Research needs for the Battle against Respiratory Viruses (BRaVe)

Background document 2013

World Health Organization
Acknowledgements

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Find out more on the Battle against Respiratory Viruses (BRaVe) initiative on the WHO web site:

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Abbreviations and acronyms

ALRI  acute lower respiratory infection
ARDS  acute respiratory distress syndrome
ARI    acute respiratory infections
CAP    community-acquired pneumonia
COPD   chronic obstructive pulmonary disease
CRP    C-reactive protein
DALY   disability adjusted life years
HCoV   human coronavirus
Hib    *Haemophilus influenzae* type B
HIV    human immunodeficiency virus
HRV    human rhinovirus
huMPV  human metapneumovirus
ILI    influenza-like illness
NAAT   nucleic acid amplification test
PCT    procalcitonin
PIV    parainfluenza virus
RNA    ribonucleic acid
RSV    respiratory syncytial virus
RVI    respiratory viral infection
SARI   severe acute respiratory infection
WHO    World Health Organization
Foreword

Battle against respiratory viruses: the timing is right

Acute respiratory infections are a major global public health problem. Despite progress made in the 20th century with the introduction of antibiotics, vaccines and (recently) antivirals, there are no specific interventions for most respiratory infections of viral origin. These infections continue to cause frequent morbidity, and sometimes cause severe outcomes including death, especially in developing countries. Current practices for treating these illnesses (e.g. the frequent use of antibiotics) are ineffective and often result in adverse consequences, including antimicrobial resistance.

The discovery of antiviral medicines in the late 20th century led to significant breakthroughs in the fight against infectious diseases. Progress in molecular biology, genetic engineering and other disciplines has enabled scientists to design and produce antivirals that target key viral proteins, or block critical processes involved in viral replication. For example, there are effective antivirals for human immunodeficiency virus (HIV), influenza, herpes, and hepatitis B and C viruses. These antiviral therapies have been introduced widely into clinical practice in some countries, illustrating their potential value in reducing morbidity and mortality. When these medications are combined with advances in diagnostics tests and improvements in clinical management, it seems that effective treatment of respiratory viral infections (RVIs) is a real possibility.

Although advances in the development of influenza vaccines and therapeutics have shown the potential for mitigating the impact of seasonal and pandemic influenza, effective strategies that combine vaccines, therapeutics and improved clinical management are currently lacking for most RVIs. Targeting such infections will be a key challenge of the 21st century. We now have the research tools to develop effective modalities against respiratory viruses. However, how can this new knowledge be rapidly and effectively incorporated into public health strategies?

To succeed in the battle against respiratory viruses, we need to develop and implement a coherent, integrated research agenda. Only through collective engagement can we assemble the ideas and resources to find new weapons, particularly vaccines and therapeutics, against respiratory viruses, and make them available to those in need. This research agenda will be the framework by which the research and public health communities will identify gaps, and work together to fill those gaps.
Introduction: needs for a research agenda

Recent decades have seen many important studies on respiratory viral infections (RVIs), yet there is still only a limited evidence base for understanding the burden of such infections, and for mitigating their impact, and there are few effective pharmacologic interventions other than for influenza. We need to know more about specific areas and to develop new interventions, to support the strategy of reducing the health impacts of these pathogens, particularly the severe illnesses that cause hospitalizations and deaths. The principal objectives of this research agenda are to:

- identify the specific research needed to improve medical and public health responses to RVIs and their sequelae over both the short-to-medium (1–5 years) and the medium-to-long (5–10 years) term;
- provide a framework – reflecting public health research priorities – for allocating research resources, including studies applicable in under-resourced countries and those addressing areas that have been relatively less studied (e.g. operational and social sciences research);
- facilitate discussion, coordination and interactions among fundamental and clinical investigators from both public and private sectors, funders, pharmaceutical industry representatives and public health professionals;
- highlight the need and the potential benefits of a multidisciplinary approach to addressing knowledge gaps in prevention and treatment of RVIs.

This document will help in targeting funding towards priority areas, monitoring the progress in filling knowledge gaps, and facilitating the development of evidence-based policies to prevent and mitigate RVIs. The following section outlines important factors to take into account in considering the rationale and scope of such a research agenda.

Respiratory viral infections are common and widespread

RVI is one of the most common health conditions globally, and has enormous but under recognized impacts on public health. Everyone has experienced colds or influenza-like illness (ILI), and young children average up to a dozen episodes per year. In addition to their high frequency, RVIs are major causes of severe acute respiratory infection (SARI), which can lead to severe outcomes including hospitalization and death (Box 1). RVIs are implicated in approximately 50% of community-acquired pneumonia (CAP) in young children, over 90% of bronchiolitis cases in infants and young children seeking medical attention, and over 90% of asthma exacerbations in children. In adults, they are implicated in 30–50% of CAP, 80% or more of asthma exacerbations, and 20–60% of exacerbations of chronic obstructive pulmonary disease (COPD). In addition, RVIs predispose those infected to a range of secondary bacterial infections including otitis media, sinusitis and CAP. Acute lower respiratory infections (ALRIs) are estimated to cause 3.9 million deaths per year, and pneumonia alone is the leading single cause of mortality in children under 5 years of age, with approximately 1.2 million children dying each
year. Estimates indicate that about 99% of these deaths occur in developing countries, and 80% occur out of hospital.

**Direct and indirect costs of acute respiratory infections**

Acute respiratory infections (ARIs) cause severe complications for patients, and impose an enormous burden on communities. Communities can be directly affected; for example, through the need for outpatient care and hospital services. One recent systematic analysis estimated that, in 2010, 14.9 million episodes of severe or very severe ALRI resulted in hospital admissions in young children worldwide, although only 62% of children with severe ALRI were hospitalized. Communities can also be indirectly affected; for example, ARIs are responsible each year for major losses in productivity, in part due to absenteeism. ALRIs are the leading cause of burden of disease worldwide, accounting for 94.5 million disability adjusted life years (DALYs), equivalent to 6.2% of total DALYs.

**Suboptimal management**

Current management of RVIs is suboptimal in most countries, and often results in both use of ineffective treatments and failure to use treatments of proven benefit. Because it is commonly thought that ARIs are caused by bacteria, most such infections are treated with antibiotics. Even when a viral etiology is diagnosed, the illness is unlikely to be treated with specific antivirals, because these are generally unavailable, except possibly for influenza treatments in some settings.

**Inappropriate antibiotic use**

Inappropriate antibiotic use for RVIs is a widely prevalent problem that increases the risks for antibiotic side-effects and emergence of antimicrobial resistance, as well as the cost of care. At the same time, RVIs are major causes of secondary infections with bacteria. Measures undertaken to prevent and treat the initiating RVIs could have major impacts on these adverse downstream consequences.

**Innovative approaches targeting broad-spectrum pathogens are needed**

With the availability of more sophisticated diagnostic tests, multiple respiratory viruses are now often detected in ARIs, especially in children. Such observations raise questions about disease causation, pathogenesis and the dynamics of infection with multiple agents; they also suggest that it would be beneficial to consider innovative therapeutic approaches that do not focus on a single virus.

**Complex mechanisms of disease**

Host responses to RVIs are important in disease pathogenesis, but such responses are diverse across population groups and are incompletely understood. Furthermore, mixed infections (both viral–viral and viral–bacterial) increase the complexity of pathogen–host interactions. Improved therapeutic strategies for RVIs will depend on a better understanding of the mechanisms of disease in different syndromes and target populations.
**Syndromic approach**

Except possibly during widespread outbreaks due to a specific virus (e.g. epidemic influenza), RVIs cannot be addressed effectively or efficiently with a vertical approach that focuses on one agent at a time from public health and clinical perspectives. A syndromic approach that addresses the pathogenesis, prevention and optimal management of clinical problems such as CAP and other forms of SARI makes most sense; it also allows for the introduction of technological advances in diagnostics and therapeutics to those in greatest need.

**Global health security threat**

Respiratory viruses are pathogens that may have a major effect on global health security. In recent years, we have witnessed the emergence and discovery of a number of new respiratory viruses including severe acute respiratory syndrome (SARS) and other coronaviruses, avian H5N1 influenza and pandemic (H1N1) 2009 influenza, and there is a high likelihood of new respiratory viruses emerging that could cause extensive disease and economic losses. The expectation is that the impact of these unpredictable events will be mitigated to some extent by non-pharmaceutical interventions, specific antiviral and potentially immunomodulatory therapies, and clinical management strategies effective for common RVIs. Studies in the period between pandemics can generate evidence that will inform responses to both recognized and novel RVI threats.

**Treatments and vaccines**

The treatment of RVIs will be an important complement to vaccination strategies directed at specific respiratory viruses and their secondary bacterial complications; for example, at *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (Hib). Currently, we have vaccines for influenza, although these are incompletely protective and underused, and require annual administration. A recent position paper\(^1\) from a World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on immunization promotes maternal immunization against influenza to protect both mother and infants, and this approach will be an important strategy to protect infants against respiratory syncytial virus (RSV) and possibly other RVIs, once effective vaccines are available.

Despite years of investigation, there are as yet no effective vaccines for RSV, picornavirus or other common respiratory viruses, except for several adenovirus serotypes. The large number of respiratory virus families, types and serotypes means that effective vaccines for most such viruses are unlikely to be

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\(^1\) Available at [http://www.who.int/wer/2012/wer8747.pdf](http://www.who.int/wer/2012/wer8747.pdf)
developed in the foreseeable future. Consequently, it makes sense to pursue an integrated approach to RVIs by developing more effective therapeutics while continuing to pursue vaccine development for particular threats – for example, RSV and parainfluenza virus (PIV), and human metapneumovirus – and improving vaccines for influenza.

Mitigation

It is almost impossible to eradicate respiratory viruses because of their extraordinary diversity, complex evolution and ability to be maintained in human populations (in part through transmission by mild or subclinical infections). However, with the possible exception of measles infection, mitigation of the impacts of respiratory viruses is now achievable.

Opportunities

In spite of the issues outlined above, we are at a turning point. The prospects of new antivirals, new molecular diagnostics, novel vaccines and new management approaches offer opportunities to tackle RVIs, but to exploit these opportunities, we need new weapons and strategies, and particularly, a focus on scientific research. The overall goal for the proposed research agenda is to develop both the evidence and the tools needed to strengthen public health actions and decision-making, in order to limit the impact of acute RVIs and their consequences in both individuals and populations. In prioritizing research activities, both data-driven hypotheses and feasibility should be considered; hence, the ranking of particular projects is likely to evolve as better data or tools become available for addressing particular questions.

The research needs for viral respiratory infections encompass six key areas, which are covered in this document:

1. Defining the burden of disease
2. Understanding disease pathogenesis and host dynamics
3. Expanding treatment options
4. Improving SARI diagnosis and diagnostic tests
5. Improving clinical management of SARI and CAP
6. Optimizing public health strategies.
References (Introduction)


1. Defining the burden of disease of respiratory viral infections (16-31)

Respiratory illnesses, exemplified by pneumonia, are the leading cause of death from infectious diseases; they account for approximately 20% of mortality in children under 5 years of age, particularly in resource-limited settings. With improvements in diagnostic technologies, there has been an increase in studies that specify the responsible viral pathogen. However, more research is needed to better estimate the burden of RVI pathogens relative to bacterial or mixed etiologies in different settings.

These viruses also cause considerable morbidity in older children and adults, and mortality in older adults and those with underlying conditions. For example, in the United States (US), 90% of seasonal influenza and 78% of RSV-associated respiratory and circulatory deaths occur in adults aged 65 years and older. Although many studies on RVIs focus on children under 5 years of age (Box 2) and elderly adults, too little is known about the overall impact across the age spectrum. Similarly, population- or hospital-based studies have highlighted the importance of specific RVIs such as influenza and RSV in causing serious disease (Box 1).

The figures given in Box 1 do not include the contributions of other viruses to the global burden. Such gaps in knowledge tend to hide the “real” burden of RVIs in the global population. Therefore, the causative pathogens and particularly the contributions of RVIs need to be better characterized in different clinical syndromes, settings and target populations.

Data on disease burden are unavailable from many countries, especially those that are under-resourced and, at present, there is no globally integrated surveillance system for RVIs other than influenza. Understanding the geographical patterns, seasonality and distributions of RVIs would allow for more appropriate and targeted clinical management in situations where the burden of disease currently remains hidden. Furthermore, the wider scale use of effective vaccines for viral infections (e.g. influenza) and bacterial infections (e.g. Hib and pneumococcal conjugate) will probably lead to changes in the etiologies and, perhaps, patterns of serious respiratory illnesses. For example, in older adults with high uptake rates for influenza vaccine, the frequency of RSV-associated hospitalizations is comparable to that caused by influenza.
Box 1: Disease burden of respiratory infections *(8, 16, 25, 32, 33)*

A. Estimated global impacts of RVI in pneumonia and SARI:

- **CAP cases per year:** 429.2 million
  - 200 million cases of viral CAP per year
  - Approximately 3.5–4 million deaths (7% of total annual mortality)
  - Economic costs of US$ 17 billion per year in the US alone
- **CAP cases in children per year:** 156 million
  - 151 million CAP cases in developing countries
  - RVI in 43–67% of paediatric CAP cases
  - 14.6 million SARI + severe CAP cases
  - 1.4 million deaths in developing countries (>95% in developing countries)

B. Specific viral pathogens in children <5 years of age:

- **Influenza-associated acute lower respiratory tract infections (2008)**
  - 20 (13–32) million cases (13% of all paediatric ALRI)
  - 1–2 million cases of influenza-associated severe ALRI (7% of all severe paediatric ALRI)
  - 28 000–111 500 deaths (99% in developing countries)
- **RSV-associated ALRI (2005)**
  - 33.8 (19.3–46.2) million cases (22% of all paediatric ALRI)
  - 2.8–4.3 million hospital admissions
  - 66 000–199 000 deaths (99% in developing countries)

*Global data on estimated impact of other RVIs is currently unavailable.

ALRI, acute lower respiratory infection; CAP, community-acquired pneumonia; RSV, respiratory syncytial virus; RVI, respiratory viral infection; SARI, severe acute respiratory-tract infection; US, United States
Further information is needed on the role of RVIs in causing other clinical syndromes, in order to improve strategies to reduce the overall morbidity and mortality of acute respiratory disease. Available evidence indicates that respiratory viruses are the primary agents involved in multiple common respiratory syndromes (e.g. rhinosinusitis, ILI, bronchiolitis, laryngotracheobronchitis, acute bronchitis, exacerbations of asthma and COPD), and that they either directly cause other illnesses affecting the upper respiratory tract (e.g. otitis media and sinusitis) and lower respiratory tract (e.g. pneumonia), or foster secondary bacterial infections at these sites. In addition, some RVIs – particularly influenza and adenovirus – have been associated with severe illnesses involving other organ systems (e.g. encephalopathy–encephalitis and myocarditis). RVIs also cause serious worsening or complications of non-respiratory conditions (e.g. myocardial infarction, congestive heart failure, stroke and diabetes) that contribute heavily to the burden of RVI-associated hospitalizations and mortality.

It appears that RVIs may sometimes also be associated with chronic sequelae, such as the development of asthma. The role of viruses in the development of specific cancers is well-understood; for example, in relation to the role of human papilloma virus (HPV) in cervical cancer, and of hepatitis viruses B and C in liver cancers. However, little is known about any potential association between RVIs and malignancy. Human adenoviruses are oncogenic in other animals, but are not known to be so in humans. Whatever this situation, given that lung cancer is one of the leading non-communicable causes of death, further knowledge could be of crucial importance.
More research is needed to define the age-related burden of RVIs 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 RVI and bacterial etiologies with outcomes. Where possible, the synergies between increased surveillance and vaccine or antiviral probe studies are likely to improve the overall strength of results.

**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, 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.
References (Section 1)


2. Understanding disease pathogenesis and host dynamics of respiratory viral infections

To develop more effective treatments and public health interventions, we need better understanding of the mechanisms by which respiratory viruses are transmitted and cause disease. Little is known about the pathogenesis of RVIs, and it is likely that interactions between virus, host and environment vary among specific pathogens and among key patient groups. For example, viral replication patterns and innate immune responses differ between mild upper respiratory infections and severe lower respiratory infections, and between patient groups at high risk of complications (e.g. infants, pregnant women, elderly adults and immunocompromised hosts). Data on the kinetics of viral replication would be a useful first step in determining infection control measures. Disease severity following infection depends on multiple factors, including pre-existing immunity, host genetic factors and underlying conditions, viral replication kinetics in the upper and lower respiratory tract, inefficient or aberrant host innate and adaptive immune responses triggered by viral replication, environmental conditions, and virulence factors related to mutations in key viral proteins.

Specific data on viral replication dynamics and host pro-inflammatory and immune responses (especially in the lower respiratory tract) in key patient groups are important to determine the nature, timing (initiation and cessation), and potency of candidate immunomodulatory and host-directed therapeutic interventions. Such data may also serve to discourage use of potentially harmful interventions. For example, systemic corticosteroids have been commonly used in management of RSV-associated bronchiolitis and of influenza-associated acute lung injury or acute respiratory distress syndrome (ARDS). However, available data do not indicate benefit and, in the case of influenza, actually appear to indicate harm in terms of prolongation of viral replication, adverse drug effects, and increased risks of nosocomial infections and mortality.

Elevated temperatures have been associated with host-defense immunological mechanisms against influenza infection, such as the proliferative response of lymphocytes or the increased production and activity of cytokines. Animal models reveal an increased risk of mortality associated with antipyretics during influenza infection. Although antipyretics are widely used in humans, there is little evidence on their potential adverse events. More research on these practices is therefore important.

Viruses and (commensal) bacteria are often present together in the respiratory tract, but relatively little is known about their interplay and how this affects transmission and disease pathogenesis. The importance of bacterial pneumonias and, sometimes, bloodstream infections following influenza is well documented. Various mechanisms have been implicated in promoting secondary bacterial infections, including increased bacterial adherence, altered tracheobronchial clearance, inhibition of functions of polymorphonuclear leukocytes (PMN) and macrophages, anergy of pattern recognition receptors, and viral virulence factors such as PB1-F2. Animal model studies of pneumococcal pneumonia following influenza suggest that antiviral therapy can lessen disease severity and that some commonly used antibiotics might enhance adverse inflammatory responses.
The frequency of bacterial complications and the mechanisms involved following other RVIs are less well studied. Furthermore, many common respiratory viruses such as human rhinovirus (HRV), RSV and human coronavirus (HCoV) are associated with mixed viral–bacterial infections involving sites in the upper respiratory tract (e.g. otitis media and sinusitis), in part related to altered Eustachian tube function and inadequate sinus drainage. Further understanding of the processes involved in secondary bacterial infections may help to improve strategies for prevention and management.

Sensitive methods for nucleic acid detection have led to the frequent detection of multiple viral pathogens in respiratory samples, especially in infants and young children. Two or three respiratory viruses are detected in 10–20% of paediatric pneumonia cases (Box 3). The pathogenic consequences of these viral co-infections have not yet been clarified, but may depend on the particular viruses involved, the timing of acquisition (concurrent or sequential), the interval between acquisition, and host factors.

Improved understanding of virus–host interactions in key patient groups is fundamental to developing rationally designed therapeutics and vaccines. This includes understanding the basis of transmission and the pathology associated with infection, as well as the basis of mechanisms and consequences of viral and bacterial co-infections. Complementary basic and clinical research approaches will be required.

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**Box 3: Distribution of pathogens in children with lower respiratory infections/pneumonia**

<table>
<thead>
<tr>
<th>Pathogen Type</th>
<th>Age Range 1 (22)</th>
<th>Age Range 2 (50)</th>
<th>Age Range 3 (35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected bacteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>7.9</td>
<td>5.1</td>
<td>9.8</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected viruses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>32.2</td>
<td>14.5</td>
<td>37.3</td>
</tr>
<tr>
<td>Rhinoviruses</td>
<td>24.3</td>
<td>23</td>
<td>18.9</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza viruses</td>
<td>2.5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>7.2</td>
<td></td>
<td>24.8</td>
</tr>
<tr>
<td><strong>Mixed infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed viral</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed bacterial/viral</td>
<td>26.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient with 1 pathogen (either virus or bacteria)</td>
<td>47.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient with 2 pathogens (either virus or bacteria)</td>
<td>31.5</td>
<td>30.5</td>
<td></td>
</tr>
<tr>
<td>Patient with 3 or more pathogens (either virus or bacteria)</td>
<td>9.2</td>
<td>8.1</td>
<td></td>
</tr>
</tbody>
</table>

*Age range of children: 1 month to 15 years old; *Age range of children: under 5 years old; *Age range of children: under 5 years old
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).

References (Section 2)


3. Expanding treatment options for respiratory viral infections (51-61)

A number of antivirals have been tested for treatment of RVIs; they include interferons, ribavirin, amantadine, oseltamivir, zanamivir, antibody preparations for RSV and capsid-binding anti-HRV compounds. The agents of proven therapeutic value are mainly those for influenza, such as oseltamivir, which reduces disease severity and mortality. For example, during the (H1N1) 2009 pandemic in Japan, the combination of early diagnosis, rapid testing and oseltamivir treatment, in addition to other factors, resulted in the lowest mortality rate in the world, with no influenza deaths in pregnant women. However, oseltamivir fails to adequately control viral replication in some patients, and resistance is emerging as a problem — H1N1 virus resistant to oseltamivir was circulating globally in 2007–09. Consequently, more potent antiviral combinations, especially for seriously ill persons, are needed.

In addition to oseltamivir, other neuraminidase inhibitors, including intravenous and long-acting inhaled formulations, are in clinical development, as are several agents with novel mechanisms of anti-influenza action (e.g. DAS181, favipiravir, nitazoxanide and AVI-7100). Recent reports of results with inhaled interferon-beta or an oral anti-HRV inhibitor are promising, with reduced rhinovirus–associated cold symptoms and modulated risk of exacerbations in asthmatic patients. However, there are no drugs to treat most RVIs, and the relatively high cost of anti-influenza agents hinders their optimal use, especially in low- and middle-income countries.

Most antiviral drugs have been developed by identifying viral proteins that can be inhibited by small molecular chemical entities or, in some instances, larger biotherapeutics. Consequently, most approved antiviral drugs are highly specific for a particular virus or family of viruses (e.g. neuraminidase inhibitors and adamantanes for influenza). The advantage of this strategy is selectivity, and it may lower the risk of adverse host effects. The disadvantages are a limited antiviral spectrum, the risk of antiviral resistance and limitations on the number of virus-encoded proteins with properties suitable for developing pharmaceutically acceptable inhibitors.

Recent non-clinical studies using ribonucleic acid interference (RNAi) screens have examined the cellular interactions of selected viruses, and determined that large numbers of host-cell functions are essential to viral replication. Through this approach, host-directed therapies could be identified and used as short-term inhibitors. In some instances, a particular host function or pathway is required for the replication of many different viruses. This raises the possibility of developing antiviral drugs with broad-spectrum activity.

A related area of research is understanding and modulating host innate immune and other inflammatory responses to RVIs. These host responses are thought to account for much of the symptomatology of acute RVIs, and, in some cases, contribute to tissue damage in key target organs like the lung. However, more information is needed on RVI pathogenesis in different syndromes and patient groups. Some of the pathways involved in these host responses are also those necessary for efficient viral replication. Consequently, a drug has the potential to inhibit viral replication and potentially deleterious host responses. There is also evidence of inadequate host responses in some RVIs (e.g. deficient interferon
responses in severe influenza pneumonia and perhaps RSV infections), which may open the possibility of therapeutic intervention.

For some RVIs, prophylaxis is a viable option. Vaccination is an effective intervention for influenza, although protective efficacy varies across patient groups and seasons, and vaccine availability may be severely limited during a pandemic. Influenza antivirals are effective for chemoprophylaxis but prophylactic use has been limited by cost and, in some target groups, concerns about the emergence of resistance. For RSV, there is currently no vaccine or chemoprophylaxis, but passive immunization with either human immunoglobulin or anti-F monoclonal antibody (e.g. palivizumab) during the RSV season is partially protective in high-risk groups such as preterm infants. The available RSV interventions are too expensive for broad use in developing countries, although imminent patent expiry may mean more affordable versions of these products will be developed.

More research is needed to expand treatment options across the range of respiratory viral pathogens. Data from seasonal burden-of-disease studies indicate that therapeutics for RSV and HRV infections should be prioritized. New data from burden-of-disease and pathogenesis studies will also inform prioritization. Antiviral resistance and human pharmacokinetics, including pharmacokinetic–pharmacodynamic relationships and drug–drug interactions for combinations, are cross-cutting issues that need to be integrated in 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 neuraminidase inhibitors (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.
References (Section 3)


56 Nguyen HT, Fry AM, Gubareva LV. Neuraminidase inhibitor resistance in influenza viruses and laboratory testing methods. Antiviral Therapy, 2012, 17(1 Pt B):159-173. PM:22311680


59 Shaw ML. The host interactome of influenza virus presents new potential targets for antiviral drugs. Reviews in Medical Virology, 2011, 21(6):358-369. PM:21823192


4. Improving SARI diagnosis and diagnostic tests (62-73)

RVIs are often unrecognized or ignored by clinicians, especially in developing countries, because of the lack of rapid, inexpensive and reliable diagnostic tests, and the sense that no effective treatments are available. To reduce the burden of RVIs, good diagnostic tests are needed, especially at the point of care. Such tests would raise awareness of health-care workers about the viral etiology of the disease, guide therapeutic choices and improve clinical management of RVIs.

Establishing the etiology of RVIs remains challenging, although new molecular technologies – in particular multiplex nucleic acid amplification tests (NAATs) – are promising tools that can be used in developing country settings. Compared to older tests, NAATs are better able to detect fastidious or non-cultivable pathogens such as human metapneumovirus (huMPV), HCoV and HRV, or low quantities of pathogens, but results can be difficult to interpret. Detecting viral RNA at the same time as pneumonia or SARI may indicate direct causality (e.g. bronchiolitis or viral pneumonia), indirect or predisposing causality (e.g. secondary bacterial or mixed infection) or an unrelated incidental finding. The high prevalence of RNA for some respiratory viruses (e.g. HRV) in apparently healthy infants and young children (detected by qualitative assays) may represent subclinical or mild infections, or prolonged excretion after a recent illness. Determining background rates in control groups and quantitative RNA levels in the respiratory tract or other sites (e.g. blood) may therefore be important.

In resource-limited settings, other issues related to NAATs include high start-up equipment costs, sensitivity to extreme environmental conditions, and access to reliable power supply, reagents and technical support. Studies of the etiology of paediatric pneumonia (e.g. using RNA detection methods) will help in assessing some of these issues; such studies include the Pneumonia Etiology Research for Child Health (PERCH) and the Global Approach for Biological Research on Infectious Epidemics in Low income countries (GABRIEL).

Another area of active investigation is the measurement of biomarkers that may distinguish patients with bacterial etiologies from those with viral or non-bacterial etiologies. Such biomarkers may help to inform clinical decision-making. For example, serum procalcitonin (PCT) levels are elevated in patients with bacterial pneumonia and septic shock, whereas they are generally not elevated in those with RVI, unless there is secondary bacterial or mixed infection. PCT levels are more dynamic and increase faster than other markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in bacterial infections. Rapid decreases in PCT appear to indicate prompt response to antibiotic therapy and the potential for short antibiotic courses, but confirmatory studies are needed. Other studies suggest that, in patients with influenza, CRP levels may be informative for assessing risk of progression or bacterial complications.

Improved diagnostic methods over the past decade present a much more complicated picture of respiratory infections. Work on diagnostic tests should focus on three main goals: improving clinical management of patients; assisting surveillance and burden-of-disease determinations; and supporting other areas of RVI research (e.g. the evaluation of novel therapeutics). Platforms applicable to multiple
pathogens and sample types should be developed as a priority. The priority research questions for this section are aimed at better assessment and understanding of the complexity of respiratory infection.

**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.

**References (Section 4)**


5. Improving clinical management of SARI and CAP (50, 74-87)

In all resource settings, timely and appropriate clinical management can reduce morbidity and, potentially, mortality related to RVIs. Better evaluation algorithms, diagnostics, and safe and effective treatments are needed. Identifying valid prognostic markers and scoring systems can help to determine the correct type and level of care. Supportive-care interventions, such as oxygenation, rehydration and (sometimes) non-invasive ventilation, may provide benefit in ALRI by preventing progression to severe illness and death, especially in settings lacking modern intensive care capacities. However, there is an insufficient evidence base for such basic supportive-care measures.

Some well-known effective interventions, such as oxygen therapy, are rarely used in many developing countries. Every year, 11–20 million children are admitted with pneumonia. At least 13.3% (1.5–2.7 million) have hypoxemia, which contributes to the more than 1.2 million deaths caused by pneumonia. Investment in oxygen systems to improve detection and management of hypoxemia should be part of health system support. However, there are many obstacles to using oxygen therapy. Scientific evidence is still lacking on the efficacy and cost-effectiveness of oxygen use in low-resource settings. This has prevented the publication of guidelines on oxygen use using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach1 and the inclusion of oxygen on the global essential list of medicines2. Also, despite advances in technology for oxygen concentrators and pulse oximeters, and the increased affordability of such devices, more innovation is needed to reach resource-limited settings and ensure sustainable use of these techniques.

In many practice settings, antibiotics (including over-the-counter ones obtained by patients or their family members) are frequently used to treat probable RVIs. Inappropriate antibiotic use drives resistance; it also raises the costs of care and the risk of adverse events. Clinicians are often poorly informed on the appropriate use of available antivirals and on the avoidance of interventions such as systemic corticosteroids that might cause harm in certain RVIs (e.g. influenza and viral pneumonia).

More research is needed to improve clinical management strategies, and to help health professionals adopt new attitudes to and practices in RVIs. The rapid communication of clinical management guidance during the pandemic (H1N1) 2009 appeared to affect practice patterns. However, follow-up studies have found reversion to pre-pandemic patterns; for example, delayed antiviral use for severe influenza in

1 http://www.who.int/kms/guidelines_review_committee/en/index.html
2 http://www.who.int/medicines/services/essmedicines_def/en/index.html
multiple countries, and associated increases in mortality. These examples show that it is crucial to forge and sustain a paradigm shift regarding health-care workers’ beliefs and practices on clinical management of RVIs.

Better integration of research activities and clinical practice is crucial in developing the most relevant evidence base for policy decisions. All ages and settings must be considered in improving clinical management practices. Clinical research can be undertaken, with designs ranging from observational studies to randomized controlled trials (traditional or adaptive). Improved clinical research design, combined with advances in basic science, will help to identify those ARI patients who are most ill and require intervention; assess and develop effective interventions for SARI and CAP; and 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.
References (Section 5)


6. Optimizing public health strategies (88-102)

Vaccines remain at the heart of disease prevention and control strategies. However, among respiratory viruses, only influenza has vaccines, and these are underused. Furthermore, the need for annual immunization with current influenza vaccines, due to waning immunity and changing viral antigenicity, highlights the importance of developing new vaccines with more durable and broader spectrum immune responses. Development of vaccines against other respiratory viruses is a well-recognized research need, and studies to develop vaccines for RSV and PIV have been ongoing for decades. Unfortunately, vaccine development is a long process, and there are significant technical challenges with respiratory viruses. Immune responses to infections by pathogens such as RSV, huMPV and PIV are incomplete, so reinfections can occur. Consequently, effective vaccines will need to induce more effective protective responses than natural infection. Both live-attenuated and subunit RSV vaccines are in development, but it is uncertain whether vaccines will become available for RSV or other respiratory viruses within the next 5–10 years. Once available, maternal immunization, as shown for influenza vaccines, would offer the possibility of protecting young infants.

Considering these potential limitations, further evidence is needed on effective implementation of public health approaches, such as hand hygiene, cough etiquette and other population-based prevention measures. Comparative scenarios weighting the cost-effectiveness of sets of measures to be implemented would be an asset for policy makers, helping to transfer knowledge into action.

Common misperceptions on RVIs are shared by health-care workers and the general population. These misperceptions increase the burden of RVI disease, because they are likely to delay or prevent effective intervention. More high-quality data would provide policy makers with strategies to help both groups comply with recommended interventions and adhere to policies. Health-care workers are especially important; they are a key group to mobilize and educate the public, because they are generally trusted and seen as reliable sources of information.

Another issue is that public health policies are increasingly questioned by individuals in the media and general population. One consequence is that adherence to recommended interventions may, in certain situations, be very low in the population. In many countries, recent decades have seen a switch from a paternalistic model, in which governmental guidance was generally accepted and followed, to one based on individual choice and freedom of action as personal rights.
More research is needed on strategies to prevent and control RVIs, and on the timely and effective integration of innovation and advances in science in decision-making and public health practices. Particular attention should be given to communicating to different stakeholders, especially health-care workers, who are pivotal in implementing change in health-care systems. Having better data on current knowledge and practices will allow more refined strategies and improved local adaptation and implementation. The link between evidence and practice should be emphasized.

**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.

**References (Section 6)**


93 Lau JT, Griffiths S, Choi KC et al. Avoidance behaviors and negative psychological responses in the general population in the initial stage of the H1N1 pandemic in Hong Kong. *BMC Infectious Diseases*, 2010, 10:139. PM:20509887


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