Battle against Respiratory Viruses (BRaVe)

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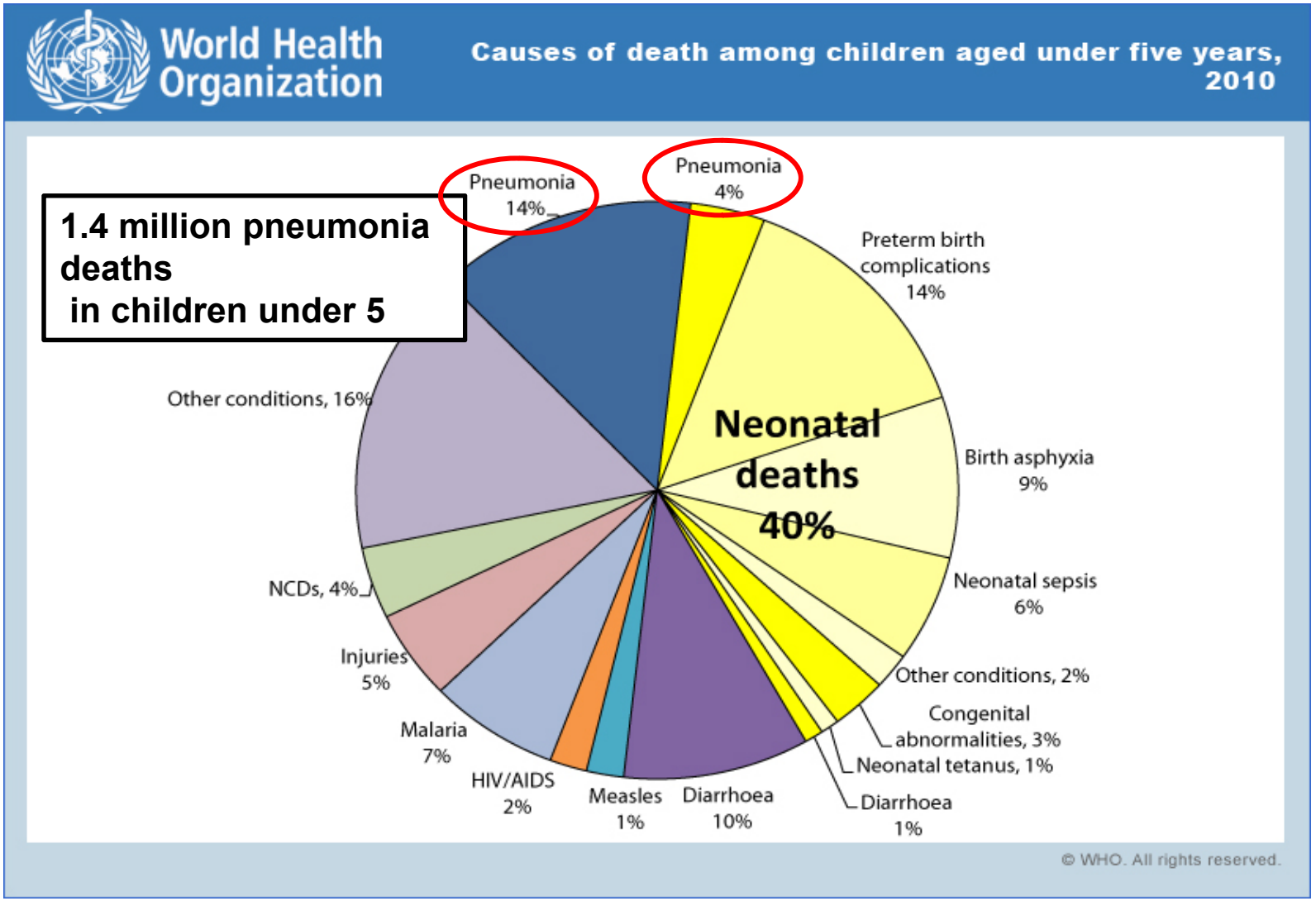
Burden of acute respiratory infections

- 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]

[1] World Health Organization (2008) The global burden of disease: 2004 update [2] Liu, L. et al. Lancet. 2012 [3] Fendrick, A.M. et al. Arch Intern Med, 2003 [4] Welte, T. et al. *Thorax.* 2012

18% of child deaths due to pneumonia



WHO Global Health Observatory, www.who.int/gho/child_health/mortality/causes/en/index.html,

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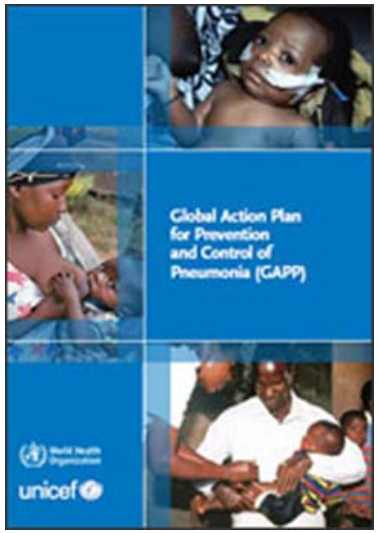
Global awareness on pneumonia

- **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.



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Pneumonia – causative agents in children under 5 years old

Pneumococcal pneumonia- year 2000 (O'Brien et al., 2009) 13.8 million episodes (9% of pneumonia)
Hib pneumonia- year 2000 (Watt et al., 2009) 7.9 million episodes (5% of pneumonia)
RSV pneumonia- year 2005 (Nair et al; 2010) 33.8 million episodes (22% of pneumonia) 3.4 million episodes (23% of severe pneumonia)
Flu pneumonia- year 2008 (Nair et al; unpublished*) 20.45 million episodes (13%of pneumonia) ~1 million episodes (7% of severe pneumonia)

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

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

* 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

[1] Falsey,A.R. et al. N. Engl. J. Med, 2005
[2] Hayden, F.G. Rev. Med. Virol, 2004

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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**[1]
  - Spread over all continents in less than 9 weeks
  - Use of antivirals to reduce severe disease: no deaths in pregnant women in Japan[2]
  - Increased used of antivirals reduced H1N1 mortality over the pandemic period[3]
- September 2012: discovery of a new **coronavirus** (KSA, Qatar, Jordan)
- New threats expected in the coming years (urbanization, globalization, obesity, pollution, …)

[1] Dawood,F. et al. Lancet Infectious Diseases, 2012; [2] Kamigaki,T. et al. PLoS. Curr, 2009, [3] Miller, PE. et al. PLoS One, 2012

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

[1] Woodhead, M. ERS, 2002 [2] Kim, S-H. et al. AJRCCM, 2011 [3] Brun-Buisson, C. et al. AJRCCM, 2011

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**

[1] Pavia, A.T. Clin. Infect. Dis. 52 Suppl 4, 2011 [2] Mermond, S. et al. Clin. Infect. Dis. 54 Suppl 2, 2012 [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[1]

- 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, …

[1] Liu, L. et al. Lancet. 2012

What is the BRaVe initiative?

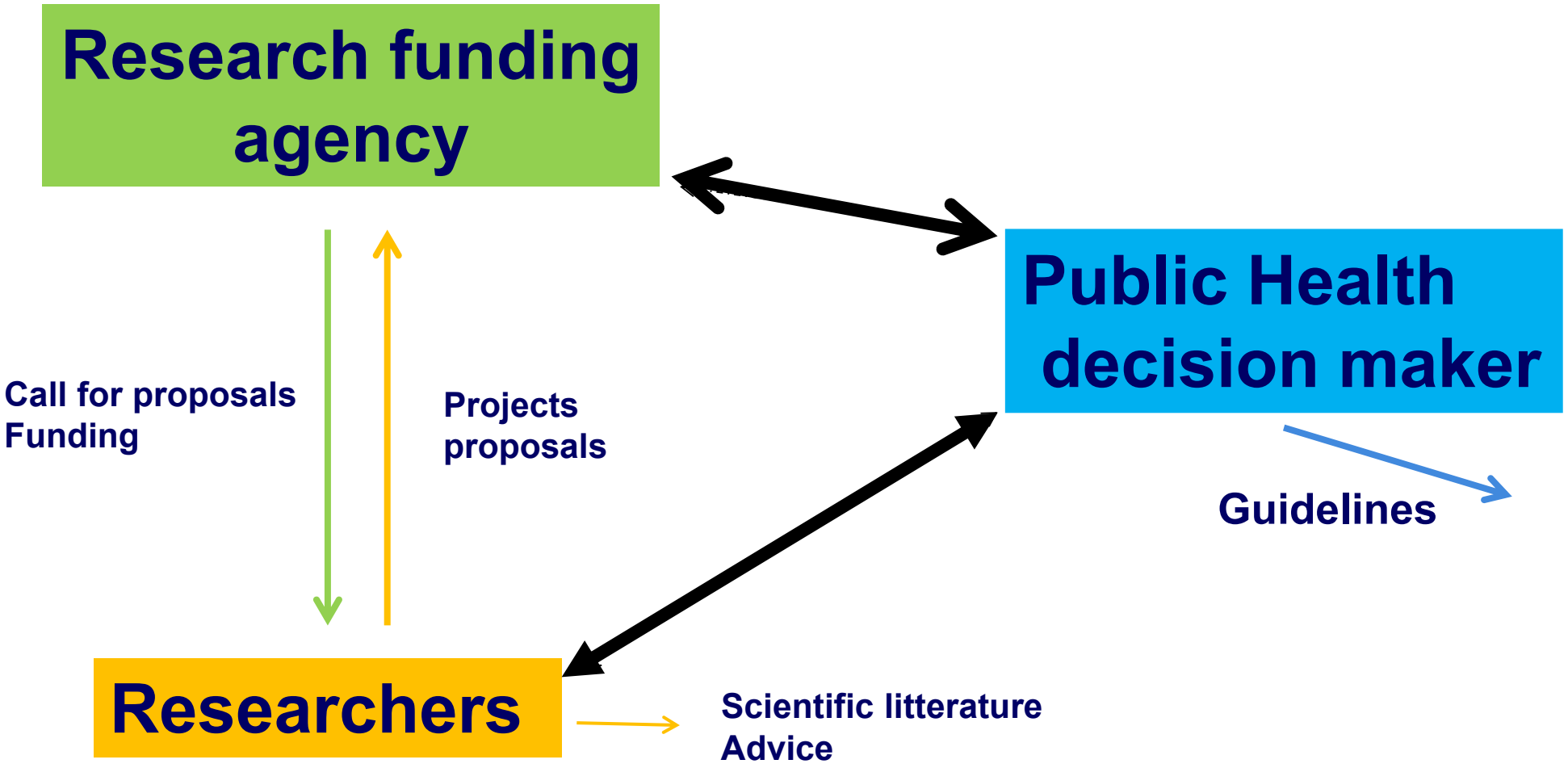
- The BRaVe initiative aims at reducing public health (severe disease) and economical impact due to viral respiratory infections by
  - Filing the gaps in knowledge
  - Developing innovative therapeutic and preventive interventions
  - Proposing comprehensive strategies including viral etiologies

- 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



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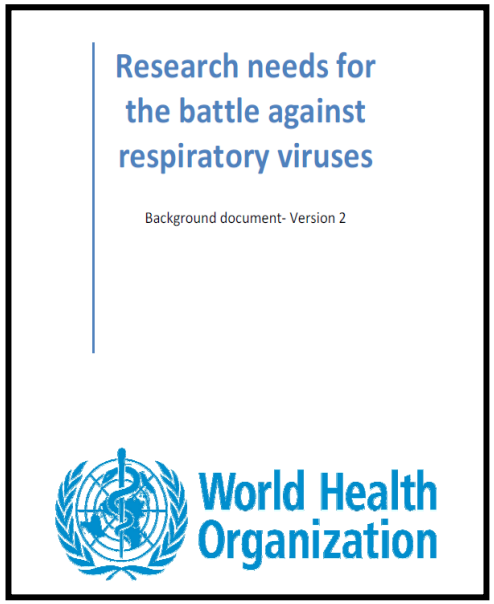
What has been done so far ?

- 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/ALRIs**
- 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

http://www.who.int/influenza/patient_care/en/

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

	Rhinovirus (n=580)	RSV (n=1655)	Adenovirus (n=902)	Parainfluenza 1 (n=94)	Parainfluenza 2 (n=49)	Parainfluenza 3 (n=315)	Influenza A (n=544)	Influenza B (n=139)
Pneumonia	18%	16%	8%	9%	6%	14%	9%	8%
Wheezy bronchitis	22%	12%	2%	2%	4%	8%	6%	6%
Bronchiolitis	3%	34%	1%	2%	10%	5%	1%	1%
Otitis media	23%	59%	24%	27%	20%	30%	26%	19%
Fever >38°	44%	63%	81%	77%	76%	63%	94%	89%

* 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