Review
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# Addressing the public health burden of respiratory viruses: the Battle against Respiratory Viruses (BRaVe) Initiative

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Given the enormous estimated burden of respiratory virus infections worldwide, a substantial number of research priorities exist in order to better understand their epidemiology, pathogenesis, prevention and clinical management across different populations and resource settings. New therapeutics and specific vaccines for noninfluenza respiratory virus infections could provide enormous benefits in reducing the morbidity and mortality associated with these frequent infections and provide the foundation for responding to newly emerging threats. The BRaVe Initiative is a new WHO-led effort to catalyze multidisciplinary research on strategies to prevent and treat medically important respiratory virus infections with the goal of timely integration of scientific advances and technical innovations into public health practice.

Acute respiratory infections (ARI) kill an estimated 3.9 million people annually and in developing countries are the leading cause of mortality in children under 5 years of age [1]. Specific respiratory virus infections (RVIs), such as influenza and respiratory syncytial virus (RSV), are major contributors to this burden of disease, as are other respiratory bacterial and viral pathogens (**Box 1**). WHO and UNICEF have developed a global action plan to both prevent, particularly through increasing coverage with *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) vaccines, and more effectively treat major causes of bacterial community-acquired pneumonia (CAP) in children and reach the Millennium Development Goal (MDG) of halving childhood mortality. While progress has been made in reducing pneumonia mortality by an estimated 0.45 million children from 2000 to 2010 [1], the current initiative does not adequately address the contribution of RVIs and mixed viral–bacterial infections to this burden of disease or take steps to mitigate it. One recent review [2] found that the share of pneumonia cases linked to RVIs is much larger than previously estimated, reaching 50% or more in some studies utilizing molecular diagnostic techniques. Additionally, emerging respiratory viruses have the potential to trigger regional epidemics that threaten to spread globally, as recently seen with the avian influenza A(H7N9) virus or the Middle East respiratory syndrome coronavirus (MERS-CoV).

A recent systematic review estimated that in 2010, 11.9 million episodes of severe and 3 million episodes of very severe acute lower respiratory illness (ALRI) resulted in hospital admissions in young children worldwide [3]. Using hospital-based studies the authors estimated that approximately 265,000 in-hospital deaths and a fourfold greater number of out-of-hospital deaths occurred in young children, with 99% of these deaths in developing countries. Among ALRI syndromes, respiratory viruses have been detected by molecular diagnostic techniques in 43–67% of CAP cases in children [2], over 90% of bronchiolitis cases in infants, and approximately 85% of asthma exacerbations in children. In adults, approximately 20–40% of CAP cases, up to 80% of asthma exacerbations and 20–60% of chronic obstructive pulmonary disease exacerbations are linked to RVIs. Preceding RVIs are key predisposing events to secondary bacterial infections in the lung and other sites in the

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■ antivirals ■ emerging respiratory viruses ■ influenza virus ■ pneumonia ■ public health policies ■ respiratory syncytial virus ■ respiratory viral infections ■ severe acute respiratory infection ■ vaccines ■ WHO research agenda

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**Box 1. Estimates of the global burden of specific respiratory viral and bacterial pathogens in children younger than 5 years of age.**

***Influenza-associated acute lower respiratory infections (2008)*** [89]

- 20 million (range: 13–32 million) cases (13% of all pediatric ALRI)
- 1–2 million cases of influenza-associated severe ALRI (7% of all severe pediatric ALRI)
- 28,000–111,500 deaths (99% in developing countries)

***RSV-associated acute lower respiratory infections (2005)*** [90]

- 33.8 million (range: 19.3–46.2 million) cases (22% of all pediatric ALRI)
- 2.8–4.3 million hospital admissions
- 66,000–199,000 deaths (99% in developing countries)

**Streptococcus pneumoniae-*associated pneumonia (2000)*** [91]†

- 13.8 million (range: 10.8–17.2 million) cases (8.6% of 160 million clinical pneumonia cases)
- 542,000–805,000 deaths (95% of all pneumococcal deaths in Africa and Asia)

**Haemophilus influenza *type b-associated pneumonia (2000)*** [92]†

- 7.91 million (range: 7.23–12.9 million) cases
- 41,600–101,600 deaths (16% of an estimated 1.8 million pneumonia deaths in HIV-negative children)

†*Estimates do not include meningitis, or nonmeningitis or nonpneumonia cases. In 2000* S. pneumoniae *was estimated to cause approximately 11% (8–12%) of all deaths in children* [91].
*ALRI: Acute lower respiratory illness; RSV: Respiratory syncytial virus.*

respiratory tract [4,5], and are likely precipitating factors in syndromes affecting other organ systems (cardiac ischemia, myocardial infarction, congestive heart failure, venous thromboembolism, stroke and loss of diabetic control) [2,6–11]. This 'hidden' burden of RVIs is not well appreciated, especially in low-resource settings where it may be disproportionately high. Thus, RVIs remain a huge challenge for attaining the current MDGs and will be of crucial importance in the coming years in health-related development issues, given their wide distribution and their high impact on most vulnerable populations.

RVIs are frequent events in all age groups and result in an enormous burden on health systems, as well as economic costs in direct medical expenses and indirect productivity losses. Direct medical expenses include outpatient clinic visits, emergency department visits, hospitalizations and treatment costs, including over-the-counter medication and drug prescriptions. Indirect productivity losses include missed workdays for patients (when adults) and missed workdays for caregivers. In Europe, pneumonia costs are estimated at approximately €10.1 billion annually and indirect costs of lost work days amount to €3.6 billion [12]. Based on the 2003 population size, seasonal influenza epidemics resulted in an average of 610,660 life-years lost (undiscounted), 3.1 million hospital days and 31.4 million outpatient visits in the USA [13]. Direct medical costs averaged US$10.4 billion annually, and projected lost earnings due to illness and loss of life amounted to US$16.3 billion annually. The total economic burden of annual influenza epidemics using projected statistical life values amounted to US$87.1 billion [13]. Even common acute upper respiratory illnesses exact a significant economic toll. A US-based study estimated that noninfluenza, viral respiratory tract illnesses, mostly common colds, cost US$40 billion in 2001, with direct costs representing 45% and indirect costs 55% of the total [14].

In addition to the annual impact of common RVIs, emerging respiratory viruses such as SARS CoV, avian influenza A(H5N1) virus, influenza A(H1N1)pdm09 virus, MERS-CoV and, most recently, avian influenza A(H7N9) virus represent threats to global health security [15–18,101,102]. There is a high likelihood of new respiratory viruses emerging that have the potential to cause diseases and economic losses on an international scale. For instance, the global economic losses from the SARS outbreak in 2003 is estimated to have been close to US$40 billion. This includes direct medical related costs and affected industries losses (tourism, retail service sector) but also wider impacts on globalized and integrated economies adding the losses resulting from both temporary and persistent economic shock [19].

Studies on nonpharmaceutical interventions, specific antiviral and potentially immunomodulatory therapies, and clinical management strategies during the inter-pandemic period could provide evidence that will inform responses to such future RVI threats, as well as improve clinical care in the inter-pandemic period. It is

also important to recognize that, in case of a pandemic or major outbreak, as observed in the 2009 pandemic, the time constraints of vaccine production would mean that no vaccine would likely be available before 4–6 months. Furthermore, current seasonal influenza vaccines are only moderately protective [20] and vaccines with broader and more durable immunity are needed [21]. The initial response to reduce mortality would therefore rely on the use of public health interventions including use of antivirals and potentially biotherapeutics like convalescent plasma [22–24].

Randomized controlled trials indicate that early antiviral treatment of influenza can reduce symptoms and physician-diagnosed complications in ambulatory patients [25], and observational studies from seasonal, influenza A(H1N1) pdm09 and avian influenza A(H5N1) influenza A viruses have reported mortality benefits from timely antiviral therapy in hospitalized patients [26–29]. Such findings demonstrate the potential of pharmacologic interventions for other noninfluenza RVIs. Unfortunately, current specific pharmacologic interventions for RVIs are largely limited to vaccines and antivirals for influenza. Furthermore, except for several approved agents of limited applicability (e.g., antibody prophylaxis for RSV, aerosolized ribavirin for RSV and oral adenovirus vaccine), no vaccines or therapeutics of proven value are currently available for most noninfluenza respiratory viruses.

## Development of the BRaVe Initiative

The idea for the BRaVe Initiative started with the observations that the broader use of influenza antiviral agents and vaccines has provided important public health benefits. While prevention with vaccines is a well-understood public health intervention, the notion that viral respiratory infections could be treated successfully is a relatively new concept for the medical community at large. In order to reduce the continuing mortality due to respiratory infections and to prepare for pandemic and epidemic threats, it was recognized that there is a need to articulate new approaches at the global level and to foster accelerated discovery, development, and implementation of improved therapeutic and management strategies.

In November 2009, WHO convened a 3-day consultation that brought together over 90 public health decision-makers, investigators, representatives from funding organizations, and other key stakeholders from 35 countries; this led to the publication of its first Public Health Research Agenda on Influenza in early 2010 [103]. Elements of this agenda specifically addressed research needs for developing improved diagnostics, vaccines, therapeutics, clinical management strategies and better overall public health responses to influenza. In the past several years, some progress has been made in developing novel influenza therapeutics [30] and more immunogenic vaccines [21,31,102]. However, the paucity of specific pharmacologic interventions for RVIs and the modest number of preventive and clinical management strategies of proven effectiveness remained obvious.

In early 2012 this led to discussions between WHO colleagues and experts in the scientific community to explore ways in which to extend efforts on influenza to the broad range of acute RVIs with the aim of reducing their morbidity and mortality. Development of an integrated research framework and response platform, designated the BRaVe Initiative, was conceived to address these needs, and a concept paper [103] was circulated among partners in February–March 2012. BRaVe quickly took shape with input from partner organizations and experts outside WHO and became a cross-cutting effort within WHO to link resources and expertise across different clusters within the organization (the Health Security and Environment, Health Systems and Innovations, and Family, Women's and Children's Health clusters).

Subsequently, two informal technical consultations were held by WHO to identify the key knowledge gaps and the research needs and tools to address these gaps. The first meeting on 5–6 July 2012 convened with the support of Fondation Mérieux and the Wellcome Trust, and consisted of approximately 40 individuals representing academic investigators, funders and WHO staff, and the pharmaceutical industry as observers **(Box 2)** [Department of Pandemic and Epidemic Diseases, WHO, Unpublished Data]. This 2-day meeting was organized into plenary sessions that covered state-of-the-art research reviews and explored the diverse challenges facing public health officials in controlling severe ALRIs, using influenza in general and the responses to the 2009 pandemic in particular as prime examples. A key outcome was agreement on increasing research efforts to develop new preventive and treatment options through engagement of multiple stakeholders.

The second consultation on 6–7 November 2012 gathered 60 participants from 42 different institutions to review and refine the draft research

**Box 2. International research groups, and public health and funding organizations represented at the BRaVe Technical Consultations, July and/or November 2012[†].**

- Afro-European Medical and Research Network: www.aemrnetwork.ch
- Biomedical Advanced Research and Development Authority (BARDA): www.medicalcountermeasures.gov
- Bill & Melinda Gates Foundation: www.gatesfoundation.org
- Chinese Center for Disease Control and Prevention: www.chinacdc.cn/en
- European Centre for Disease Prevention and Control (ECDC): www.ecdc.europa.eu
- International Federation of Pharmaceutical Manufacturers & Associations (IFPMA): www.ifpma.org
- International Forum for Acute Care Trialists, Surviving Sepsis Campaign (InFACT): www.infactglobal.org
- International Respiratory & Severe Illness Center (INTERSECT): http://depts.washington.edu/intrsect
- International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC): http://isaric.tghn.org
- International Centre for Diarrhoeal Disease Research, Bangladesh: www.icddrb.org
- Fondation Mérieux: www.fondation-merieux.org
- Global Approach to Biological Research on Infectious Epidemics in Low income countries Network (GABRIEL): www.globe-network.org
- National Institute of Allergy and Infectious Diseases (NIAID), NIH: www.niaid.nih.gov
- Pneumonia Etiology Research for Child Health (PERCH): www.jhsph.edu/research/centers-and-institutes/ivac/projects/perch
- RIKEN Center of Research Network for Infectious Diseases (CRNID): www.crnid.riken.jp/english
- Wellcome Trust: www.wellcome.ac.uk
- International Society for Influenza and other Respiratory Virus Diseases (ISIRV): www.isirv.org
- The World Federation of Pediatric Intensive and Critical Care Societies: www.wfpiccs.org
- South East Asia Infectious Disease Clinical Research Network (SEAICRN): www.seaicrn.org
- US CDC: www.cdc.gov

*[†]This list does not include the institutional affiliations of the many academic investigators participating in these meetings.*

agenda based on in-depth, topic-specific discussions [104]. On the second day, an assessment exercise divided participants into small working groups to further refine the research questions. Initial research questions from each topic were assessed in the light of several criteria, including urgency of addressing the question, feasibility of conducting appropriate studies (design, duration and costs), public health impacts of the outcomes and overall likelihood of success and beneficiaries. The first round of the exercise focused on individual questions, while the second round was a comparative assessment of questions within each topic. Throughout these discussions, the importance of identifying research activities that would contribute to reducing RVI-associated morbidity and mortality in low-resource settings, where the burden is greatest, was emphasized. Other general themes were linked to this common goal (**Box 3**). In addition to revising the research agenda, a call to action [105] stressing the importance and the urgency of addressing these issues was agreed by the participants.

The purpose of the present article is to describe the outcomes of these deliberations and to share the recently agreed research priorities with the broader scientific and public health communities. The intention is to inform investigators in both public and private sectors, decision-makers in funding organizations and other stakeholders about public health research needs, in the hope of accelerating progress on developing better data and tools for RVI intervention.

## The BRaVe research agenda

The principle objectives of the research agenda are to:

- Identify specific research priorities for RVIs and their sequelae over the next 5–10 years;
- Provide a framework for resource allocation that addresses needs in under-resourced countries, and operational and social sciences research issues based on public health needs;
- Facilitate interactions and collaboration among basic science and clinical investigators in both public and private sectors, public health experts, and representatives from funding organizations and the pharmaceutical industry to address the gaps;
- Monitor the progress in filling knowledge gaps in order to facilitate the development of new evidence-based policies.

The BRaVe Initiative is intended to change the usual approach to WHO's involvement with the research community. While WHO guidelines rely on the existing scientific literature and gathering expert opinion, this process means that evidence to address emergent public health questions is rarely available in a timely manner. Both the lack of appropriate studies and the

delays in the publication process contribute to this dilemma. WHO wants to foster research on priority public health questions from the outset and to work closely with the research community in developing evidence to rapidly inform policy development.

The first version of the research agenda for this initiative has been organized into six tracks that address particular aspects of the global problem of RVIs (**Box 4**) [106]. From the start, division into these particular tracks has been recognized as an arbitrary but logistically helpful means to facilitate discussions and identify priority areas for research. Since each of these tracks overlap or interact with other ones, advances in knowledge or development of new modalities in one will have implications for work in others. For example, an improved point-of-care (POC) diagnostic assay could serve to facilitate field studies of disease burden, disease pathogenesis and potential therapeutics, as well as enable improved individual case management. Better understanding of RVI transmission and ALRI disease pathogenesis will be fundamental to developing improved preventive and treatment strategies. Consequently, it is expected that research priorities will evolve as new data and tools become available.

The following sections describe these tracks in more detail and also give specific examples discussed during the two WHO consultations of recent or ongoing projects that are expected to yield new information that will address current gaps.

### Track 1: defining the burden of respiratory viral infections

The disease burden caused by RVIs is enormous and encompasses the contributions of the primary infections, secondary bacterial ones, and extrapulmonary complications often related to underlying conditions (e.g., ischemic heart disease, congestive heart failure, cerebrovascular disease and diabetes). Recognizing and quantifying the different components of the burden of disease due to direct and indirect consequences of RVIs is a clear need. While attention is given to the impacts of seasonal influenza and pandemic events, it is not widely appreciated that the cumulative burden caused by the more than 200 different types of other respiratory viruses (picornaviruses, paramyxoviruses, CoVs, adenoviruses and bocavirus) often outweighs that of influenza (**Box 1**) [2]. Furthermore, while RVI morbidity and mortality in children is high in developing countries (**Box 1**), older adults typically have the highest mortality in well-resourced ones. For example, one retrospective study found that in the USA an estimated 90% of seasonal influenza- and 78% of RSV-associated respiratory

**Box 3. General themes on research needs related to respiratory virus infections.**

- Insufficient data exist on the burden of disease due to RVIs in developing world settings, such as geographic patterns, seasonality and impacts across the full age spectrum
- Better understanding of the mechanisms of RVI transmission and disease pathogenesis are central to developing better means of prevention and therapy
- Robust surveillance systems that can link epidemiologic, microbiologic, clinical and pathogenesis data are needed in representative locations worldwide
- Frequency and consequences of respiratory viral coinfections, secondary bacterial infection and RVIs in at-risk populations (HIV, malnutrition, tuberculosis and pregnancy) are poorly understood
- Complementary basic and clinical research approaches are required to address essential research needs and develop new interventions and tools to combat respiratory viruses
- Patient-oriented research is a critical part of understanding disease pathogenesis, improving clinical care processes, evaluating therapeutics and improving the evidence base
- Better integration of patient-oriented research activities and clinical practice will foster development of the most relevant evidence for public health decision-making
- Regulatory, funding, ethical and other hurdles remain significant for conducting clinical trials, especially in response to rapidly emerging threats and in low-resource settings
- Multidisciplinary approaches that build on existing structures and delivery systems are needed to improve the clinical management of acute RVIs
- Funding for pathogenesis studies and intervention studies remains difficult to obtain
- Collective engagement across public and private sectors is needed to develop new vaccines and therapeutics against respiratory viruses, and assure equity in making them available to those in need
- Integrated strategies, building on multidisciplinary knowledge, are needed to provide decision-makers with effective interventions to address RVIs efficiently

*RVI: Respiratory virus infection.*

**Box 4. Research tracks and representative topic areas for respiratory viral infection studies in the BRaVe Initiative.**

***Defining the burden of disease***
- BOD of specific RVIs across age spectrum and settings
- Respiratory virus transmission dynamics
- Nosocomial infections and their prevention
- Long-term consequences of RVIs
- Pharmacoeconomic modeling of RVI impact and intervention strategies

***Understanding disease pathogenesis & host dynamics***
- Viral–host cell interactions
- Viral and bacterial replication and host immune dynamics in the respiratory tract
- Viral effects on immune response
- Viral–viral and viral–bacterial coinfections
- Mechanisms of underlying host conditions and environmental factors in disease severity
- Host genetic factors in susceptibility

***Expanding treatment options***
- New antivirals (RSV, HRV and influenza)
- Combination anti-influenza therapies in the seriously ill
- Broad-spectrum antiviral agents
- Host-directed therapies
- Immunomodulatory treatments and adjunctive therapies
- Prophylactic interventions (vitamins and probiotics)

***Improving SARI diagnosis & diagnostic tests***
- Low-cost, multiplex nucleic acid amplification tests
- Specimen collection techniques and devices
- Reference reagents
- Quality assurance standards
- Diagnostic test development and validation
- Biomarkers of etiology and prognosis
- Detection and characterization of emerging RVI threats

***Improving clinical management of SARI/CAP***
- Clinical algorithms for triage
- Protocols and algorithms for clinical management
- Oxygen therapy standards and delivery
- Risk reduction for nosocomial RVIs
- Pharmacoeconomic assessments of therapeutic strategies
- Innovative clinical research methods

***Optimizing public health strategies***
- Evidence base for current nonpharmaceutical interventions
- Vaccine development for key noninfluenza RVIs
- Modeling and pharmacoeconomic analyses to assess RVI mitigation measures
- Knowledge, Attitude and Perception (KAP) studies on RVIs in key groups
- Communication strategies to the general public and to healthcare workers

*BOD: Burden of disease; CAP: Community-acquired pneumonia; HRV: Human rhinovirus; RSV: Respiratory syncytial virus; RVI: Respiratory virus infection; SARI: Severe acute respiratory illness.*

and circulatory deaths occur in adults aged 65 years and older [32], and a recent Dutch study found circulation of common respiratory viruses (influenza A and B, RSV and parainfluenza) to be associated with mortality in elderly individuals [9].

In general, there is a notable lack of high-quality data on the developing world burden of specific RVIs, especially in older children and adults, except for influenza and RSV (Box 1). Disease burden data are not available from many under-resourced countries, and in contrast to influenza, a globally integrated surveillance system for RVIs does not exist at present. A substantial number of ALRI or severe acute respiratory illness (SARI) etiologic studies have been undertaken in recent years, but some have not used sensitive molecular and other microbiologic techniques to detect a broad spectrum of viral and bacterial pathogens. Two ongoing initiatives will help redress this knowledge gap in children less than 5 years of age. The PERCH study, funded by the Bill and Melinda Gates Foundation, is a 5-year case–control study in children aged 1–59 months admitted to hospital for severe or very severe pneumonia by WHO criteria at seven sites in Asia and Africa, using state-of-the-art multiplex nucleic acid amplification test (NAAT) diagnostics [107]. Targeted to locations that have introduced Hib and pneumococcal conjugate vaccines, PERCH will help understand the extent of serotype replacement in pneumococcal pneumonia, the portion of pneumonias associated with specific RVIs, the impact of emerging respiratory viruses, and the effects of increasing urbanization and crowding on RVI epidemiology and severity in young children. The Pneumonia Multi-Centric Pilot Study under the auspices of the GABRIEL network, sponsored by the Fondation Mérieux, is undertaking a similar 2-year SARI etiology study in nine country sites [108].

Since many bacterial respiratory infections have a preceding or concurrent viral component, increasing bacterial vaccine use will not only provide clinical benefit but also likely increase the proportion of pneumonias attributable to respiratory viruses. In this regard vaccine probe studies can be useful in establishing evidence for linkage and RVI burden of disease. For example, one large double-blind RCT of a seven-valent pneumococcal conjugate vaccine in South African infants found a 31% reduction in CAP hospitalizations associated with influenza and six other respiratory viruses compared with placebo, although not in bronchiolitis cases [5]. A recent observational study in Greece found a halving of RVI-associated hospitalizations in children who received the pneumococcal vaccine [33]. These data suggest that most CAPs in hospitalized children may require an antecedent RVI, and that the impact of apparent bacteria-only infections might be reduced if the preceding RVI component could be prevented or modulated by early treatment.

Conversely, licensed viral vaccines (e.g., trivalent influenza vaccine) can be used in probe study designs to determine the proportions of CAP and invasive bacterial infections prevented by specific immunization. Similarly, when available, specific antiviral interventions can be used to examine viral–bacterial interactions. For example, oseltamivir administration reduced pneumococcal pneumonia severity in a murine model of sequential infection [34], and a recent meta-analysis of oseltamivir RCTs found evidence for reductions in physician-diagnosed lower respiratory tract complications leading to antibiotic prescriptions [25]. In children, reductions in new acute otitis media diagnoses have been found with early oseltamivir therapy of influenza [35,36].

### Track 2: understanding disease pathogenesis & host dynamics

Many studies have examined the replication dynamics of specific respiratory viruses at the cellular level, including the use of primary human respiratory cell systems, and sophisticated technologies like host-directed RNAi screens are being applied increasingly to understand the complex interplay between host cellular factors and pathways during replication, especially for influenza [37–39]. This work needs to be extended to other respiratory viruses, as such approaches may yield tractable targets for inhibiting the replication of single or multiple respiratory viruses [40]. Viral sequence analysis and studies of viral gene effects in animal model systems have been key to understanding viral–host interactions. For example, most respiratory viruses, including influenza and RSV, have mechanisms for modulating host antiviral responses and promoting their replication. Recently, two new possible virulence factors have recently been proposed for influenza, the N40 truncated form of PB1 and the Orf X open reading frame in the *PA* gene [41].

By contrast, data on virus replication patterns at the patient level, especially in the lower respiratory tract, are much more limited. Major differences exist in quantitative respiratory viral replication patterns in the upper respiratory tract depending on age, immune status and virus. Furthermore, the availability of more sensitive NAATs for RVI diagnosis has frequently led to the detection of multiple respiratory viruses in those with ALRI, especially in infants and young children. For example, RNA from two or three respiratory viruses have been detected in 10–20% of pediatric pneumonia cases [42,43]. Certain respiratory viruses, particularly human rhinoviruses, are associated with multiple infections throughout life, frequent subclinical infections and detection of viral RNA for weeks surrounding a symptomatic infection [4,44]. Such observations raise questions about disease causation for different viruses (e.g., frequency of subclinical infection and significance of viral RNA detection) and the pathogenesis of dual or sequential infections with multiple agents. More quantitative data and serial sampling might help to resolve uncertainties, but the inability to routinely sample the lower respiratory tract without invasive procedures is a significant limitation. In any case, the finding of frequent viral coinfections also encourages development of innovative therapeutic approaches, not focusing on a single virus.

Host immune and proinflammatory responses to respiratory virus infections play key roles in disease pathogenesis and end-organ damage in the case of severe infections. These responses are diverse across ALRI syndromes (e.g., bronchiolitis, bronchitis, asthma exacerbation, viral pneumonia and acute lung injury), population groups and virus type, and remain incompletely understood. For example, studies in avian H5N1 patients found strong correlations between upper respiratory tract viral RNA levels and systemic cytokine and chemokine responses, indicating a central role of viral replication in driving these responses [45]. Mixed infections, both viral–viral and viral–bacterial, increase the complexity of pathogen–host interactions. Improved therapeutic strategies for RVIs will depend on better understanding of the mechanisms of disease in different syndromes and target populations.

A number of studies examining contributory factors in severe influenza have been published but few have involved prospective systematic data collection with sequential sampling to examine viral and host response dynamics over time. One recent example is the MOSAIC study, which has enrolled 257 hospitalized patients to improve understanding of influenza disease pathogenesis [111]. Preliminary results indicate that various host mediators (e.g., I-tac, tarc, IL-15, IP-10 and IL-6) and gene transcriptome patterns show altered expression. This study has also contributed data to a multicenter study demonstrating that a particular single-nucleotide polymorphism allele in *IFITM3* is associated with increased influenza disease severity in Caucasians [46], a finding recently confirmed in Chinese patients [47]. The contributions of such alleles to pathogen-specific and overall severe infections needs to be assessed across diverse population groups. In general, more information is needed about the underlying mechanisms for established major

host factors (e.g., lack of breastfeeding, pregnancy, obesity, smoking and specific comorbidities) and environmental conditions (e.g., passive smoking, indoor air pollution) associated with increased RVI disease severity. Understanding and addressing the contributions of such factors in resource-limited settings, where the burden of RVIs is estimated to be particularly high, presents enormous challenges, but failure to do so threatens the achievement of the current MDGs.

### Track 3: expanding treatment options

The extensive use of influenza antivirals during the 2009 pandemic response in Japan provides one country-specific perspective and suggests the potential value of antivirals for other RVIs. Japan experienced very low mortality during the 2009 pandemic in association with widespread neuraminidase inhibitor (NAI) use, including in young children and pregnant women [48,49]. Other observational studies have found substantial mortality benefits even with delayed oseltamivir treatment (e.g., 4–5 days after appearance of symptoms) [27,29,50–52], and ecological studies also indicate an association between NAI supply or use and decreased mortality [53]. However, oseltamivir does not rapidly control viral replication in some hospitalized patients [51], some patients progress and die despite early antiviral treatment [54], and emergence of resistance has been a problem, as shown in part by the global circulation of oseltamivir-resistant seasonal influenza H1N1 virus in 2007–2009. Slow antiviral responses and resistance emergence have been reported recently in several avian A(H7N9)-infected patients [55].

Consequently, efforts at developing more potent influenza antiviral combinations for treatment, especially in seriously ill and immunocompromised persons, are needed. Currently, four NAIs are approved for use in Japan (oral oseltamivir, inhaled zanamivir, inhaled laninamivir and intravenous peramivir but, except for oseltamivir, very limited published data exist on use in hospitalized patients. A variety of other agents with mechanisms of action different from NAIs (e.g., favipiravir, nitazoxanide, the sialidase DAS181, the oligonucleotide AVI-7100, anti-hemagglutinin monoclonal antibodies and other novel agents) are in various stages of clinical development [30]. Arbidol (recently designated umifenovir), an agent with antihemagglutinin activity, was approved in Russia in 1995 and is undergoing further clinical testing there. Significant reductions in mortality have been reported in critically ill influenza A(H1N1)pdm09-infected patients given neutralizing antibodies in the form of convalescent plasma and recently hyperimmune IVIg [23,24]. In addition to inhibiting influenza viruses resistant to antivirals in one or both available classes, these interventions may offer useful agents for combination therapy in serious ill patients.

By contrast, the pipeline for developing inhibitors for other respiratory viruses is much more limited. Aerosolized ribavirin is approved for use in treating RSV lower respiratory disease in children but its use is largely limited to severely immunocompromised hosts. While passive immunization with anti-F monoclonals is partially protective against serious RSV illness in at-risk infants, therapeutic use of palivizumab has been clinically ineffective [56]. Other RSV inhibitors are in clinical development (e.g., RI-001, a high-titer RSV immunoglobulin, and several fusion inhibitors, MDT-637 and GS-506). One inhaled siRNA designated ALN-RSV01 may reduce the risk of bronchiolitis obliterans syndrome after RSV infection in lung transplant patients, which increases interest in developing this general class of inhibitors [57]. Recent case reports of the beneficial effects of inhaled DAS181 in treating severe parainfluenza virus (PIV) infections [58], of oral CMX001 in severe adenovirus infections in immunocompromised hosts [59], and Phase II placebo-controlled RCTs reporting some benefits with inhaled IFN-β [112] and with an oral capsid-binding anti-human rhinovirus agent [113] in treating colds in asthmatics are encouraging, but development of alternative antivirals for these and other RVIs is needed.

Broader spectrum RNA virus antivirals (e.g., favipiravir, nitazoxanide and arbidol) raise the possibility of treating a range of RVIs without identifying the causative virus. Host pathway-directed agents offer the potential for broad-spectrum and reduced resistance development [40,60]. Of note, some pathways involved in host immune responses are also necessary for efficient viral replication, so that an inhibitor has the potential to modulate both viral replication and possibly deleterious host responses [38,40]. There is also evidence for inadequate host responses in some RVIs; for example, deficient interferon responses in severe influenza pneumonia [61], which may open the possibility of therapeutic intervention. Resolving such questions will depend on advances in understanding the viral replication dynamics and host immune responses in key patient groups, especially in the lower respiratory tract, as well as the potency of candidate immunomodulatory and host-directed therapeutics.

Assessing the effectiveness and safety of low-cost adjunctive therapies with regard to possible therapeutic value makes sense for vitamin and mineral supplements (e.g., vitamin D, vitamin A, zinc and selenium), especially in populations with documented or suspected deficiencies [62–66]. Prophylactic studies might be considered with these and other relatively low-cost, low-risk interventions like probiotics [67]. Another area of interest is the therapeutic value of various immumomodulatory interventions (e.g., statins, glitazones, COX-2 inhibitors and macrolides), particularly for treatment in conjunction with antivirals in severe illness, and of commonly used symptom relief medications (e.g., NSAIDS) [68]. However, it remains to be determined whether either or both of the apparently conflicting strategies of upregulation or downregulation of innate immune responses are appropriate for particular patient groups, as well as which responses to modulate, to what extent, and at what time points in the course of illness to start and to stop.

### Track 4: improving SARI diagnosis & diagnostic tests

Many challenges with regard to developing low-cost, reliable POC diagnostic tests applicable in low-resource setting are apparent, although these tests can be quite helpful in surveillance activities when used and interpreted correctly. Even in well-resourced settings, the performance characteristics and costs of available POC assays do not necessarily justify their use in individual patient management, as assay sensitivity in children is often better than in adults and the elderly, in whom upper respiratory tract virus titers are usually lower. Standardization in collection procedures, sites of sampling, and timing during the course of illness can critically affect performance. Recent development of relatively low-cost POC tests using battery-operated readers have shown improved performance for influenza diagnosis. Similar incremental improvements in POCs are likely to continue and will expand options for both surveillance and clinical management. The use of sequential sampling to support therapeutic monitoring in seriously ill patients (e.g., responses to antiviral administration and detection of antiviral resistance emergence) and other areas of RVI research (e.g., the evaluation of novel therapeutics) are important topics for continued study.

Commercial opportunities have led to an increasing number of POC antigen assays and of laboratory-based multiplex NAATs in well-resourced settings, but providing incentives for companies to expand to less well-resourced markets is challenging. Most of the next-generation multiplex NAATs, panels and cards for viral respiratory infections are being developed in the private sector. Financial considerations such as protecting and/or exploiting intellectual property will increase the costs of many of the newer technologies. However, success is possible in low-resource settings, as exemplified by the Foundation for Innovative New Diagnostics (FIND)'s model in developing a rapid multidrug-resistant tuberculosis test, based on a NAAT, that enjoyed considerable application and associated cost reduction. Similarly, the introduction in resource-limited settings of rapid diagnostic tests for malaria have been shown to be cost effective in terms of appropriate treatment for those with malaria and reduced use of antimalarials for nonmalaria fever patients [69,70]. Careful pharmacoeconomic evaluations will be needed to clarify the role of existing and newer RVI diagnostics, particularly in lower resource settings.

The development of prognostic markers for RVIs and the validation of biomarkers that may help identify those at risk for progression to severe disease and distinguish patients with bacterial from those with viral or nonbacterial etiologies are important investigative areas. Studies on serum procalcitonin and C-reactive protein to facilitate the judicious use of antibiotics are promising in this regard [71,72], but further work, especially in developing world settings, is required. Preliminary studies using sophisticated analyses of host transcriptomics has indicated that particular patterns might help distinguish viral from bacterial pneumonias [73]. While such approaches are of considerable scientific interest, broader application would depend on finding an appropriate balance between the scope of testing and cost of the assay.

### Track 5: improving clinical management

Standards of care for ALRIs vary widely across the globe, and as many as 1.5 million childhood deaths may have hypoxia as contributory factor each year. The availability of oxygen, oximeters, related basic support equipment and trained staff are insufficient in some countries [74]. In addition, the development of WHO oxygen use guidelines and essential medicine qualification are currently hindered by insufficient high-quality evidence. While it seems obvious that accurate detection of hypoxemia and availability of oxygen would improve both rational use of oxygen therapy and quality of care, further research studies are

needed to address operationalization of detection and case management of hypoxemia for improving health system support in CAP and ALRIs. Related important clinical support questions that require further study, especially in low-resource settings, encompass strategies for using noninvasive and invasive mechanical ventilatory support.

One key mechanism for increasing accessibility to existing therapeutics is WHO's essential medicines list (EML) and the related prequalification program [114], the goals of which are to make effective, quality-assured drugs affordable and accessible, as well as promote transparency and collaboration among regulatory authorities and WHO. The WHO prequalification program [115] has approved 269 products as of mid-2012. The EML neither replaces regulatory authority processes nor is a list of inexpensive medicines for low-resource countries. The last EML revision in 2011 included 325 active substances and currently includes oseltamivir for influenza and ribavirin for selected viral hemorrhagic fevers.

Another aspect of improving clinical management is the avoidance of treatments that are ineffective and in some cases potentially harmful. Antibiotics are commonly used for treating RVIs, a circumstance that increases the risk of adverse drug effects, increases cost of care and contributes to the problem of antimicrobial resistance. Of note, epidemiologic studies have linked early childhood antibiotic exposure, most commonly for ARIs, with obesity and possibly inflammatory bowel disease in later life [75,76]. Systemic corticosteroids have been commonly used in management of RSV-associated bronchiolitis and of influenza-associated pneumonia and acute respiratory distress syndrome, but, unlike use in the croup syndrome, the available data do not indicate benefit [77]. In the case of influenza-associated acute respiratory distress syndrome or intensive care unit (ICU)-acquired pneumonia, there appears to be harm in terms of corticosteroid side effects and increased risks of nosocomial infections and mortality [78–81]. Animal models and some epidemiologic observations have also suggested an increased risk of mortality associated with antipyretic use during influenza infection [82,83]. Since antipyretics are widely used in treating ARIs, further studies of their potential benefits and adverse events are warranted.

In response to the 2009 pandemic, a number of new networks like the International Forum for Acute Care Trialists (InFACT) [84,116] and in the UK the Mechanisms of Severe Acute Influenza Consortium (MOSAIC) [110] were formed to undertake prospective studies of disease pathogenesis and treatment. Delays in study initiation limited enrollments in most studies, and no prospective RCT of adjunctive therapeutics like corticosteroids or statins were completed, although a number of observational studies have been reported. ICUs were disproportionately impacted during the pandemic and are likely to be the sites in future where many critically ill patients, owing to recognized or newly emerging RVIs, are managed. Past RCTs of supportive care for such patients provide examples of determining the best practices for ventilator use, fluid management and infection reduction in the ICU setting [85]. However, another key pandemic lesson was that ICU surge capacity needs advance training and preparation; technology like ventilators can be ineffective and potentially harmful if there are not sufficient trained staff.

In the early stages of an outbreak with a new pathogen, smaller observational studies with prospective data collection may be all the research community can conduct. These studies are often key, as some initial clinical and microbiologic data are needed to develop preliminary management recommendations. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) was launched in 2012 [117], in part to increase preparedness for novel SARI and emerging infection events, and facilitate data collection by putting mechanisms in place to respond to the next outbreak. Preparedness includes both developing infrastructure for clinical studies, in part by collaborating on studies during the inter-pandemic period, and ensuring that the necessary funding, administrative structure, data-sharing and sample-analysis methods are in place. For example, ISARIC recently posted comments and data collection instruments regarding the novel CoV cases in the Middle East [118,119], and has developed with the WHO and made publicly available a clinical protocol for SARI in response to the emergence of avian influenza A(H7N9) [120]. Going forward, collaborations between investigators in InFACT and ISARIC have focused on harmonization of clinical studies, clarity on end points, developing an adaptive clinical trial RCT system to assess a range of adjunctive therapies for SARI management, and empiric research on understanding the ethical, logistic and administrative constraints on clinical research in epidemics.

### Track 6: optimizing public health strategies

Vaccines remain the optimal means of disease prevention, but among the respiratory viruses,

only vaccines against influenza are currently available. Studies to develop vaccines for RSV and PIV have been ongoing for decades, and both live-attenuated and subunit RSV vaccines are in clinical development. However, significant technical challenges exist with regard to vaccines for RVIs. In addition to the large diversity of antigenic types for some respiratory virus families (e.g., picornaviruses and adenoviruses), immune responses to infections by important pathogens such as RSV, human metapneumovirus and PIV are incomplete, meaning that reinfections occur throughout life. Such findings suggest that effective vaccines might need to induce more effective protective responses than natural infection. Once such vaccines are available, the strategy of maternal immunization, already shown to be effective for influenza [121], would be a logical approach to protecting infants. In low-resource settings, maternal influenza immunization combined with immunization of children at 6–9 months of age has the potential to significantly reduce pneumonia mortality [86]. However, even for countries using influenza vaccines, the requirement for annual immunization, related to waning immunity and changing viral antigenicity, limited protective effectiveness [122] especially in high-risk populations such as the elderly and very young children, poor uptake in many countries and delay in distributing vaccines for novel viruses emphasize the importance of developing new influenza vaccines with more durable and broader spectrum immune responses [21,31,105].

Renewed work on public health approaches to reducing disease transmission at both the individual (e.g., hand hygiene, cough etiquette, masking) and community (e.g., school closures, avoidance of mass gatherings) levels is needed. While some of these interventions such as hand hygiene [87] and school closures [88] appear to be useful in specific circumstances, much more evidence is required to inform such public health measures and recommendations. Additionally understanding the relative contributions of different routes of RVI transmission in different settings would have implications for preventive interventions and hence for cost–effectiveness studies. Pharmacoeconomic studies and modeling of comparative scenarios to include the possible unintended consequences of the interventions to be implemented are needed.

Misperceptions about RVIs are common in both the general public and healthcare providers. This has contributed to both using inappropriate therapies (e.g., unnecessary antibiotics) and to not using ones of proven values (i.e., influenza vaccines and antivirals). Particular research attention should be given to understanding the optimal methods of communication to different stakeholders, especially healthcare workers. Better data on current knowledge, attitudes and practices in different countries and resource settings would allow improved local adaptation and implementation. As public trust in political leaders is typically much less than for those in the clinical and public health communities, communication and preparation efforts should be linked closely with credible voices in these communities. In the wake of the 2009 pandemic, many countries are re-evaluating their responses in the context of their own cultures, political systems and healthcare systems. This reappraisal provides an opportunity to generate greater awareness among stakeholders of the impact of currently circulating respiratory viruses and potential threats to improve current responses and future preparedness.

## Future perspective

The next steps in this undertaking will include efforts to raise awareness about the public health and research needs represented in the BRaVe Initiative among funding organizations, academic groups and industry. Better understanding of the activities currently in progress globally will require sharing information on active protocols and research results. WHO proposes the creation of a forum (think-tank) with stakeholders including academic investigators, public health decision-makers, representatives from funding organizations and the private sector to prioritize gaps and agree on a timetable for developing workable solutions. As currently envisioned, this forum would be at least a 3-year initiative that would address three key topics in parallel: new antiviral treatments for viral respiratory infections; innate (both protective and deleterious) and adaptive immune responses in pathogenesis of disease, including the roles for immunomodulatory therapies and vaccines for noninfluenza respiratory viruses; and optimization of clinical management, diagnostics, and public health strategies, especially in low-resource settings. An additional near-term goal is revision of the joint WHO–UNICEF global action plan on pneumonia to include RVI-associated pneumonias. Increased awareness and coordination among stakeholders is expected to link public health communities around major cross-cutting issues and accelerate innovative solutions to address the major issue of respiratory viral infections.

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## Executive summary

### *Background*

- Acute respiratory infections kill an estimated 3.9 million people annually and in developing countries are the leading cause of mortality in children under 5 years of age.
- Respiratory viruses are major contributors to this burden of disease but their contribution to respiratory illnesses and associated complications remains underestimated and incompletely understood.
- Emerging respiratory viruses have the potential to trigger regional or worldwide epidemics as recently seen with the avian influenza A(H7N9) virus or the Middle East respiratory syndrome coronavirus.
- No specific public health strategies for respiratory viral infections other those caused by influenza viruses and to some extent respiratory syncytial virus are currently available.

### *Development of the BRaVe Initiative*

- WHO, with its partners, has undertaken the development of an integrated research agenda and response initiative, the Battle against Respiratory Viruses (BRaVe) Initiative to address these needs.
- Two informal technical consultations were held by WHO in July and November 2012 to identify the key knowledge gaps and the research needs and tools to address these gaps.
- A call to action was posted on the WHO website in March 2013 and the research agenda in May 2013.

### *BRaVe Initiative research agenda*

- The principle objectives of the research agenda are to: identify specific research priorities for respiratory virus infections and their sequelae over the next 5–10 years; provide a framework for resource allocation that addresses needs in under-resourced countries, as well as operational and social sciences research issues; facilitate interactions and collaboration among partners to address the gaps; and monitor progress in filling knowledge gaps in order to facilitate the development of new evidence-based policies.
- The BRaVe Initiative is intended to change the usual approach to WHO's involvement with the research community.
- The following tracks have been identified crucial for further research; priority research questions have been highlighted:
  - Track 1: defining the burden of respiratory viral infections;
  - Track 2: understanding disease pathogenesis and host dynamics;
  - Track 3: expanding treatment options;
  - Track 4: improving SARI diagnosis and diagnostic tests;
  - Track 5: improving clinical management;
  - Track 6: optimizing public health strategies.
- Priority research questions were agreed within each tracks.

### *Next steps*

- Collective engagement across public and private sectors is needed to develop new vaccines and therapeutics against respiratory viruses and assure equity in making them available to those in need.
- Complementary basic and clinical research approaches are required to address essential research needs and develop new interventions and tools to combat respiratory viruses.
- WHO proposes the creation of a forum with stakeholders including academic investigators, public health decision-makers, representatives from funding organizations and the private sector to prioritize gaps and agree on a timetable for developing workable solutions.

## References


Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1. Liu L, Johnson HL, Cousens S *et al.* Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* 379(9832), 2151–2161 (2012).

▪ **Overview of childhood mortality trends over the past decade indicating the current public health priorities to address and the contributions of pneumonia and respiratory infections.**

2. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. *Lancet* 377(9773), 1264–1275 (2011).

▪ **Rigorous review that examines the role of respiratory viruses in community-acquired pneumonia in adults and children.**

3. Nair H, Simoes EA, Rudan I *et al.* Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* 381(9875), 1380–1390 (2013).

▪ **Recent study on the global burden of ALRI in children and its impacts on individuals and healthcare systems.**

4. Gern JE. The ABCs of rhinoviruses, wheezing, and asthma. *J. Virol.* 84(15), 7418–7426 (2010).

5. Madhi SA, Klugman KP. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. *Nat. Med.* 10(8), 811–813 (2004).

6. Casscells SW, Granger E, Kress AM, Linton A, Madjid M, Cottrell L. Use of oseltamivir after influenza infection is associated with reduced incidence of recurrent adverse cardiovascular outcomes among military health system beneficiaries with prior cardiovascular diseases. *Circ. Cardiovasc. Qual. Outcomes* 2(2), 108–115 (2009).

7. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N. Engl. J. Med.* 352(17), 1749–1759 (2005).

8. Madjid M, Curkendall S, Blumentals WA. The influence of oseltamivir treatment on the risk of stroke after influenza infection. *Cardiology* 113(2), 98–107 (2009).

9. van AL, van den Wijngaard C, van PW *et al.* Mortality attributable to 9 common infections: significant effect of influenza A, respiratory syncytial virus, influenza B, norovirus, and parainfluenza in elderly persons. *J. Infect. Dis.* 206(5), 628–639 (2012).

10. Warren-Gash C, Bhaskaran K, Hayward A *et al.* Circulating influenza virus, climatic factors, and acute myocardial infarction: a time series study in England and Wales and Hong Kong. *J. Infect. Dis.* 203(12), 1710–1718 (2011).

11. Zhu T, Carcaillon L, Martinez I *et al.* Association of influenza vaccination with reduced risk of venous thromboembolism. *Thromb. Haemost.* 102(6), 1259–1264 (2009).

12. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 67(1), 71–79 (2012).

13. Molinari NA, Ortega-Sanchez IR, Messonnier ML *et al.* The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 25(27), 5086–5096 (2007).

14. Fendrick AM, Monto AS, Nightengale B, Sarnes M. The economic burden of non-influenza-related viral respiratory tract infection in the United States. *Arch. Intern. Med.* 163(4), 487–494 (2003).

15. Anderson LJ, Baric RS. Emerging human coronaviruses – disease potential and preparedness. *N. Engl. J. Med.* 367(19), 1850–1852 (2012).

16. Gao R, Cao B, Hu Y *et al.* Human infection with a novel avian-origin influenza A (H7N9) virus. *N. Engl. J. Med.* 368(20), 1888–1897 (2013).

17. Uyeki TM, Cox NJ. Global concerns regarding novel influenza A (H7N9) virus infections. *N. Engl. J. Med.* 368(20), 1862–1864 (2013).

18. Zaki AM, van BS, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N. Engl. J. Med.* 367(19), 1814–1820 (2012).

19. Lee JW, McKibbin WJ. Estimating the global economic costs of SARS. In: *Learning from SARS: Preparing for the Next Disease Outbreak: Workshop Summary.* Knobler S. Seale MAL (Eds). Institute of Medicine (US) Forum on Microbial Threats, National Academies Press, DC, USA (2004).

20. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect. Dis.* 12(1), 36–44 (2012).

21. Girard MP, Tam JS, Pervikov Y, Katz JM. Report on the first WHO integrated meeting on development and clinical trials of influenza vaccines that induce broadly protective and long-lasting immune responses: Hong Kong SAR, China, 24–26 January 2013. *Vaccine* 31(37), 3766–3771 (2013).

22. Cheng Y, Wong R, Soo YO *et al.* Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur. J. Clin. Microbiol. Infect. Dis.* 24(1), 44–46 (2005).

23. Hung IF, To KK, Lee CK *et al.* Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin. Infect. Dis.* 52(4), 447–456 (2011).

24. Hung IF, To KK, Lee CK *et al.* Hyperimmune intravenous immunoglobulin treatment: a multicentre double-blind randomized controlled trial for patients with severe A(H1N1)pdm09 infection. *Chest* 144(2), 464–473 (2013).

▪ **Up-to-date summary of developments in influenza vaccinology including the prospects for developing vaccines that elicit broadly protective and long-lasting immune responses.**

25. Hernan MA, Lipsitch M. Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomized clinical trials. *Clin. Infect. Dis.* 53(3), 277–279 (2011).

26. Chan MC, Lee N, Lui GC *et al.* Comparisons of oseltamivir-resistant (H275Y) and concurrent oseltamivir-susceptible seasonal influenza A(H1N1) virus infections in hospitalized adults, 2008–2009. *Influenza Other Respi. Viruses* 7(3), 235–239 (2013).

27. Louie JK, Yang S, Acosta M *et al.* Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1)pdm09. *Clin. Infect. Dis.* 55(9), 1198–1204 (2012).

28. Muthuri SG, Myles PR, Venkatesan S, Leonardi-Bee J, Nguyen-Van-Tam JS. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009–2010 influenza A(H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. *J. Infect. Dis.* 207(4), 553–563 (2013).

29. Yang SG, Cao B, Liang LR *et al.* Antiviral therapy and outcomes of patients with pneumonia caused by influenza A pandemic (H1N1) virus. *PLoS ONE* 7(1), e29652 (2012).

30. Hayden FG. Newer influenza antivirals, biotherapeutics and combinations. *Influenza Other Respi. Viruses* 7(Suppl. 1), 63–75 (2013).

▪ **Overview of current and investigational antivirals and other therapeutics for influenza treatment.**

31. Hughes B, Hayden F, Perikov Y, Hombach J, Tam JS. Report of the 5th meeting on influenza vaccines that induce broad spectrum and long-lasting immune responses. World Health Organization, Geneva, 16–17 November 2011. *Vaccine* 30(47), 6612–6622 (2012).

32. Thompson WW, Shay DK, Weintraub E *et al.* Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 289(2), 179–186 (2003).
33. Kouni S, Karakitsos P, Chranioti A, Theodoridou M, Chrousos G, Michos A. Evaluation of viral co-infections in hospitalized and non-hospitalized children with respiratory infections using microarrays. *Clin. Microbiol. Infect.* 19(8), 772–777 (2012).
34. McCullers JA, Bartmess KC. Role of neuraminidase in lethal synergism between influenza virus and *Streptococcus pneumoniae*. *J. Infect. Dis.* 187(6), 1000–1009 (2003).
35. Heinonen S, Silvennoinen H, Lehtinen P *et al.* Early oseltamivir treatment of influenza in children 1–3 years of age: a randomized controlled trial. *Clin. Infect. Dis.* 51(8), 887–894 (2010).
36. Whitley RJ, Hayden FG, Reisinger KS *et al.* Oral oseltamivir treatment of influenza in children. *Pediatr. Infect. Dis. J.* 20(2), 127–133 (2001).
37. de Chassey B, Meyniel-Schicklin L, Aublin-Gex A, Andre P, Lotteau V. Genetic screens for the control of influenza virus replication: from meta-analysis to drug discovery. *Mol. Biosyst.* 8(4), 1297–1303 (2012).
38. Ludwig S. Disruption of virus–host cell interactions and cell signaling pathways as an anti-viral approach against influenza virus infections. *Biol. Chem.* 392(10), 837–847 (2011).
39. Stertz S, Shaw ML. Uncovering the global host cell requirements for influenza virus replication via RNAi screening. *Microbes. Infect.* 13(5), 516–525 (2011).
40. Smith SB, Dampier W, Tozeren A, Brown JR, Magid-Slav M. Identification of common biological pathways and drug targets across multiple respiratory viruses based on human host gene expression analysis. *PLoS ONE* 7(3), e33174 (2012).
41. Jagger BW, Wise HM, Kash JC *et al.* An overlapping protein-coding region in influenza A virus segment 3 modulates the host response. *Science* 337(6091), 199–204 (2012).
42. Bezerra PG, Britto MC, Correia JB *et al.* Viral and atypical bacterial detection in acute respiratory infection in children under five years. *PLoS ONE* 6(4), e18928 (2011).
43. Mermond S, Zurawski V, D'Ortenzio E *et al.* Lower respiratory infections among hospitalized children in New Caledonia: a pilot study for the Pneumonia Etiology Research for Child Health project. *Clin. Infect. Dis.* 54(Suppl. 2), S180–S189 (2012).
44. Winther B, Hayden FG, Hendley JO. Picornavirus infections in children diagnosed by RT-PCR during longitudinal surveillance with weekly sampling: association with symptomatic illness and effect of season. *J. Med. Virol.* 78(5), 644–650 (2006).
45. de Jong MD, Simmons CP, Thanh TT *et al.* Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat. Med.* 12(10), 1203–1207 (2006).
46. Everitt AR, Clare S, Pertel T *et al.* IFITM3 restricts the morbidity and mortality associated with influenza. *Nature* 484(7395), 519–523 (2012).
47. Zhang YH, Zhao Y, Li N *et al.* Interferon-induced transmembrane protein-3 genetic variant rs12252-C is associated with severe influenza in Chinese individuals. *Nat. Commun.* 4, 1418 (2013).
48. Sugaya N, Kohno S, Ishibashi T, Wajima T, Takahashi T. Efficacy, safety, and pharmacokinetics of intravenous peramivir in children with 2009 pandemic H1N1 influenza A virus infection. *Antimicrob. Agents Chemother.* 56(1), 369–377 (2012).
49. Yamada T, Yamada T, Morikawa M *et al.* Pandemic (H1N1) 2009 in pregnant Japanese women in Hokkaido. *J. Obstet. Gynaecol. Res.* 38(1), 130–136 (2012).
50. Dubar G, Azria E, Tesniere A *et al.* French experience of 2009 A/H1N1v influenza in pregnant women. *PLoS ONE* 5(10), pii: e13112 (2010).
51. Lee N, Chan PK, Wong CK *et al.* Viral clearance and inflammatory response patterns in adults hospitalized for pandemic 2009 influenza A(H1N1) virus pneumonia. *Antivir. Ther.* 16(2), 237–247 (2011).
52. Li IW, Hung IF, To KK *et al.* The natural viral load profile of patients with pandemic 2009 influenza A(H1N1) and the effect of oseltamivir treatment. *Chest* 137(4), 759–768 (2010).
53. Miller PE, Rambachan A, Hubbard RJ *et al.* Supply of neuraminidase inhibitors related to reduced influenza A (H1N1) mortality during the 2009–2010 H1N1 pandemic: an ecological study. *PLoS ONE* 7(9), e43491 (2012).
54. Nukiwa N, Kamigaki T, Oshitani H. Fatal cases of pandemic (H1N1) 2009 influenza despite their early antiviral treatment in Japan. *Clin. Infect. Dis.* 51(8), 993–994 (2010).
55. Hu Y, Lu S, Song Z *et al.* Association between adverse clinical outcome in human disease caused by novel influenza A H7N9 virus and sustained viral shedding and emergence of antiviral resistance. *Lancet* 381(9885), 2273–2279 (2013).
56. Geevarghese B, Simoes EA. Antibodies for prevention and treatment of respiratory syncytial virus infections in children. *Antivir. Ther.* 17(1 Pt B), 201–211 (2012).
57. DeVincenzo JP. The promise, pitfalls and progress of RNA-interference-based antiviral therapy for respiratory viruses. *Antivir. Ther.* 17(1 Pt B), 213–225 (2012).

▪ **Extensive review on RNAi-based therapeutics and their application as antivirals for respiratory virus infections.**

58. Chen YB, Driscoll JP, McAfee SL *et al.* Treatment of parainfluenza 3 infection with DAS181 in a patient after allogeneic stem cell transplantation. *Clin. Infect. Dis.* 53(7), e77–e80 (2011).
59. Florescu DF, Pergam SA, Neely MN *et al.* Safety and efficacy of CMX001 as salvage therapy for severe adenovirus infections in immunocompromised patients. *Biol. Blood Marrow Transplant.* 18(5), 731–738 (2012).
60. Shaw ML. The host interactome of influenza virus presents new potential targets for antiviral drugs. *Rev. Med. Virol.* 21(6), 358–369 (2011).
61. Agrati C, Gioia C, Lalle E *et al.* Association of profoundly impaired immune competence in H1N1v-infected patients with a severe or fatal clinical course. *J. Infect. Dis.* 202(5), 681–689 (2010).
62. Camargo CA Jr, Ganmaa D, Frazier AL *et al.* Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics* 130(3), e561–e567 (2012).
63. Murdoch DR, Slow S, Chambers ST *et al.* Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. *JAMA* 308(13), 1333–1339 (2012).
64. Roth DE, Caulfield LE, Ezzati M, Black RE. Acute lower respiratory infections in childhood: opportunities for reducing the global burden through nutritional interventions. *Bull. World Health Organ.* 86(5), 356–364 (2008).
65. Scott JA, Brooks WA, Peiris JS, Holtzman D, Mulholland EK. Pneumonia research to reduce childhood mortality in the developing world. *J. Clin. Invest* 118(4), 1291–1300 (2008).
66. Singh M, Das RR. Zinc for the common cold. *Cochrane Database Syst. Rev.* 2, CD001364 (2011).
67. Popova M, Molimard P, Courau S *et al.* Beneficial effects of probiotics in upper respiratory tract infections and their mechanical actions to antagonize pathogens. *J. Appl. Microbiol.* 113(6), 1305–1318 (2012).

68. Fedson DS. Treating influenza with statins and other immunomodulatory agents. *Antiviral Res.* doi:10.1016/j.antiviral.2013.06.018 (2013) (Epub ahead of print).
69. Shillcutt S, Morel C, Goodman C *et al.* Cost–effectiveness of malaria diagnostic methods in sub-Saharan Africa in an era of combination therapy. *Bull. World Health Organ.* 86(2), 101–110 (2008).
70. Thiam S, Thior M, Faye B *et al.* Major reduction in anti-malarial drug consumption in Senegal after nation-wide introduction of malaria rapid diagnostic tests. *PLoS ONE* 6(4), e18419 (2011).
71. Gilbert DN. Procalcitonin as a biomarker in respiratory tract infection. *Clin. Infect. Dis.* 52(Suppl. 4), S346–S350 (2011).
72. Zimmerman O, Rogowski O, Aviram G *et al.* C-reactive protein serum levels as an early predictor of outcome in patients with pandemic H1N1 influenza A virus infection. *BMC Infect. Dis.* 10, 288 (2010).
73. Vernet G, Saha S, Satzke C *et al.* Laboratory-based diagnosis of pneumococcal pneumonia: state of the art and unmet needs. *Clin. Microbiol. Infect.* 17(Suppl. 3), 1–13 (2011).
74. Belle J, Cohen H, Shindo N *et al.* Influenza preparedness in low-resource settings: a look at oxygen delivery in 12 African countries. *J. Infect. Dev. Ctries* 4(7), 419–424 (2010).

▪ **Insightful country-specific picture on capacity and equipment to deliver oxygen therapy that highlights the difficulty of implementing a simple life-saving intervention in resource-limited settings.**

75. Kronman MP, Zaoutis TE, Haynes K, Feng R, Coffin SE. Antibiotic exposure and IBD development among children: a population-based cohort study. *Pediatrics* 130(4), e794–e803 (2012).
76. Trasande L, Blustein J, Liu M, Corwin E, Cox LM, Blaser MJ. Infant antibiotic exposures and early-life body mass. *Int. J. Obes. (Lond.)* 37(1), 16–23 (2013).
77. de Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. *Am. J. Respir. Crit. Care Med.* 185(1), 12–23 (2012).
78. Brun-Buisson C, Richard JC, Mercat A, Thiebaut AC, Brochard L. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* 183(9), 1200–1206 (2011).
79. Kim SH, Hong SB, Yun SC *et al.* Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. *Am. J. Respir. Crit. Care Med.* 183(9), 1207–1214 (2011).
80. Martin-Loeches I, Lisboa T, Rhodes A *et al.* Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection. *Intensive Care Med.* 37(2), 272–283 (2011).
81. Ranzani OT, Ferrer M, Esperatti M *et al.* Association between systemic corticosteroids and outcomes of intensive care unit-acquired pneumonia. *Crit. Care Med.* 40(9), 2552–2561 (2012).
82. Eyers S, Weatherall M, Shirtcliffe P, Perrin K, Beasley R. The effect on mortality of antipyretics in the treatment of influenza infection: systematic review and meta-analysis. *J. R. Soc. Med.* 103(10), 403–411 (2010).
83. Sullivan JE, Farrar HC. Fever and antipyretic use in children. *Pediatrics* 127(3), 580–587 (2011).
84. InFACT: a global critical care research response to H1N1. *Lancet* 375(9708), 11–13 (2010).
85. Dellinger RP, Levy MM, Rhodes A *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit. Care Med.* 41(2), 580–637 (2013).
86. Brooks WA. A four-stage strategy to reduce childhood pneumonia-related mortality by 2015 and beyond. *Vaccine* 27(5), 619–623 (2009).

▪▪ **Perspectives on a comprehensive strategy to address the burden of childhood pneumonia, including those of viral origin.**

87. Aiello AE, Coulborn RM, Aragon TJ *et al.* Research findings from nonpharmaceutical intervention studies for pandemic influenza and current gaps in the research. *Am. J. Infect. Control* 38(4), 251–258 (2010).
88. Copeland DL, Basurto-Davila R, Chung W *et al.* Effectiveness of a school district closure for pandemic influenza A (H1N1) on acute respiratory illnesses in the community: a natural experiment. *Clin. Infect. Dis.* 56(4), 509–516 (2013).
89. Nair H, Brooks WA, Katz M *et al.* Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 378(9807), 1917–1930 (2011).
90. Nair H, Nokes DJ, Gessner BD *et al.* Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 375(9725), 1545–1555 (2010).
91. O'Brien KL, Wolfson LJ, Watt JP *et al.* Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 374(9693), 893–902 (2009).
92. Watt JP, Wolfson LJ, O'Brien KL *et al.* Burden of disease caused by *Haemophilus influenzae* type b in children younger than 5 years: global estimates. *Lancet* 374(9693), 903–911 (2009).


## Websites


101. WHO Disease Outbreak News (2013). www.who.int/csr/don/archive/disease/coronavirus_infections/en/index.html
102. WHO Disease Outbreak News. www.who.int/csr/don/en
103. WHO Public Health Research Agenda on Influenza. www.who.int/influenza/resources/research/en/index.html
104. WHO meeting on development and clinical trials on influenza vaccines that induce broadly protective and long-lasting immune responses 2013. www.who.int/vaccine_research/meetings/fluvaccines_devclinicaltrials_jan13/en/index.html
105. WHO Battle against Respiratory Viruses (BRaVe) Initiative. www.who.int/influenza/patient_care/clinical/brave/en/index.html
106. Meeting report for the WHO informal technical consultation 'Research needs for the Battle against Respiratory Viruses'. www.who.int/influenza/patient_care/clinical/BRaVE_meeting_report_november2012.pdf
107. BRaVe Call to Action. www.who.int/influenza/patient_care/clinical/call_to_action/en/index.html
108. BRaVe Research Agenda. www.who.int/influenza/patient_care/clinical/BRaVe_Research_Agenda_2013.pdf
109. Pneumonia Etiology Research for Child Health (PERCH) study details 2012. www.jhsph.edu/research/centers-and-institutes/ivac/projects/perch/perch-study-details.html
110. Global Approach for Biological Research on Infectious Epidemics in Low income countries (GABRIEL) pilot study 2011. http://globe-network.org/sites/default/files/documents/public/gabriel/research-projects/pneumonia-multi-centric-pilot-study-project-sheet.pdf
111. Mechanisms Of Severe Acute Influenza Consortium (MOSAIC) 2011. www1.imperial.ac.uk/medicine/about/institutes/centre_respiratory_infection/mosaic
112. Synairgen press release 2012. www.synairgen.com/media/1536/19%20april%202012%20Phase%20II%20press%20release%20final.pdf

113. Biota press release 2012. www.biotapharma.com/uploaded/154/1021819_20hrvphaseiibstudyachieve.pdf
114. WHO Essential Medicines List. www.who.int/selection_medicines/en
115. WHO Prequalification Program. http://apps.who.int/prequal
116. International Forum for Acute Care Trialists (InFACT). www.infactglobal.org
117. International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). http://isaric.tghn.org
118. ISARIC post on ProMEDhttp. www.promedmail.org/direct.php?id=20121208.1443486
119. ISARIC Novel Coronavirus Case Record Form 2013. http://isaric.tghn.org/articles/isaric-novel-coronavirus-crf-version-1
120. ISARIC and WHO SARI and Natural History Protocols. http://isaric.tghn.org/articles/isaric-and-who-sari-and-natural-history-protocols
121. WHO Strategic Advisory Group of Experts on immunization (SAGE) position paper 2012. www.who.int/wer/2012/wer8747.pdf
122. Centers for Disease Control and Prevention, Mortality and Morbidity Weekly Report, 22 February 2013. www.cdc.gov/mmwr