Battle against Respiratory Viruses (BRaVe)

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World Health Organization, Geneva
Burden of acute respiratory infections

- Acute respiratory infections (ARI) represent an important public health problem with 3.9 million deaths\(^1\) per year worldwide across the age spectrum.

- In developing countries, the consequences of ARI are a very high\(^2\):
  - Pneumonia alone is the leading cause of death in children under 5 years old with 1.4 million deaths per year.
  - 97% of pneumonia death occurs in developing countries.

- In developed countries, the impact of ARI is high on the health system:
  - Total economic impact of non–influenza-related viral respiratory infections approaches $40 billion annually in the USA\(^3\).
  - In Europe, pneumonia costs are estimated at around ~€10.1 billion annually and indirect costs of lost work days amount to €3.6 billion\(^4\).

18% of child deaths due to pneumonia

1.4 million pneumonia deaths in children under 5

Global awareness on pneumonia

- WHO and UNICEF developed the Global Action Plan on Pneumonia (2009)

- Protect children from pneumonia includes promoting exclusive breastfeeding and hand washing, and reducing indoor air pollution;

- Prevent pneumonia with vaccinations;

- Treat pneumonia, making sure that every sick child has access to the right kind of care - either from a community-based health worker, or in a health facility if the disease is severe - and can get the antibiotics and oxygen they need to get well.
# Pneumonia – causative agents in children under 5 years old

<table>
<thead>
<tr>
<th>Pneumococcal pneumonia- year 2000 (O’Brien et al., 2009)</th>
<th>13.8 million episodes (9% of pneumonia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib pneumonia- year 2000 (Watt et al., 2009)</td>
<td>7.9 million episodes (5% of pneumonia)</td>
</tr>
<tr>
<td>RSV pneumonia- year 2005 (Nair et al; 2010)</td>
<td>33.8 million episodes (22% of pneumonia)</td>
</tr>
<tr>
<td></td>
<td>3.4 million episodes (23% of severe pneumonia)</td>
</tr>
<tr>
<td>Flu pneumonia- year 2008 (Nair et al; unpublished*)</td>
<td>20.45 million episodes (13% of pneumonia)</td>
</tr>
<tr>
<td></td>
<td>~1 million episodes (7% of severe pneumonia)</td>
</tr>
</tbody>
</table>
Diversity of respiratory viruses and illnesses

- Influenza is important but not the only one

- At least 6 families of viruses and more than 150 viruses

- Most of them are found linked with pneumonia among other infections

<table>
<thead>
<tr>
<th>Human</th>
<th>Virus</th>
<th>Species/Sub-Sero-Genotypes</th>
<th>RNA/DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rhinovirus</td>
<td>A, B, C, &gt;140 serotypes</td>
<td>RNA</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
<td>A (H3N2, H1N1..), B, C</td>
<td>RNA</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>A and B</td>
<td>RNA</td>
</tr>
<tr>
<td></td>
<td>Parainfluenza</td>
<td>Type 1, 2, 3 and 4</td>
<td>RNA</td>
</tr>
<tr>
<td></td>
<td>Metapneumovirus</td>
<td>A1, A2, B1, B2</td>
<td>RNA</td>
</tr>
<tr>
<td></td>
<td>Coronavirus</td>
<td>OC43, E229, HKU1, NL63</td>
<td>RNA</td>
</tr>
<tr>
<td></td>
<td>Enterovirus</td>
<td>&gt;100 serotypes</td>
<td>RNA</td>
</tr>
<tr>
<td></td>
<td>Adenovirus</td>
<td>7 species, &gt; 50 serotypes</td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td>Bocavirus</td>
<td>4 species</td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td>Polyomavirus</td>
<td>KI, WU, Merkel...</td>
<td>DNA</td>
</tr>
</tbody>
</table>

* Courtesy of Laurent Kaiser, University of Geneva
Under-appreciated burden of RVIs…

- The burden from respiratory viruses other than influenza far exceeds that of influenza.

- Respiratory syncytial virus in children under 5, in 2005\(^1\):
  - 33 million episodes of RSV-associated Acute Lower Respiratory Infection
  - 66 000 - 199 000 RSV-associated deaths

- But RVIs are not only for children

\(^1\) Nair, H. et al. Lancet, 2010
... in adults and for other conditions

- RVIs affect all ages and cause a wide range of illnesses, including:
  - Pneumonia
  - Exacerbation of asthma and COPD
  - Exacerbation of CHF
  - Loss of diabetes control
  - Myocardial infarction, stroke

- Respiratory syncytial virus in adults, US\(^1\):
  - 177,000 hospital admissions
    - 11\% for pneumonia
    - 11\% for COPD
    - 7\% for asthma

- Rhinovirus\(^2\):
  - 30-50\% of asthma exacerbations
  - 14-43\% of COPD exacerbations

Respiratory viruses as a threat for global health security

- 2003: emergence of SARS (10% mortality), spread in ~30 countries
- 2003: re-emergence of H5N1 (60% mortality), spread in 15 countries
- 2009 pandemic A(H1N1)
  - 201,200 respiratory deaths and 83,300 cardiovascular deaths
  - Spread over all continents in less than 9 weeks
  - Use of antivirals to reduce severe disease: no deaths in pregnant women in Japan
  - Increased use of antivirals reduced H1N1 mortality over the pandemic period
- September 2012: discovery of a new coronavirus (KSA, Qatar, Jordan)
- New threats expected in the coming years (urbanization, globalization, obesity, pollution, ...)

Inappropriate therapeutics paradigm

- Excessive antibiotics use
  - Growing antimicrobial resistance, particularly for *S. pneumoniae*\(^1\)
  - Side effects
  - Cost

- Inappropriate use of other treatments
  - Corticosteroid in pandemic H1N1 illness\(^2,3\) associated with:
    - Higher mortality rate
    - More super-infection or secondary bacterial infection
    - Longer stay in ICU
  - Use of influenza antivirals for other influenza-like illnesses

What is new?

- **New molecular diagnostic technologies** allow for rapid testing for multiple etiologies (viral and bacterial).

- Viruses are present in most acute respiratory infections:
  - Co-detection: **viral-viral** in up to 20% of LRTI\(^1\); **bacterial-viral** in 30%\(^2,3\)
  - Triggering of secondary bacterial infections

- **Impacts and roles of viruses in respiratory infections still need to be better understood.**

- **New antivirals offer possibility of effective treatment**:
  - HIV-AIDS, hepatitis B and C, herpesviruses (including varicella)
  - Influenza particularly in severe cases and risk groups
  - **But no antivirals for other RVIs**

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\(^3\) Bezerra, P.G. et al. PLoS. One, 2011
Challenges

- Progress has been made to reach Millennium Development Goal 4
  - Deaths due to pneumonia decreased from 1.85 million in 2000 to 1.4 million in 2010 for children under 5

- However, challenges remain:
  - Lack of consideration for viral respiratory infections which are still often regarded as mild and/or untreatable.
  - Access to care
  - Insufficient use of beneficial interventions like oxygen therapy.
  - Inappropriate interventions
  - Evidence sometimes missing for specific public health questions and for specific settings, …

\footnote{Liu, L. et al. Lancet. 2012}
What is the BRaVe initiative?

- The BRaVe initiative aims at reducing public health (severe disease) and economical impact due to viral respiratory infections by
  - Filing the gaps in knowledge
  - Developing innovative therapeutic and preventive interventions
  - Proposing comprehensive strategies including viral etiologies

Rationale:
- Huge burden of respiratory infections
- Over than half of them caused by viruses
- No or limited interventions
- Need for more drugs, vaccine and generic interventions such as oxygen therapy
Characteristics of the BRaVe initiative

New approach:

- Development and implementation of a public health research agenda identifying the key questions on acute viral respiratory infections for which we need evidence to make public health decisions.

- Closer partnership between public health decision makers, research community, and funding partners.

- Engage pharmaceutical industry and academia to develop new drugs (antivirals, monoclonal antibodies, adjunct therapy).
Research and public health decision making

Research funding agency

Call for proposals
Funding

Projects proposals

Public Health decision maker

Guidelines

Researchers

Scientific literature
Advice

“Strong recommendation, low evidence”
What has been done so far?

- BRaVe initiative concept paper developed by WHO Secretariat
- Development of a research agenda for the BRaVe (2 high level consultations supported by the Wellcome Trust and Foundation Mérieux)
  - 45 experts from 42 institutions from 19 countries
- "Call to action" from the research community
  - Signed by 44 experts and/or institutions
Overview of BRAVE research agenda

- **Track 1.** Defining the burden of viral respiratory infections
- **Track 2.** Understanding disease pathogenesis and host dynamics of respiratory viral infections
- **Track 3.** Expanding treatment options for viral respiratory infections
- **Track 4.** Improving SARI diagnosis and diagnostic tests
- **Track 5.** Improving clinical management of SARI/ALRI
- **Track 6.** Shifting perceptions and optimizing public health strategies
Research needs: Approaches for public health

- Less competition – more efficiency
  - Allocate long term grants for centers of excellence to carry out multiple studies on the same topic.

- Less verticality (pathogen focus) more trans/multi disciplinary approaches

- More coordination between different groups
  - Standardization of research protocols between settings
  - Create platform for faster sharing of results -either positive or negative - to rapidly inform public health decision

- Promote probe studies and alternative research strategies like adaptive trial designs to speed up evidence building.
Next steps for WHO

- Upcoming months
  - Report of the WHO technical consultations
  - Publication of BRaVe research agenda
  - Discussion with funding agencies

- Medium term
  - Revision of the joint WHO-UNICEF Global Action Plan on Pneumonia including viral pneumonia
Expectations for the BRaVe vision

- Coalition of research funding partners to join the battle against respiratory viruses: be BRaVe

- Research funding partners to support studies in line with the BRaVe research agenda.
  
  - Please provide the name of contact person in your organization

- Research funding partners to support a "think tank" that will bring together various stakeholders interested in addressing this problem.

- Facilitate public-private partnerships to ensure faster availability of new treatments (new antivirals, if possible with broad spectrum activity, host-directed therapies, immunomodulators) and vaccines.
Contacts at WHO

WHO secretariat
- Pr. Nikki Shindo: shindon@who.int
- Dr. Charles Penn: pennc@who.int
- Ms. Anaïs Legand: leganda@who.int
- Dr Sylvie Briand: briands@who.int

Early supporters of this initiative

Thank you to the track leads:
- T1. Dr Abdullah Brooks (Bangladesh),
- T2. Pr. Menno de Jong (The Netherlands),
- T3. Pr. Fred Hayden (USA) and Dr David Spiro (USA),
- T4. Dr Dan Jerningan (USA),
- T5. Dr Jeremy Farrar (Vietnam),
- T6. Dr Ximena Aguilera (Chile)

Pr. Fred Hayden

Wellcome Trust – Fondation Mérieux
Thank you

谢谢

Merci

Спасибо

Gracias

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Respiratory viruses and illnesses

Occurrence of pneumonia and other infections in 4227 children with laboratory confirmed respiratory infections at Turku University Hospital, Finland

<table>
<thead>
<tr>
<th></th>
<th>Rhinovirus (n=580)</th>
<th>RSV (n=1655)</th>
<th>Adenovirus (n=902)</th>
<th>Parainfluenza 1 (n=94)</th>
<th>Parainfluenza 2 (n=49)</th>
<th>Parainfluenza 3 (n=315)</th>
<th>Influenza A (n=544)</th>
<th>Influenza B (n=139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>18%</td>
<td>16%</td>
<td>8%</td>
<td>9%</td>
<td>6%</td>
<td>14%</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Wheezy bronchitis</td>
<td>22%</td>
<td>12%</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
<td>8%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>3%</td>
<td>34%</td>
<td>1%</td>
<td>2%</td>
<td>10%</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Otitis media</td>
<td>23%</td>
<td>59%</td>
<td>24%</td>
<td>27%</td>
<td>20%</td>
<td>30%</td>
<td>26%</td>
<td>19%</td>
</tr>
<tr>
<td>Fever &gt;38°</td>
<td>44%</td>
<td>63%</td>
<td>81%</td>
<td>77%</td>
<td>76%</td>
<td>63%</td>
<td>94%</td>
<td>89%</td>
</tr>
</tbody>
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* Adapted from O. Ruuskanen et al, The lancet, 2011
Interactions ISARIC and WHO

- Shared vision about the importance of clinical management and clinical research regarding respiratory pathogens
- ISARIC investigator participation in WHO consultations including the development of the BRaVe initiative
- ISARIC members signing the BRaVe call to action
- WHO participation (observer status) in meetings that led to ISARIC, in 1st Council meeting, in working groups,
- WHO sponsoring efforts to develop common protocols