Research needs for the Battle against Respiratory Viruses (BRaVe)

Meeting report for World Health Organization (WHO) informal technical consultation, Geneva, 6–7 November 2012
FOREWORD

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The Battle against Respiratory Viruses (BRaVe) is a cross-cutting effort at the World Health Organization (WHO) that combines resources and expertise to better confront the problem of viral respiratory diseases. The different clusters include Health Security and Environment; Health Systems and Innovation; and Family, Women’s and Children’s Health.

This document reports on the findings of the WHO informal technical consultation “Research needs for the Battle against Respiratory Viruses”, which was held in November 2012. The consultation followed an informal consultation “Towards effective treatment of severe acute respiratory illnesses: Focus on influenza and acute viral infections”, at which the BRaVe research agenda was first presented.
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INTRODUCTION

OBJECTIVES OF THE MEETING

Acute respiratory infections kill an estimated 3.9 million people per year. These infections are one of the top five causes of mortality worldwide, and in many developing countries they are the leading killer in children under 5 years of age.

The World Health Organization (WHO) and United Nations Children’s Fund (UNICEF) have developed a global action plan to tackle this problem, through a combination of interventions to prevent and treat community-acquired pneumonia (CAP) in children. In the past decade, useful strategies have been implemented globally, including increased coverage with pneumococcal and *Haemophilus influenzae* type B vaccines, to reduce the burden of acute respiratory infections and reach the Millennium Development Goal of halving childhood mortality.

More effort is needed to address viral respiratory infections. These infections affect all age groups, but particularly the very young, the elderly and those with chronic medical conditions. In addition to increasing the risk of secondary bacterial infections, respiratory viruses are implicated in about half of CAP cases in children, more than 90% of bronchiolitis cases in infants, and 85–95% of asthma exacerbations in children. In adults, they are implicated in 30–50% of CAP cases, 80% of asthma exacerbations, and 20–60% of chronic obstructive pulmonary disease exacerbations.

Hence, common respiratory viruses cause an enormous burden to health systems, and economic costs to society (directly through medical expenses, and indirectly through productivity losses). Furthermore, emerging respiratory viruses, such as severe acute respiratory syndrome, H5N1 avian influenza, and pandemic (H1N1) 2009 influenza threaten global health security.

Current pharmacologic interventions for respiratory viral infections are largely limited to vaccines and antivirals for influenza. Although their use has provided important public health benefits, and has demonstrated the potential of such measures for respiratory viruses, no vaccines or therapeutics of proven value are currently available for respiratory viruses other than influenza.

The aim of the Battle against Respiratory Viruses (BRaVe) is to address these challenges. The first steps will be to:

- identify gaps in knowledge, and the tools needed to develop effective interventions;
- articulate a research agenda that reflects public health research priorities;
- increase research efforts to develop new preventive and treatment options, including those applicable in under-resourced settings, through engagement of stakeholders and implementation of this research agenda;
- foster multidisciplinary approaches, to improve clinical management of acute respiratory infections.

BRaVe is a cross-cutting effort at WHO that combines resources and expertise to better confront the problem of viral respiratory diseases by linking different clusters. In November 2012, the WHO informal technical consultation “Research needs for the Battle against Respiratory Viruses” gathered 60 participants from 42 different institutions, to review and assess research needs to combat respiratory viruses. Annex 1 gives the agenda for the meeting, and Annex 2 the list of participants.
On the first day of the consultation, the revised research agenda was presented and discussed in plenary session, to foster multidisciplinary discussions. The second day involved an assessment exercise. In the morning, participants were divided into small working groups to further assess and refine the research questions by tracks (Annex 3). In the afternoon, the results were presented in plenary session.

A call to action (Annex 4) was also presented to the participants for their signatures. It targets decision-makers, highlighting the involvement of the research community. Signatories state the importance and the urgency to address, in an integrated and effective way, the issues linked to viral respiratory infections. Already, 48 people have joined this initiative (see Annex 4).

Together, the refined research agenda and the call to action will be presented to relevant stakeholders, so that the research needs identified can be addressed.

Documents relevant to the BRaVe initiative will be available from the WHO web site.

**CROSS-CUTTING TOPICS**

Cross-cutting topics that emerged during the consultation were:

- the importance of coinfection (viral–viral and viral–bacterial) in the etiology of respiratory diseases, and the need for further studies;
- the critical nature of basic and clinical research in developing tools to combat respiratory viruses, and the need to ensure that these two types of research are closely articulated;
- concern that settings with limited resources would not adequately benefit from many of the ‘fruits’ of basic research.

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# Defining the Burden of Disease of Viral Respiratory Infections

**Presentation:** Abdullah Brooks, Bangladesh (delivered by Frederick Hayden)

**Discussion**

## 1.1 Unrecognized Infection

The extent of viral infection, both asymptomatic and symptomatic, is unknown, but is probably much higher than is generally accepted. For example, asymptomatic rhinoviral infections may be present in up to 40% of children under 1 year of age, and mortality associated with such infections may also be greater than realized. Similarly, recent studies using the latest polymerase chain reaction (PCR) techniques have uncovered a higher than expected prevalence of asymptomatic coronavirus infections.

Although children represent a substantial portion of the burden of disease, older adults and the elderly are also quite affected by viral respiratory infections, but are often neglected in discussions about burden of disease. Studies designed to quantify or compare the impact of viral respiratory infections in children and adults would be useful in defining and understanding the global burden of viral respiratory infections.

### Coinfection

The contribution of viral and bacterial coinfection to the burden of viral respiratory infections is greatly underestimated. Furthermore, there are large gaps in knowledge of the etiology of coinfection – particularly in resource-limited settings – and research addressing these gaps is currently insufficient.

Given that many bacterial infections might also have a viral component, mortality from infections assumed bacterial only might be reduced if the viral component were addressed. To illustrate the role coinfection may play in morbidity of severe respiratory infections, results from a Greek study were informally presented during the discussion. In the Greek study, rhinoviral-associated hospital administrations of children were halved when a pneumococcal conjugate vaccine was administered. Thus, rhinovirus seems to be important in severe pneumonia requiring hospitalization.

Additional research is needed to assess the role of overgrowth of endogenous respiratory bacteria and the subsequent immune response in viral infections; such overgrowth might be interpreted as pneumonia, particularly when no pneumococcal pathogen is found. A better understanding is also needed of how host factors and comorbidities (e.g. asthma and cystic fibrosis) might affect the endogenous bacteria lining the airways of the respiratory system.

Care must be taken with data analysis when studying coinfection, particularly with the advent of large multiplex PCR assays and protocols. Where multiple or mixed pathogens are identified, deciphering the etiology and pathogenesis of a respiratory infection requires careful interpretation of data; it is also important to use appropriate comparison groups when studying burden of disease.

## 1.2 General Issues

Although the current burden of viral respiratory infections is not known precisely, it is largely ignored or underestimated in the public health community. Convincing this community of the heavy burden of viral respiratory infections is all the more difficult because, when a patient presents with symptoms of a respiratory infection, clinicians often assume bacterial infection (and hence administer antibiotics) rather than considering the possibility of a viral infection.
It is likely that the magnitude of the economic burden is also underappreciated, especially in light of the ageing population that may be infected, particularly in the Northern hemisphere.

1.3 Restitution of the Assessment Exercise

More research is needed to define the age-related burden of respiratory viral infections and what might be achieved with more effective interventions. Both hospital-based and community-based surveillance systems are required to provide quality data that link respiratory viral infections and bacterial etiologies with outcomes. The overall strength of results could be increased by synergies between improved surveillance and vaccine or antiviral probe studies.

Priority Research Questions

1.1 Assess the overall burden of disease generated by respiratory viruses, including their economic consequences, by:

- identifying the key respiratory viruses responsible for the major burden on health-care systems in different settings (e.g. rural versus urban, tropical versus temperate), and seasons or times of the year;
- assessing the proportions of specific viral, bacterial and mixed-pathogen infections in pneumonia and other serious acute lower respiratory infection (ALRI) syndromes in different age groups and settings;
- assessing the proportion of specific viral pathogen infections in exacerbation of other underlying conditions, particularly asthma, chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD);
- assessing the interactions between acute respiratory viral infections and other infectious diseases, including human immunodeficiency virus (HIV) and tuberculosis (TB).

1.2 Characterize the dynamics of respiratory virus transmission, the associated factors and their impact at:

- individual, household, and institutional levels, and assess the utility of selected non-pharmaceutical interventions;
- population level (including factors in seasonality, interference and routes of transmission).

1.3 Assess the occurrence of respiratory virus infection and infectiousness in nosocomial settings, and identify cost-effective means to prevent transmission.

1.4 Determine the longer term consequences of respiratory viral infections in infants and young children (e.g. development of asthma or chronic lung disease).

1.5 Evaluate the potential reductions in burden of disease and the potential health-care effects gained or realized in treating respiratory viral diseases.

1.6 Measure the comparative advantage (e.g. in terms of technical demands and costs) of reducing disease burden with different combinations of preventive and therapeutic measures (e.g. individual hygiene measures, vitamins, oxygen therapy, antiviral therapies and intensive care) for known pathogens.
2 UNDERSTANDING DISEASE PATHOGENESIS AND HOST DYNAMICS OF RESPIRATORY VIRAL INFECTIONS

Presentation: Menno de Jong, The Netherlands

Discussion

2.1 ASYMPTOMATIC INFECTION AND COINFECTION

In terms of pathogenesis, the presence of a particular virus without associated symptoms could lead to the assumption that the virus is not relevant to, or does not contribute to, coinfection. For example, a patient who had a rhinovirus infection 6 weeks ago may now be asymptomatic, even though rhinovirus can still be detected. If the patient acquires another viral or bacterial respiratory infection, the question is: Does the presence of the rhinovirus make no difference, or does the asymptomatic rhinovirus modulate the pathogenesis of the subsequent infection in some way (either positive or negative)?

Insight into coinfection might be gained from continuing influenza vaccine trials, in that vaccine candidates could serve as probes to tease out contributions of viral or bacterial components of infection. Also, some of the drug trials targeting respiratory infection might be able to provide more information on the acute effects of different viruses. Another area where further research is needed is in understanding viral replication, especially in the context of host immune responses (e.g. the “cytokine storm”). Identification of cellular or molecular markers in common pathways of infection is likely to be the most useful approach to this issue.

STANDARDIZED METHODOLOGIES AND NEW APPROACHES

Viral kinetics remain largely unknown. When assessing pathogenesis and viral load, in particular, the data are essentially a snapshot; thus, care must be used when interpreting such data. Given this situation and the complexity of coinfection, the multiple control groups needed for studies must be carefully selected.

Standardizing laboratory methods – in particular, collection of serial specimens – would allow better comparison and sharing. Sample collection from the lower respiratory tract is difficult and invasive (and is likely to remain so), unless a patient is already intubated. Critical-care specialists rarely consider a diagnosis of respiratory infection, and patients are rarely tested.

It continues to be difficult to source funding for studies of coinfection or product development. Improving communication with funding organizations and grant managers should be a high priority. Several issues remain of interest; for example, how best to implement a systems biology approach with respect to coinfections, reduce delays in hospitalization for patients with a coinfection, and identify the contribution of coinfections.

2.2 RESTITUTION OF THE ASSESSMENT EXERCISE

Improved understanding of virus–host interactions in key patient groups will be fundamental to the design of effective therapeutics and vaccines. Areas for investigation include the basis of transmission, the pathology associated with infection, and the mechanisms and consequences of viral and bacterial coinfections. Complementary basic and clinical research approaches are required to address the essential research objectives outlined below.
**Priority research questions**

2.1 Understand the interactions of different respiratory viruses with host-cell pathways, and their roles in pathogenesis and as potential targets for intervention.

2.2 Characterize viral and bacterial replication dynamics and host immune responses in the upper and lower respiratory tracts during infection in key patient groups.

2.3 Understand the interplay between viral, bacterial (including the human microbiome) and host factors in disease pathogenesis.

2.4 Understand the effect of the virus on immune responses, including the basis of protection and the role of viruses in inhibiting effective responses.

2.5 Understand the pathogen, host and environmental factors and mechanisms that determine viral and bacterial transmission.

2.6 Clarify the issue of disease causation for different viruses (e.g. frequency of subclinical infection, and significance of viral ribonucleic acid [RNA] detection), and the contributory roles of specific pathogens during infection with multiple agents.

2.7 Identify host genetic factors that determine susceptibility to respiratory viral infections and the severity of such infections, and assess the implications for therapeutic interventions.

2.8 Determine the underlying mechanisms for established major risk factors in the host (e.g. pregnancy, obesity, smoking and comorbidities) and the environment (e.g. passive smoking and indoor air pollution) associated with increased disease severity.

2.9 Promote efforts to obtain etiology and pathogenesis data from fatal cases, through strategic use of limited postmortem sampling (e.g. needle biopsies of affected and unaffected lungs).
3 EXPANDING TREATMENT OPTIONS FOR VIRAL RESPIRATORY INFECTIONS

Presentation: Frederick Hayden, David Spiro, United States of America (USA)

Discussion

3.1 PREPAREDNESS AND THERAPIES

PREPAREDNESS FOR NEXT OUTBREAK AND VALUE OF OBSERVATIONAL STUDIES

Research and clinical communities place a heavy emphasis on data derived from randomized controlled trials (RCTs). However, with respect to antiviral treatment of influenza, knowledge gained through observational studies could be just as valuable as that gained through RCTs. Small observational studies can be informative, although their findings must be interpreted with caution. However, in the early stages of an outbreak with a new pathogen, or with a small number of linked cases (e.g. the recent cases of coronavirus in the Middle East), small observational studies are all that the research community can conduct. Furthermore, the research community is somewhat obliged to conduct these studies, because some level of data is needed to develop initial treatment recommendations, and the more data that are available, the easier it is to develop recommendations. Ideally, prospective studies for an unexpected outbreak would be planned and ready to go, so that data collection could begin immediately. However, even when such preparations are in place, making treatment recommendations based on limited data can be problematic, particularly in relation to children, because they may be naive to respiratory infections, and little may be known about side-effects, complications and so on.

A real-world example of this was provided for pandemic (H1N1) 2009 influenza, when health leaders were asked to put together guidance for care of children and adults, at short notice and with little data. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) was formed in part to increase preparedness and facilitate data collection, by putting mechanisms and infrastructure in place to deal with the next outbreak. Preparedness goes beyond developing RCT infrastructure, it also includes ensuring that the necessary funding, administrative issues and so on are in place. This process should include input from the public health community and those providing diagnostic support, as well as from clinicians.

SPECIFIC THERAPIES

The effective use of neuraminidase inhibitors (NAIs) was discussed, based on Japan’s experience during the pandemic (H1N1) 2009. Clear benefits of NAIs have been demonstrated in several studies, with substantial reduction in mortality seen even when treatment with NAIs was delayed. An ecological study also suggested an association between NAI supply and decreased mortality.

Some issues remain; for example, disease progression in some patients despite receiving NAIs, and problems of resistance. Newer drugs will be needed to complement those currently available. Some studies revealed that NAIs are ineffective in animals experimentally infected with highly pathogenic influenza viruses, but both the polymerase inhibitor T-705 and antibody therapy are effective, if given 3 days or longer after infection, respectively. Studies also found that immunocompromised animals treated with combination therapies die as soon as the treatment ceases, and virus continues to replicate even in the presence of the drugs.

Participants discussed the value of respiratory syncytial virus (RSV) monoclonal antibody therapy (Synagis), particularly with respect to use in healthy infants. The cost of the current therapy is prohibitively high, at approximately US$ 1000 per dose. However, antibody grown in tobacco plants
appears to be as efficacious as the monoclonal antibody in animal models, and might be able to reduce the cost 20-fold.

Large multisite studies of oseltamivir and combination therapies for influenza, as well as a smaller parainfluenza treatment study, are currently being conducted at the National Institutes of Health (NIH) treatment centre. However, identifying patients who have an infection that is severe enough to warrant treatment, but not so severe that they are unable to inhale the powdered antiviral, remains an issue.

**GENERAL COMMENTS**

The value of observational studies needs to be better communicated to clinicians and the public at large; however, there was no consensus on how this might be achieved.

### 3.2 RESTITUTION OF THE ASSESSMENT EXERCISE

More research is needed to expand treatment options across the range of respiratory viral pathogens. The prioritization process will be informed by emerging data from studies of burden of disease and pathogenesis, but the available data from studies of seasonal burden of disease indicate that therapeutics for RSV and rhinovirus infections should be emphasized. Careful studies of antiviral resistance and human pharmacokinetics (including pharmacokinetic–pharmacodynamic relationships and drug–drug interactions for combination therapies) are cross-cutting issues that need to be integrated into therapeutic development strategies.

**PRIORITY RESEARCH QUESTIONS**

**3.1** Develop and test new antivirals and combinations of antivirals for major respiratory viral pathogens according to their burden:
- given current burden-of-disease data, prioritize the development of inhibitors for RSV and rhinovirus infections;
- given concerns about resistance to adamantane and NAIs, also prioritize development of influenza inhibitors with novel mechanisms of action;
- test the effectiveness of combination antiviral therapy in seriously ill, hospitalized patients with influenza.

**3.2** Develop novel antiviral modalities and test their effectiveness in relevant target populations; test:
- existing broad-spectrum antivirals (e.g. favipiravir and nitazoxanide);
- broad-spectrum antivirals against emerging viral threats (e.g. interferons for novel coronavirus);
- host pathway-directed therapies, particularly those potentially inhibiting replication of multiple viral pathogens.

**3.3** Determine the host factors (e.g. genetic differences in drug metabolism) and drug pharmacokinetic factors that predict responses to antiviral treatment, risk of adverse events and risk of emergence of resistance.

**3.4** Optimize dose regimens of existing antivirals for particular target populations.
3.5 Assess the effectiveness and safety of low-cost adjunctive therapies with regard to potential to modulate the course of infection and of illness, including host immune responses. Therapies to test include:

- vitamin and mineral supplements (e.g. probiotics, selenium, vitamin A, vitamin D and zinc), especially in populations with deficiencies;
- immunomodulatory interventions (e.g. corticosteroids, cyclo-oxygenase 2 inhibitors, glitazones and statins), particularly for treatment in conjunction with antivirals in severe illness;
- commonly used medications for symptom relief (e.g. non-steroidal anti-inflammatory drugs NSAIDs).

3.6 Define the criteria for using combinations of treatments, especially for antivirals and antibiotics, and for antivirals and immunomodulatory agents.

3.7 Develop affordable prophylactic interventions (e.g. vitamin and mineral supplements) for high-risk groups, to determine the ability of such interventions to reduce the vulnerability of patients before infection.
IMPROVING SEVERE ACUTE RESPIRATORY-TRACT INFECTION DIAGNOSIS
AND DIAGNOSTIC TESTS

Presentation: Daniel Jernigan, USA

Discussion

4.1 FEATURES AND UTILITY OF TESTS

GENERAL FEATURES OF RAPID DIAGNOSTIC TESTING

Although the specificity of many diagnostic assays for severe acute respiratory-tract infection (SARI) is relatively high, the sensitivity of most needs to be improved. Low or variable sensitivity of diagnostic assays probably explains why fewer clinicians are now using such assays, and in turn, why fewer antivirals are being prescribed. The Centers for Disease Control and Prevention (CDC) is actively working to educate clinicians on recent developments in diagnostic testing; for example, through online continuing medical education content and videos of collection of respiratory samples.

Direct detection of virus is generally limited to the first couple of days of infection – often before symptoms arise. Additional markers may be measurable later in disease. However, in lieu of such markers, informative comparison groups might indirectly provide relevant information, hence the need for appropriate outpatient and inpatient controls that will allow effective interpretation of data. Serial swabs may help to determine what is happening over the course of an infection. Similarly, it would be useful to perform diagnostic time-course studies of patients receiving antiviral therapy, to help in determining the effectiveness of the treatment and course of clinical management.

Although some PCR-based assays can pick up some examples of known antiviral resistance, none can currently identify novel resistance. Sequencing platforms, however, would identify both the resistance markers already identified and novel ones. At the moment, sequencing is more resource-intensive than PCR-based assays. The larger, more complex PCR assays testing multiple samples or multiple pathogens generate large amounts of data, raising questions about data storage and analysis. Cloud-based storage and sharing may offer a convenient solution, particularly for multisite studies. Bioinformatics and data-sharing will play a significant role in managing and interpreting diagnostic testing data.

All of the new-generation multiplex PCR assays, panels and cards for viral respiratory infections are being developed in the private sector; also, financial considerations such as protecting or exploiting intellectual property have driven up prices of many of the newer technologies. Recommendations for taking advantage of the new technologies include being diligent and focused on what is tested (e.g. find an appropriate balance between the scope of testing and the cost of the assay).

PUTTING THE GLOBAL UTILITY OF RAPID DIAGNOSTIC TESTING IN PERSPECTIVE

Procalcitonin (PCT) tests are valuable in helping to diagnose patients with bacterial infection, and thus facilitate judicious prescription of antibiotics. The high cost of rapid diagnostic testing prevents its widespread use in resource-limited settings. Most of the studies with PCT and associated tests have been conducted in resource-rich settings; little is known of how the PCT tests would perform in resource-limited settings where other diseases are endemic.

The practicality of rapid diagnostic testing in resource-limited or remote, rural areas remains questionable. Even if, in 5–10 years from now, effective agents have been discovered and are available for a number of respiratory viruses, most resource-limited settings are unlikely to have the necessary...
diagnostic infrastructure and instrumentation to process and analyse samples. It would take considerable time for the sample to make the journey to an appropriate facility and for results to be returned.

Decisions have to be made, taking many considerations into account, about whether or not it is worth having or using a diagnostic tool. Most of the advances in diagnostic capability are not currently relevant to resource-limited settings. However, the industry believes that decreasing costs and favourable timing of new diagnostic technologies will ultimately lead to broader support by health systems.

It would be useful to develop a message about the need or desire for diagnostic tools in resource-limited settings, and to develop an understanding of what tools would be useful, given that little is currently known.

4.2 Restitution of the Assessment Exercise

The success of improved diagnostic methods over the past decade indicates that the situation with respiratory infections is more complex than previously thought. Development of diagnostic tests should focus on three main goals:

- improve clinical management of patients;
- assist surveillance and determination of burden of disease;
- support other areas of research into viral respiratory infections (e.g. evaluation of novel therapeutics).

Development of platforms applicable to multiple pathogens and sample types should be prioritized. To better assess and understand the complexity of respiratory infection, the points given below should be emphasized.

Priority Research Questions

4.1 Develop reference reagents and performance standards to promote diagnostic development and to assure accurate test performance.

4.2 Strengthen comprehensive characterization of respiratory specimens to inform diagnostic test development, validation and interpretation, through deep sequencing and public posting of genetic and epidemiologic findings.

4.3 Evaluate existing specimen collection techniques and devices, and develop new methods that improve diagnosis of respiratory diseases.

4.4 Develop simple, accurate, low-cost nucleic acid amplification tests (NAATs) for acute respiratory diseases.

4.5 Identify early biomarkers of the etiology and prognosis of pneumonia and ALRIs.

4.6 Develop protocols, algorithms and tools for rapid identification and characterization of emerging respiratory infections.
5 IMPROVING CLINICAL MANAGEMENT OF SARI/ALRI

Presentation: Jeremy Farrar, Viet Nam

Discussion

5.1 BENEFITS AND ISSUES

BENEFITS OF INTEGRATION

Better integration of research and clinical practice is needed, particularly in the context of maximising benefits and minimizing harm in patients and trial participants. Recent clinical trials compared the benefits and disadvantages of a frequently used therapy (high-frequency oscillation) that has been associated with increased mortality, and a simple intervention (placing patients in a prone position) that has been associated with reduced mortality. The increasing number and quality of electronic databases containing patient information could facilitate sharing of information and promote more informed and effective treatment of patients. For instance, in the United Kingdom of Great Britain and Northern Ireland (UK), the Health Protection Agency (HPA) works with intensive-care colleagues, clinicians, laboratory professionals and the public health community to improve patient care by increasing awareness and understanding across disciplines.

ISSUES IN RESOURCE-LIMITED SETTINGS

Diagnostic capabilities in some resource-limited settings might impede timely treatment of respiratory infections. Further education or training would help to improve diagnosis of respiratory infections. However, resource-limited settings are unlikely to benefit in the near-term from many of the diagnostic tools and antiviral therapies. Therefore, clinical management should rely on better use and implementation of what is currently available.

Problems of cost and accessibility are ultimately resolvable, as has been seen in the case of access to antiretroviral therapies. Furthermore, although resource-limited settings do not have access to the latest technology, crucial research questions still can be addressed by conducting studies in such settings. For example, results from a multicentre RCT conducted in Eastern Africa demonstrated that fluid resuscitation in children with severe infection increased mortality. Planned for sites in Uganda and Niger, the Children’s Oxygen Administration Trial (COAST) will provide evidence for the most clinically effective and cost-efficient targeted use of oxygen as a life-saving treatment.

5.2 RESTITUTION OF THE ASSESSMENT EXERCISE

Better integration of research activities and clinical practice is crucial in developing the most relevant evidence base for policy decisions. All ages and all settings have to be considered when improving clinical management practices. Clinical research can be undertaken with designs ranging from observational studies to RCTs (traditional or adaptive). Improved clinical research design, in conjunction with advances in basic science, will help to:

- identify the patients who are most ill, and thus most likely to require intervention;
- assess and develop effective interventions;
- promote more timely exchange of data and knowledge.
**Priority Research Questions**

5.1 Develop algorithms to identify high-risk patients and prognostic markers at an early stage of the disease.

5.2 Validate specific protocols, including supportive-care interventions such as rehydration and oxygen, to reduce the risk of severe outcomes. For instance, the use of a pulse oximeter for early diagnosis and case management of hypoxemia warrants more study.

5.3 Develop and validate clinical management algorithms for optimizing SARI outcomes in resource-limited settings, including use of a range of therapeutics and supportive or adjunct therapies.

5.4 Develop further evidence on oxygen therapy (protocols for use and benefits), to enable its inclusion in the WHO list of essential medicines.

5.5 Promote research on oxygen delivery and dispensing devices that are better adapted to all settings (including household and low-resource settings), particularly low-cost and easy-to-maintain ventilatory support systems.

5.6 Determine feasible approaches to reducing risks of nosocomial transmission of viral respiratory infections in health-care and household settings.

5.7 Compare the risk–benefit and cost-effectiveness of various therapeutic strategies (e.g. treatment of mild cases, versus all cases, versus severe cases only).

5.8 Assess the conditions in the health-care systems to ensure the optimal implementation of recommended changes.

5.9 Promote innovative clinical research design, and sharing of data and knowledge.
6 SHIFTING PERCEPTIONS AND OPTIMIZING PUBLIC HEALTH STRATEGIES

Presentation: Ximena Aguilera, Chile

Discussion

6.1 EXPERIENCES AND CONSIDERATIONS

DIFFERENT EXPERIENCES IN DIFFERENT SETTINGS

Coordination, communication and flexibility were identified as being critical for successful planning and maintenance of preparedness activities, in managing widespread respiratory viral infections. There is a need to develop and maintain strong relationships with communities, and capable communication networks or systems during “peace time”, to be ready for the next epidemic or pandemic.

In some settings, there is a need to develop and implement different types of preparedness, taking into account difference in cultural contexts. Despite international guidelines, many countries do things according to their own cultures, their own political systems and their own public assistance programmes. Certain aspects of these approaches may have more relevance in some settings than international guidelines.

New pandemic planning is taking place in many parts of the world, but probably in an uncoordinated manner. Being prepared for something unexpected remains a crucial issue. No one can anticipate what the next viral outbreak might look like, or how it might spread. Modeling studies could be particularly helpful, if made appropriate for a particular outbreak using relevant criteria.

In Thailand, the (H1N1) 2009 pandemic had a strong political impact. Politicians looked to clinicians and the public health community for ways to stop the pandemic, then realized this would not be possible. However, based on preparedness planning, the country implemented public health responses, including increasing awareness of respiratory viral infections and education of the public on best practices to prevent transmission (i.e. non-pharmaceutical interventions). Although the public’s understanding of viral respiratory infections and availability of treatments was limited until the (H1N1) 2009 pandemic, a certain awareness has been created and should be studied, to assess current perceptions and thus improve preparedness.

Improving preparedness and public awareness rely on addressing issues of communication. The public has less trust in politicians than in the clinical and public health communities. Hence, preparedness should be linked more closely to public health communities. Improvements in communication from health leaders is needed (e.g. more opportunities and more effective modes of communication).

Isolation or cohorting might be a useful tool, not only during epidemics and pandemics, but also to address seasonal influenza and other viral respiratory infections. Hospitals are a major setting for transmission of respiratory infections. Isolation and cohorting interventions should be considered in the design and planning of new health-care facilities. For existing settings, improved clinical management may help to overcome the rigidity of the structure, thus limiting transmission.

CONSIDERATIONS IN MEASURING SUCCESS OF BEHAVIOURAL INTERVENTIONS

Health-care workers (HCWs) are at increased risk for exposure to viral respiratory infections and may transmit disease to patients. However, protection of patients is not a primary driver for HCWs receiving influenza vaccination. This situation highlighted the need to tailor public health messages differently to different audiences. In an example from the USA, personal gain was a stronger motivating factor than
protection of patients for HCWs to get vaccinated. The fact that vaccination could reduce the number of
days taken off sick was a strong factor for immunization uptake. In discussing effectiveness of the
intervention, HCWs might be less interested to hear about how many influenza cases were avoided than
about how many sick days were accrued or how there was less need to use masks or other personal
protective equipment (something that many HCWs find cumbersome). In the case of politicians, a
different metric might be relevant (e.g. how many fewer days factories were closed).

Participants raised questions about what type of data should be generated and what metrics should be
used during the maintenance phase of preparedness, to support the necessary behaviour change. It was
noted that the metrics may well not be of a public health or clinical nature.

6.2 RESTITUTION OF THE ASSESSMENT EXERCISE

More research is needed on strategies to prevent and control respiratory viral infections, and on the
timely and effective integration of innovation and advances in science with decision-making and public
health practices. Of particular importance is communication to different stakeholders, especially HCWs,
who are pivotal in implementing change in health-care systems. Obtaining better data on current
knowledge and practices will allow strategies to be refined, and local adaptation and implementation to
be improved. A strong emphasis on linking evidence and practices is needed.

PRIORITY RESEARCH QUESTIONS

6.1 Compile evidence to support the development of relevant public health strategies – preventive and
responsive; individual and community-based – to mitigate the impact of respiratory viral infections.

6.2 Survey the landscape of vaccines for non-influenza respiratory viruses, and promote efforts to
develop effective vaccines for key target groups.

6.3 Study knowledge, attitudes and practices of:
  ➢ HCWs in relation to common and severe respiratory diseases in different settings;
  ➢ the general public on respiratory viral infections, to increase adherence to public health
measures.

6.4 Assess the impact of various communication strategies to improve the management of respiratory
infections.

6.5 Develop mathematical models to guide decisions about the most effective combination of measures
to mitigate the impact of viral respiratory infections.

6.6 Assess and compare current decision-making processes related to respiratory viral infections in
different settings, health-care systems and risk groups.
7 FUNDING AGENCY PERSPECTIVES ON BASIC RESEARCH

A number of projects in research are funded every year in several areas related to RVIs. However, given the vast number of different fields of expertise needed to address RVIs issues, it is unlikely that one is fully aware of all on-going or future initiatives and perspective. In order to increase information sharing and possible synergies amongst different areas of expertise, representatives from funding research agencies were invited to present their institutions’ perspective and on-going activities as well as their process for funding research.

On-going and/or future funding streams of interest for the Battle against Respiratory (BRaVe) initiative include:

- Disease or pathogen-specific strategies (on-going for influenza, RSV and pneumonia);
- Treatment for RVIs throughout the entire treatment pipeline, from discovery to development and delivery;
- Global surveillance of respiratory viruses to improve preparedness building on and expanding existing networks;
- Cross-cutting streams for example, treatment, diagnostic and strategic information, and advocacy;
- Resource-limited-focused research such as:
  - underappreciated viruses in resource-limited settings (e.g. RSV and rhinovirus);
  - laboratory construction and refurbishing in resource-limited settings;
  - impact of respiratory viruses in community and hospital settings;
  - clinical trials and innovative therapeutics in low-resource settings.

Funding agencies represented:

- The Bill & Melinda Gates Foundation
- Fondation Mérieux
- Wellcome Trust
- The Medical Research Council
- The CONCISE initiative
- The European Union
8 MOBILE CLINICS: HOW TO IMPROVE ACCESS TO HEALTH IN REMOTE AREAS?

Presentation: Myer Glickman, UK, and Charles Senessie, Switzerland

Discussion

Mobile clinics are used in remote areas, and provide an important service to those who do not have regular access to health care. Providing health care in such a format is challenging. Collecting data can be difficult, both from a patient recall perspective and because of the high rate of loss to follow-up. Organizing and preparing staff can also be challenging. The clinics bring doctors from various locations, with different experiences and training, together with other volunteers.

Some symptoms may be overreported, because many people might come to the clinic simply because it is an ‘outing’. Once there, they may feel compelled to invent or exaggerate symptoms (e.g. a runny nose, cough and so on). For instance, the upper respiratory-tract infection rate was quite high in children and mothers, whereas few men of working age attended the clinic. Data collected from this kind of health-care setting should thus be analysed with care.

A large number of the patients attending the mobile clinic were prescribed antibiotics (probably many more than actually had bacterial infections). Rates were even higher than in the USA, which has a high prescription rate for antibiotics. Local protocols to prescribe antibiotics were followed, supplemented with physician knowledge and data on vital signs (e.g. weight, blood pressure and temperature). When a physician was unsure about a diagnosis, a referral was made. Referral rates were fairly high; thus, there is a need for strong ties to local health-care systems and representatives. Local medical students can often be recruited to support this function. Having the support of local health representatives or some other guidance can help HCWs to resist the pressure to prescribe something to patients attending mobile clinics.

Many concerns and challenges are common to efforts at providing health care in resource-limited settings. One way to obtain better incidence data and find out how many people might be sick but not seeking care is to run a mobile clinic that includes door-to-door catch-all surveillance (as has been done in Madagascar). Even if individuals were not sick at the time of interview, they were asked other questions to gather data that could be used to develop incident figures (e.g. “Were you sick in the past 2 weeks?”, “Do you know of others nearby who were sick?”, and so on).
9 VACCINES AGAINST INFLUENZA INFECTIONS: WHERE ARE WE?

Presentation: John Tam, WHO

Discussion

REGULATORY ISSUES AND LENGTH OF VACCINE APPROVAL

A recurrent issue regarding vaccines, especially for influenza, is the cost and the length of time taken to obtain vaccines approval. Research on influenza vaccines has focused on developing a better range of protection. However, development of new vaccines remains highly expensive.

To be approved, a new vaccine must have at least 50% efficacy during clinical trials. These kind of trials often require the recruitment of at least 30,000 subjects and, given their high cost, they are often supported by the pharmaceutical industry. Better standardized assays and newly identified biomarkers would help to reduce some costs and thus shorten the approval process. Novel and innovative design of clinical trials is needed. In terms of the regulatory process, it is time consuming to obtain vaccine approval, mainly because of safety of vaccines. However, it is difficult to speed up the process while maintaining high criteria for safety considerations.

In Thailand, vaccines research and development (R&D) and manufacturing focus on seasonal influenza. Standard procedures for regulatory approval are followed, and experts from both the regulatory side and the R&D side identify potential issues. This makes it possible to create interactions between the regulatory and approval arms from the beginning of the R&D process. Regulatory issues need to be thoroughly address during the entire process.

THE EUROPEAN INNOVATIVE MEDICINES INITIATIVE AND EUROPEAN REGULATORY PROCESS

At the European level, the IMI aims to foster R&D. European manufacturers have invested money; it is expected that this will force the market (i.e. have a snowball effect), ensuring that substantial funding is committed at some point.

In the meantime, European medicine agencies have started to better organize and modernize the regulatory approach. This is in preparation for the imminent licensing of both oral and nasal vaccines for influenza. The European regulatory process should move from being based on serology to being based on effectiveness.

TOWARDS VACCINES FOR OTHER RESPIRATORY VIRUSES

Research on an RSV vaccine is the most advanced. RSV causes a significant burden, especially in children, and is believed to trigger secondary bacterial infections. Several targets of action have been identified in children. This field of research is increasingly active, leading to hope that a vaccine will be developed in the medium term.

Rhinovirus is another respiratory virus that is responsible for a high burden of disease for the entire population. The virus causes respiratory infections and has other health effects; for example, it exacerbates asthma. Rhinovirus may cause the highest burden of disease on the overall population; however, identifying targets for vaccine development for this virus is difficult.
10 WAY FORWARD

Wrap-up discussion: Dr Sylvie Briand, Director, Pandemic and Epidemic Department, WHO

With the BRaVe initiative, WHO is taking on a new role.

The problem of respiratory viruses has been known for some time, but there are only a few therapeutic interventions, and these are specific for particular viruses; thus, most viral infections have not been addressed. With the BRaVe initiative, WHO wants to act as a catalyst for changes in research. The aim of this initiative is to accelerate synergies and efforts among several organizations and institutions.

Linking research and policy-making has always been a challenge. Often, guidelines published by WHO rely on the existing literature and a gathering of relevant experts. The guidelines production process is therefore lengthy or produces strong recommendations based on poor evidence. Through the BRaVe initiative, WHO wants to foster research from the beginning of the process, and work closely with the research community to develop and implement better policies.

BRaVe goes beyond discussions focusing on only one pathogen at a time; rather, the aim is to foster interventions covering multiple viral respiratory etiologies. It promotes patient- and impact-oriented interventions that are general rather than pathogen specific. For example, administration of oxygen, a well-known intervention, is currently under-used. One of the main reasons for this situation is the lack of evidence of the usefulness of oxygen in some settings. Further evidence is thus needed to implement oxygen use widely, especially in resource-limited settings.
ANNEXES

ANNEX 1: AGENDA OUTLINE

Day 1: 6 November 2012

09:00–10:00  Session 1: Opening and Introduction
Welcome and opening remarks  
(Marie-Paule Kieny, WHO)
Introduction and meeting objectives  
(Sylvie Briand, WHO)
Review of Declaration of Interests, housekeeping announcements  
(Nikki Shindo, WHO)

10:00–12:30  Session 2: Research needs presented by track leads, followed by discussion, N Shindo
Defining the burden of disease of viral respiratory infections  
(Abdullah Brooks, Bangladesh)

10:30–10:45  Refreshment break

10:45–12:30  Understanding disease pathogenesis and host dynamics of respiratory viral infections  
(Menno de Jong, The Netherlands)
Expanding treatment options for viral respiratory infections  
(Frederick Hayden, David Spiro, USA)
Improving SARI diagnosis and diagnostic tests  
(Daniel Jernigan, USA)
Improving clinical management of SARI/ALRI  
(Jeremy Farrar, Viet Nam)

12:30–13:45  Lunch break

13:45–14:15  Session 2: Cont.
Shifting perceptions and optimizing public health strategies  
(Ximena Aguilera, Chile)

14:15–16:30  Session 3: Facilitated discussions on research agenda, S. Briand

14:15–14:45  Mobile clinics: How to improve access to health in remote areas?  
(Myer Glickman, UK and Charles Senessie, Switzerland)

15:30–15:45  Refreshment break

16:30–17:00  Wrap-up day 1 and introduction to prioritization exercise of day 2, S Briand
Day 2: 7 November 2012

8:45–9:00  Summary of the 1st day and introduction to 2nd day sessions
(Sylvie Briand, WHO)

9:00–11:00  Session 5: Prioritization exercise, round 1: Scoring (Breakout session)
Scoring of each research question in the matrix (Annex 3)

11:00–11:15  Refreshment break

11:15–12:15  Session 6: Prioritization exercise round 2: Comparative assessment
(Breakout session)
Assess research question comparatively within each track

12:15–13:30  Lunch break

13:30–14:00  “Call to action” presentation and signature

14:00–14:30  State of the art: Vaccines against influenza: Where are we?
(John Tam, WHO)

14:30–16:30  Session 7: Presentation of each track results and discussion, N Shindo
Restitution and discussion: 20 minutes per track

15:30–15:45  Refreshment break

16:30–17:00  Session 8: Wrap-up and closure of the meeting, S Briand
Way forward
Closure of the meeting
### ANNEX 2: LIST OF PARTICIPANTS

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Affiliation</th>
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<td>Dr Hongjie YU</td>
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### WHO Secretariat

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<td>Dr Wilson WERE</td>
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<td>Acting coordinator</td>
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### Annex 3: Assessment Exercise Methodology

#### How to fill up the matrix?

**Aim:** Provide a tool to support decision-making of research funding agencies based upon the technical assessment of experts.

**Objectives:** Assess each research question identified in the research agenda “Research needs for the Battle against Respiratory Viruses” according the several criteria; Rate them upon their relative comparison within each track.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Urgency</th>
<th>Feasibility</th>
<th>Impacts</th>
<th>Likelihood of success</th>
<th>Beneficiaries</th>
<th>Comments</th>
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<tr>
<td><strong>Question</strong></td>
<td>How important is it to address this research question now and not in a few years from now?</td>
<td>Are meaningful results likely to be obtained within the next 5 years?</td>
<td>If started now and successful, how likely will it modify the overall problem?</td>
<td>If started now, how likely is it to have results within 5 years?</td>
<td>Who will likely be the first to benefit from the expected impact of the interventions?</td>
<td>All comments/precisions/details relevant to the question research</td>
</tr>
<tr>
<td><strong>What do we want to assess?</strong></td>
<td>If the research question requires additional preliminary results before being addressed;</td>
<td>If, based on current knowledge, the questions is easy or not to address.</td>
<td>The expected impacts on the overall problem if translated into policies for instance, i.e. reducing mortality and morbidity associated with respiratory viral infections.</td>
<td>The probability for the research question to be implemented;</td>
<td>Countries; Populations; Specific groups.</td>
<td>To link within the overall track; To get detailed information on specific project; To complete in qualitative way the overall assessment.</td>
</tr>
<tr>
<td>Scoring scale</td>
<td>○ NOT URGENT ○○ URGENT ○○○ HIGHLY URGENT</td>
<td>○ NOT FEASIBLE ○○ FEASIBLE ○○○ HIGHLY FEASIBLE</td>
<td>○ LIMITED ○○ MODERATE ○○○ HIGH</td>
<td>○ LIMITED ○○ MODERATE ○○○ HIGH</td>
<td>State the beneficiaries: LMIC; GLOBAL; ELDERLY, INFANTS, ...</td>
<td>Qualitative assessment</td>
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ANNEX 4: CALL TO ACTION

A group of clinicians, scientists, and public health experts met in Geneva on 6 and 7 November 2012 to identify crucial needs in the battle against the morbidity and mortality caused by respiratory infections. Their deliberations emphasized the following points:

1. **Severe and acute respiratory infections, including those resulting in pneumonia, are the main infectious diseases killer globally, accounting for an estimated 3.9 million deaths per year.** In children aged less than 5 years, approximately 120 million cases of pneumonia occur annually, resulting in an estimated 1.4 million deaths, primarily in developing countries.

2. **Viral respiratory infections are found in most cases of childhood pneumonias and are predisposing factors in most cases of bacterial pneumonias.** In addition, such infections cause many other acute respiratory syndromes that result in hospitalizations and deaths across all age groups, with substantial effects in infants and young children, the elderly, and those with underlying cardiopulmonary or immunocompromising conditions.

3. **New respiratory viral threats** such as severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) or highly pathogenic avian influenza A (e.g. H5N1 or H7N7) virus will continue to emerge, and present a risk of pandemic disease affecting global health security.

4. **Progress has been made towards reaching the Millennium Development Goal 4 – “Reduce child mortality”** – with respect to pneumonia mortality. In recent decades, there have been improvements in prevention (in particular, expanded use of available bacterial vaccines), and treatment (including standardized case management of pneumonia and other severe respiratory infections). However, such measures still require broader implementation or refinement (or both).

5. **The current treatment paradigm of targeting bacterial respiratory infections with antibiotics alone, is inadequate** to optimally reduce mortality from pneumonia and other acute respiratory infections. In addition, it may have negative consequences, including adverse drug effects and increased health-care costs. Inappropriate antibiotic use for viral respiratory infections also contributes to the increasingly serious problem of antibiotic resistance in bacterial pathogens.

6. **Furthermore, our understanding of the mechanisms of transmission and disease pathogenesis in key patient groups is incomplete,** limiting the development of rational and optimized preventive and therapeutic strategies. Further basic and clinical research is needed.

7. While vaccines are available for influenza, they are incompletely used; more effective, broadly protective and long-lasting immunogenic influenza vaccines are needed. Furthermore, there are no approved vaccines for other respiratory viruses, and no clarity about if and when such vaccines might become available. **There is an urgent need for development of safe and effective vaccines against respiratory viruses, particularly for respiratory syncytial virus, a leading cause of viral respiratory infection morbidity and mortality in young children and the elderly worldwide.**

8. Antiviral treatment of seasonal and pandemic influenza can reduce morbidity and mortality, especially when treatment is started early. However, cost-effective antiviral agents and other
therapies for other viral respiratory infections are not currently available. There is an urgent need to support research for new safe and effective therapeutics to target specific respiratory viruses, but also, if possible, to develop antivirals with broad-spectrum activity.

9. Respiratory viral infections are often unrecognized because of the lack of rapid, inexpensive and reliable diagnostic tests. There is an urgent need for good diagnostic tests, especially at point of care, to guide therapeutic choices and to improve clinical management.

10. In addition, better access to and use of existing care systems and practices, such as ensuring early and appropriate oxygen therapy and monitoring, is needed to improve clinical management of severe acute respiratory infection in the context of other therapeutic strategies.

The signatories of this call to action urge public health authorities, research organizations and the private sector to collaborate on developing and implementing a global plan of action to address, in a comprehensive and integrated manner, the morbidity and mortality caused by acute viral respiratory infections and their complications. The plan requires relevant basic and clinical research and the development of improved surveillance, diagnostics, therapeutics, vaccines and strengthening of clinical research infrastructures and health-care delivery systems.
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