What household data is most important
- Methods of surveillance – is passive surveillance sufficient?
- Criteria to obtain clinical specimen
- Clinical and laboratory endpoints are CRITICAL
What is our target population?
Acknowledgments

Seattle Children’s Hospital – Univ of Washington
• Helen Chu, MD, MPH
• Jane Kuypers, PhD
• Anne Cent
• Emily Martin
• Alex Murray
• Kirsten Lacombe, MSN
• Amalia Magaret PhD

Cincinnati Children’s Hospital
• Mark Steinhoff MD

Johns Hopkins University
• Joanne Katz ScD
• Michelle Hughes, Ph D

George Washington University
• James Tielsch PhD

Nepal Nutrition Intervention Project
• Mothers and children enrolled in the Mother’s Gift Study in Nepal
• Subharna Khatry MD & Steven LeClerq
• NNIPS Field Staff

Research support
• NIH
• PATH
• Bill and Melinda Gates Foundation
• Thrasher Foundation
• Seattle Children’s Hospital Pediatric Pilot Fund