Optimizing the treatment of patients
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<td>Acute Myocardial Infarction</td>
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<td>ARI</td>
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<td>CAP</td>
<td>Community-acquired Pneumonia</td>
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<td>CPT2</td>
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<td>HA</td>
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<td>IFITM3</td>
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<td>ILI</td>
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<td>IMV</td>
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<td>IRVS</td>
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<td>PCT</td>
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<td>POC</td>
<td>Point of Care</td>
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<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
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<tr>
<td>RT-PCR</td>
<td>Reverse Transcriptase Polymerase Chain Reaction</td>
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<td>SARI</td>
<td>Severe Acute Respiratory Infection</td>
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<td>TB</td>
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<td>WBC</td>
<td>White Blood Cell</td>
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Rapid case identification and improved clinical management can substantially reduce the incidence of severe illness and associated complications of seasonal, novel influenza A and pandemic influenza virus infections. It may also reduce the risk of influenza virus transmission and mitigate the impact of outbreaks on the health-care system. Optimization of clinical management must be underpinned by a better understanding of the pathogenesis of influenza virus infections, advances in rapid laboratory diagnostics, development and timely initiation of effective antiviral treatment and other interventions, and prompt access to good-quality health-care services. As summarized below, progress has been made in many aspects of influenza clinical management, particularly from new evidence developed during the 2009 A(H1N1)pdm09 virus pandemic, but there are still many unmet public health needs and unanswered questions. The following sections provide overviews with selected references that illustrate both developments and continuing evidence gaps for each of the substreams described in Stream 4 of the 2009 WHO Public Health Research Agenda for Influenza.

Substream 4.1
Factors associated with pathogenesis and clinical severity

Research recommendation 4.1.1
Investigate the role of virological factors (including replication sites, duration and viral load levels), and innate and adaptive immune responses and other host responses in the severity of disease and associated complications.

Major Progress 4.1.1
Many studies have examined viral replication patterns, and immune and other host responses, in patients with serious illness from A(H1N1)pdm09 virus infection. Relevant observations include the finding of more protracted viral replication (measured by quantitative viral RNA detection) in the upper respiratory tract of patients with severe illness (To et al., 2010). In this study, the 23 patients who had acute respiratory distress syndrome (ARDS) or died had a slower decline in nasopharyngeal viral loads, had higher plasma levels of proinflammatory cytokines and chemokines, and were more likely to have bacterial coinfections (30.4%), myocarditis (21.7%) or viremia (13.0%) than patients who survived without ARDS or had mild disease. In critically ill patients with viral pneumonia, higher levels of viral RNA and more protracted detection were found in lower respiratory than in upper respiratory tract samples (Lee et al., 2011a). These observations were made while patients were receiving oseltamivir therapy, and several of the patients had increases in viral RNA titres after cessation, in the apparent absence of emergence of oseltamivir-resistant virus; these findings indicate the need for prolonged and more potent antiviral therapy in such patients.

Influenza A(H1N1)pdm09 viral RNA, presumably reflecting high viral loads in the lungs, was detected in blood specimens of 10% of 139 hospitalized patients, and was associated with more severe disease and higher mortality (Tse et al., 2011). Detection of viral RNA in blood has been associated with pneumonia and poor prognosis in immunocompromised hosts; for example, haematopoietic stem cell transplant
One study found that 11.4% of 79 HSCT patients with influenza viral RNA detected in blood had increased risk of progression to lower respiratory tract illness, respiratory failure, and both overall and influenza-related death compared with those without such RNA (Choi et al., 2012). Profound lymphopenia (<100 cells/μL) is a risk factor in such patients. These observations suggest that timely administration of potent antiviral therapy might improve outcomes in such patients.

Severe influenza illness has been notable for findings of both excessive proinflammatory mediator levels (which probably contribute to disease pathogenesis), and of inadequate innate antiviral and influenza-specific adaptive responses. Observations in small numbers of patients with severe A(H1N1)pdm09 illness include acute T-cell anergy, perhaps mediated through an apoptosis-related mechanism, lower plasma levels of interferon-alpha and monocyte chemoattractant protein-1, suggesting impaired production of these cytokines and depletion of natural killer cells (Agrati et al., 2010). One study comparing patients hospitalized with A(H1N1)pdm09 or seasonal influenza found 2–15-fold increases in plasma proinflammatory cytokines (interleukin 6 [IL-6], CXCL8/IL-8, CCL2/MCP-1 and sTNFR-1 A) but suppressed adaptive-immunity (Th1/Th17)-related cytokine responses in severe H1N1pdm09 pneumonia (Lee et al., 2011b). Hypercytokinemia has been associated with severe outcomes in avian influenza A(H5N1) and A(H7N9) virus infections (Wang et al., 2014c).

In one severely ill A(H7N9) virus-infected patient, RNA sequence analysis of serial blood samples found RNAemia, with cytokine gene expression levels peaking at the time of peak RNAemia and then decreasing with the decline in viral load, and cytokine genes peaking again when bacterial coinfection developed (Hu et al., 2015). During influenza A(H1N1)pdm09 virus infection, failure to develop influenza-specific antibodies has been reported to be a risk factor for death; also, lack of influenza-specific T-cell responses and high plasma levels of IL-6 and IL-10 were noted in fatal cases (Guihot et al., 2014).

**Unmet public health needs and research gaps 4.1.1**

There are still few studies on the relative roles of virological factors (e.g. replication sites, duration and viral load levels), and of innate and adaptive immune and other host responses in causing severe disease and associated complications. Few reports have provided an integrated analysis that links temporal changes in these variables to clinical outcomes. Studies of larger numbers of patients across the continuum of care – including those with comorbidities, critical illness or novel influenza A virus infections – are needed to address preliminary and sometimes inconsistent findings. More comprehensive data on quantitative viral detection at different sites or sample types (e.g. nose, nasopharynx, throat, sputa, tracheal aspirates, bronchoalveolar lavage, blood and stool) would also provide valuable data regarding samples for initial diagnosis, as well as prognosis and clinical monitoring. Similarly, the measurement of biomarker levels should include concentrations in lower respiratory tract samples (sputum and bronchoalveolar lavage [BAL]), because cytokines and chemokines have been measured at 100-fold higher levels in BAL fluid than in plasma in individual patients (Wang et al., 2014c).

There is considerable heterogeneity among patient populations; hence, it is important to examine disease pathogenesis in patient groups at increased risk for complications and poor outcomes. Also, the mechanisms leading to critical illness and specific acute complications (e.g. encephalitis and other central nervous system abnormalities, myocarditis and shock) are not well understood.
**Research recommendation 4.1.2**

*Define the clinical spectrum and natural history of human disease, including risk factors (e.g. comorbidities and demographic factors) and prognostic markers for severe disease and its complications.*

**Major Progress 4.1.2**

Multiple studies have identified prognostic factors in influenza virus infections, including virus type and virulence, host factors (e.g. age, comorbidities and smoking), co-infections, pre-existing immunity and immune responses, and interventions (e.g. antiviral drugs and level of supportive care) that are linked to outcomes. These factors can also interact with each other to influence disease severity. During the 2009 pandemic in the United States of America (USA), 87% of deaths occurred in those aged under 65 years; children and working adults had estimated risks of hospitalization and death 4–7 times and 8–12 times greater, respectively, than during seasonal influenza, but risks were lower in older adults (Shrestha et al., 2011). This pattern presumably reflected both viral virulence and the impact of pre-existing immunity at the population level. In the United Kingdom, the FLUCIN study of 1520 patients hospitalized with A(H1N1)pdm09 virus infection during the first wave of the pandemic found that the risk of severe outcomes (admission to intensive care unit [ICU] or death) varied considerably with age, such that older adults who acquired infection had worse outcomes (Myles et al., 2012).

Demographic and risk factors have differed considerably among those hospitalized with avian influenza A(H5N1) and A(H7N9) or A(H1N1)pdm09 virus infection, such that those with A(H7N9) virus infection have been older (median, 63 years), more often male (71%) and have been more likely to have chronic heart disease (Wang et al., 2014a). Mortality was highest in influenza A(H5N1), intermediate in A(H7N9) and lowest in A(H1N1)pdm09 virus infections. Such observations are consistent with differences in viral virulence, possibly type and quantity of virus exposure, and underlying host factors.

Observations made during the 2009 pandemic identified obesity as a newly recognized risk factor for severe influenza disease. For example, in one study in the USA of individuals aged 20 years or over without other chronic medical conditions, the risk of death following A(H1N1)pdm09 illness increased with obesity (odds ratio [OR] = 3.1, 95% confidence interval [CI]: 1.5–6.6) and to a greater extent with morbid obesity (OR = 7.6, 95% CI: 2.1–27.9) (Morgan et al., 2010). The association with obesity has also been seen in seasonal influenza (Kwong, Campitelli & Rosella, 2011). The 2009 pandemic also highlighted the impact of influenza during pregnancy; for example, pregnant women accounted for 5% of all A(H1N1)pdm09 deaths in the USA during the pandemic (Rasmussen & Jamieson, 2012). In one Canadian study, pregnant women with A(H1N1)pdm09 infection were more likely to be admitted to ICU (2.59 versus 0.33 per 100,000 population) and more likely to die (0.80 versus 0.05 per 100,000) (Campbell et al., 2010). A recent systematic review found increased risk of low birth weight and fetal death associated with maternal influenza, with the increase in risk being related to the severity of influenza in the mother (Fell et al., 2017).

Other high-risk groups include immunocompromised hosts and those receiving chemotherapy for malignancies. Influenza-associated mortality is 15–28% in haematopoietic cell transplant (HCT) patients developing lower respiratory tract infection (LRTI) (Shah et al., 2012). Risk factors for progression to LRTI include older age, smoking, receipt of allogeneic HCT, mismatched or mismatched unrelated donor, graft versus host disease, neutropenia and lymphocytopenia, receipt
of systemic corticosteroids, pulmonary coinfections and detection of viral RNA in the serum (Chemaly et al., 2014). One study of influenza in HCT recipients found that profound lymphopenia and lack of early antiviral therapy were associated significantly with LRTI and death (Choi et al., 2011). During the 2009 pandemic, high rates of hospitalization (50%), pneumonia (23%) and death (9.5%) were also observed in those with solid tumours (Chemaly et al., 2012). Similarly, solid organ transplant recipients with A(H1N1)pdm09 virus infection had high rates of pneumonia (32%), ICU admission (16%) and death (4%) (Kumar et al., 2010).

Acute cardiovascular events are important causes of influenza-associated hospitalizations and mortality. Time-series studies controlling for seasonality, time trends and environmental conditions have estimated that influenza accounted for 3.1–3.4% of acute myocardial infarction (AMI) deaths, rising to 10.7–11.8% during peak periods of influenza virus circulation (Warren-Gash et al., 2011). One United Kingdom self-controlled case series study using linked data from 3927 patients with acute respiratory infection (ARI) and AMI found that incidence ratios were higher for ARIs that had at least one indicator of influenza compared with those that had zero indicators (Warren-Gash et al., 2012). A significantly increased risk of AMI extended at least 14 days after the ARI. The pathogenesis of cardiac disease with influenza includes indirect effects exacerbating underlying cardiovascular disease mediated by systemic inflammatory responses causing endothelial dysfunction, a procoagulant state, haemodynamic effects leading to vasoconstriction, and vascular plaque instability. Other cardiovascular complications include acute myocarditis, exacerbations of congestive heart failure, arrhythmias and cerebrovascular events. One literature survey identified 58 cases of myocarditis associated with A(H1N1)pdm2009 virus infection, 62% of whom had fulminant myocarditis (Ukimura et al., 2012). Mechanical circulatory support was associated with recovery in 13 of 17 patients with fulminant myocarditis. One study of fatal influenza B virus infections found pathologic evidence of myocardial injury in 69% of 29 cases for whom cardiac tissue samples were available, predominantly in children (Paddock et al., 2012).

Common findings in severe influenza cases include normal or low-normal white blood cell (WBC) counts, lymphocytopenia, thrombocytopenia, and increased blood levels of transaminases, lactate dehydrogenase, creatine kinase and creatinine. In the FLUCIN study, early C-reactive protein elevation of 100 mg/L or more was an independent predictor of severe outcome. In a recent study of 1770 hospitalized patients with community-acquired pneumonia (CAP), procalcitonin (PCT) concentration had a strong association with a need for invasive respiratory or vasopressor support (IRVS) (6.5% of those studied) (Self et al., 2016). Undetectable PCT (<0.05 ng/mL) was associated with a 4% risk of intensive support; for concentrations below 10 ng/mL, each 1 ng/mL increase in PCT was associated with a 1–2% absolute increase in the risk, whereas for PCT concentration of 10 ng/mL or more, the risk of IRVS was 22.4% (95% CI: 16.3–30.1%). Higher initial levels of certain biomarkers linked to inflammation, coagulation or immune function (IL-6, CD163, IL-10, lipopolysaccharide binding protein, IL-2, MCP-1 and IP-10) have been associated with disease progression in both outpatients and those hospitalized with influenza (Davey et al., 2013).

Unmet public health needs and research gaps 4.1.2
The mechanisms accounting for the increased risk of severe influenza in identified risk groups, including obesity and pregnancy, are incompletely understood and probably multifactorial. The type of comorbidity (e.g. pregnant women or immunocompromized hosts) and clinical syndrome (e.g. exacerbation of airways disease, viral pneumonia or ARDS) are important factors in influencing
influenza virus infection outcome, and may sometimes have unique management implications. For example, the FLUCIN study of hospitalized A(H1N1)pdm09 virus-infected patients found that those with asthma, particularly those receiving inhaled corticosteroids as outpatients or systemic corticosteroids as inpatients, had better outcomes (Myles et al., 2013).

The contribution of influenza virus infection to exacerbations of chronic cardiac conditions is probably underestimated, in part because patients often present without typical influenza-like illness (ILI). Further burden-of-disease studies that prospectively screen patients experiencing cardiovascular events or exacerbations of chronic cardiac conditions for influenza virus infection during the influenza season should be considered.

Another area of limited investigation has been environmental factors that increase the risk of severe influenza in key populations. Examples that warrant further study include the effects of second-hand tobacco smoke in households and other settings, and the risk profile of those who are exposed to high levels of indoor or outdoor pollution in work or home environments (Wang et al., 2016).

Clinical and laboratory features on admission to hospital have prognostic value in influenza, but there is still no highly predictive triage tool, especially one that is applicable in low-resource settings. Further validation of the utility of simple, rapid laboratory assays for predictive biomarkers is needed. In this regard, it is also unclear which comorbidities may confound the timely and accurate detection of influenza disease.

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**Research recommendation 4.1.3**

*Assess the incidence, anatomical sites, etiology and pathogenesis of secondary bacterial infections associated with influenza, as well as optimal treatment modalities and prophylactic and/or preventive measures.*

**Major Progress 4.1.3**

Secondary bacterial infections are a leading cause of illness and death with seasonal and pandemic influenza. However, the incidence of bacterial coinfections following influenza has not been well characterized, and depends on the extent of severe acute respiratory infection (SARI) surveillance, the quality of microbiologic studies and the empirical use of antibiotics. Studies that report rates of clinical outcomes without laboratory confirmation of influenza (e.g. respiratory illness requiring hospitalization during influenza season) can be difficult to interpret because of coincident circulation of other respiratory pathogens (e.g. respiratory syncytial virus [RSV]). One USA study of patients hospitalized with acute respiratory illness documented respiratory viral infection in 41%, of whom 39% had either positive bacterial tests (18%) or elevated PCT indicative of bacterial infection (21%) (Falsey et al., 2014).

The most commonly documented coinfecting bacterial species are *Streptococcus pneumoniae* and *Staphylococcus aureus*, which have accounted for 35% (95% CI: 14–56%) and 28% (95% CI: 16–40%) of infections, respectively; a wide range of other pathogens, including *Streptococcus pyogenes* and Gram-negative bacteria, have caused the remainder (Klein et al., 2016). In a murine model using influenza A virus and *S. pneumoniae* strains of differing virulence, coinfection with usually
sublethal bacterial doses led to mortality but to differing dissemination of strain-dependent risks of *S. pneumoniae* (Sharma-Chawla et al., 2016). The incidence of reduced susceptibility to commonly used antimicrobics (e.g. penicillins and macrolides) for *S. pneumoniae* has increased markedly, and detection of methicillin-resistant *S. aureus* (MRSA) strains in the community is common. Determining the optimal treatment strategies for such infections requires further study. Because exotoxin production by *S. aureus* contributes to disease, treatment with antibiotics that suppress toxin production – such as linezolid or clindamycin (added to vancomycin for MRSA) – appear to reduce mortality (Wunderink & Waterer, 2014).

Multiple pathogenic mechanisms, including innate and adaptive immune cascades, have been identified that increase the risk of bacterial infection following influenza (McCullers, 2014; Short et al., 2012). Influenza virus infection has been estimated to increase the susceptibility to pneumococcal pneumonia about 100-fold (Shrestha et al., 2013). Experimental studies suggest a lethal synergism between influenza and certain bacteria, particularly *S. pneumoniae*, since the bacterial titres rapidly rise to high levels and remain elevated after influenza virus infection. Such infection reduces the ability of alveolar macrophages to clear bacteria, and the subsequent *S. pneumoniae* infection increases viral release from infected cells (Smith et al., 2013). Also, influenza virus promotes pneumococcal growth during coinfection by providing host sialylated substrates (e.g. sialic acid and sialylated mucin) as a nutrient source (Siegel, Roche & Weiser, 2014). In epidemiological studies in South Africa, influenza virus infection was associated with elevated nasopharyngeal pneumococcal colonization (adjusted OR = 2.3; 95% CI: 1.3–4.0) and, in turn, with invasive pneumococcal pneumonia (adjusted OR = 8.2; 95% CI: 2.7–25.0) (Wolter et al., 2014).

**Unmet public health needs and research gaps 4.1.3**

Contemporary data on the frequency of influenza-associated CAP due to antibiotic-resistant bacteria are limited. Antibiotic-resistant bacterial supra-infections are recognized causes of hospital-acquired and ventilator-associated pneumonias during care of influenza patients, but the patterns of such infections are not well characterized, and they probably differ by institutions and regions. In the long term, there is a need for the development of more sensitive and specific low-cost methods for rapid diagnosis of bacterial infection and, if possible, assessment of antibiotic resistance. The optimal management of such infections has received limited study.

Remaining knowledge gaps include the connection between influenza virus and respiratory or intestinal microbiota, and how the microbiota regulates immune defense against influenza virus infection. In addition to increased use of pneumococcal and other bacterial vaccines, strategies are needed to reduce the risk of bacterial infection associated with influenza and other respiratory viral infections. In particular, interventions that might reduce the risk of severe bacterial coinfections in acutely infected influenza patients could have major benefits. So far, there is no evidence to support the use of prophylactic antibiotic treatment in patients without confirmed evidence of secondary bacterial infection. Furthermore, antibiotic use increases the risk of adverse drug effects, including severe *Clostridium difficile* infection. Timely antiviral therapy is associated with decreased risk of lethal outcomes in murine models of mixed influenza–bacterial infection, and is associated with reduced antibiotic use in outpatients with influenza (Dobson et al., 2015). However, it is unclear whether antiviral treatment in influenza patients reduces the risk of microbiologically documented bacterial infections.
Following respiratory influenza virus infection in animal models, maintaining the homeostasis of commensal microbiota in the respiratory mucosa appears critical to regulating the generation of virus-specific CD4 and CD8 T cells and antibody responses through the proper activation of inflammasomes (Ichinohe et al., 2011). Also, recent evidence suggests that the gastrointestinal (GI) microbiota plays an important role in immune adaptation and initiation in respiratory mucosal sites (Samuelson, Welsh & Shellito, 2015). In humans, there is limited evidence that A(H7N9) virus infection might decrease intestinal microbial diversity and species richness. Probiotics – in the form of *Bacillus subtilis* and *Enterococcus faecium* enteric-coated capsules administered three times per day (~108 CFU/tablet) – may have played a role in reducing or ameliorating secondary infection in one such patient (Hu et al., 2016). Consequently, there is a need for more detailed studies of the respiratory and GI tract microbiomes during and after influenza illness, including effects of antibiotic use and for randomized controlled trials (RCTs) of probiotic use in hospitalized patients with influenza-associated CAP. Pneumolysin expression by *S. pneumoniae* may be another target for protecting the host from influenza virus-induced disease (Wolf et al., 2014).

**Research recommendation 4.1.4**

*Study the role of pre-existing infections (e.g. tuberculosis and HIV) and other viral coinfections (e.g. dengue and other respiratory viruses) in the severity of influenza disease.*

**Major Progress 4.1.4**

Among HIV-infected patients on effective antiretroviral therapy, influenza virus infection, including A(H1N1)pdm09 illness, does not appear to differ in severity than among patients without HIV infection (Martínez et al., 2011; Perez, Ferres & Labarca, 2010; Riera et al., 2010; Sheth, Althoff & Brooks, 2011). Poorly controlled HIV infection and the presence of HIV-associated opportunistic infections have been associated with more severe illness and worse outcomes (Cohen et al., 2013; Ormsby et al., 2011). In South Africa, hospitalized patients with severe seasonal or pandemic influenza virus infection with HIV infection had a 2.9 times greater risk of death compared with HIV-negative patients (Cohen et al., 2013).

The importance of TB in influenza patients is somewhat less clear. In Thailand – a WHO-designated high tuberculosis (TB) burden country – prospective surveillance from 2003 to 2011 identified only two individuals with concurrent TB and influenza among 7180 hospitalized ARI patients tested for both pathogens (Roth et al., 2013). However, a South Korean report noted the first recognition of active pulmonary TB in seven patients (0.06% of laboratory-documented cases) during care for A(H1N1)pdm09 influenza (Noh et al., 2015). An ecological modelling study from South Africa suggested that primary TB deaths increased when influenza viruses were circulating (Walaza et al., 2015). Hence, it makes sense to integrate TB care into primary care (Bates, Marais & Zumla, 2015). Coinfections with respiratory viruses, usually based on detecting viral RNA or DNA with nucleic acid amplification assays, are common in very young children (Cebey-Lopez et al., 2016). It is unclear whether co-detections are associated with increased illness severity, although a recent meta-analysis of 43 studies did not find evidence for increased severity with respiratory virus coinfection in children (Scotta et al., 2016).
Unmet public health needs and research gaps 4.1.4

The mechanisms by which influenza virus infection appears to cause worse disease in HIV-infected and TB patients are still unclear. The role of treating influenza with antiviral drugs in reducing severe morbidity and mortality in these patient groups has not been rigorously studied. From a public health perspective, the possible effects of influenza illness on causing reactivation or exacerbation of TB, or possibly enhancing transmission to others, remain uncertain. Addressing these questions would require large epidemiological studies in countries at particular risk.

Influenza can be hard to differentiate from other causes of febrile illness such as dengue, malaria or other respiratory viruses, especially when influenza viruses are co-circulating with other pathogens. Rare case reports suggest that coinfection with dengue and influenza viruses can cause severe illness (Chacon et al., 2015; Lopez Rodriguez et al., 2010; Perdigão et al., 2016; Perez et al., 2010). One study in Kenya determined that coinfections of malaria and influenza were rare but may be associated with longer hospitalization (Thompson et al., 2012). Prospectively collected data regarding possible disease interactions between influenza and these common pathogens are needed, especially in paediatric populations in low-resource and middle-income settings.

Research recommendation 4.1.5

Study the role of host genetic factors on susceptibility and severity of influenza virus infection.

Major Progress 4.1.5

During and following the 2009 pandemic, genetic studies of patients infected with influenza virus identified newly recognized associations of severe illness with specific gene variants (Ciancanelli et al., 2016; To et al., 2015). Interferon-inducible transmembrane 3 (IFITM3) restricts influenza virus replication by blocking its pathway in the cytosol (Brass et al., 2009). Homozygosity for a single nucleotide polymorphism, and a putative splice site in IFITM3 (rs12252-C) was reported to be associated with severe A(H1N1)pdm09 in three out of 53 hospitalized white patients (Everitt et al., 2012). The polymorphism is rare in white people but is common in Han Chinese, where it has been associated with severe A(H1N1)pdm09 and avian A(H7N9) virus infections (Lee et al., 2017; Wang et al., 2014c; Zhang et al., 2013). A larger study in more than 5000 Caucasian patients with CAP showed an association with mild influenza (Mills et al., 2014). In a family-based study of 358 children (mostly Caucasian) with influenza admitted to paediatric intensive care units, rs12252-C was not a susceptibility allele and the splice isoform was not identified in RNA sequence data from children carrying the allele (Randolph et al., 2017).

Other genes reported in single studies to be associated with severe A(H1N1)pdm09 disease include heterozygosity for the chemokine receptor 5 (CCR5) Δ32 allele; polymorphisms in CD55, which encodes an important complement regulatory protein; the C/C genotype in the surfactant protein B gene; and certain human leukocyte antigen (HLA) alleles affecting T-cell functions (Ciancanelli et al., 2016; To et al., 2015). A higher expression variant of TMPRSS2 and a variant in TLR3 have also been associated with severe A(H1N1)pdm09 and avian A(H7N9) virus infections (Cheng et al., 2015; Lee et al., 2017). Although variants may confer population-based risk, and may even add cumulative risk (Lee et al., 2017), rare functional variants in multiple genes essential for mounting an effective antiviral response probably explain a proportion of severe cases of influenza (Casanova, 2015). For example, autosomal recessive interferon regulatory factor 7 (IRF7) deficiency from two mutant alleles leading to reduced type I and III interferon responses was reported in an otherwise healthy child with life-threatening A(H1N1)pdm09 disease (Ciancanelli et al., 2015).
Most studies have focused on influenza-related pneumonia; however, genetic factors have been associated with influenza-related encephalopathy in Asian children (Mak et al., 2011). Many Japanese children (8–10%) have a genetic factor, such as thermolabile phenotype of variants of carnitine palmitoyltransferase II (CPT2), that impairs mitochondrial metabolism in influenza-associated encephalopathy (Yao et al., 2008). In Japan, discontinuation of mass vaccination of schoolchildren was associated with an increase in influenza-associated deaths, mostly due to encephalopathy among young children, in the 1990s. The increase in influenza vaccinations among young children, together with the routine therapeutic use of neuraminidase inhibitors (NAIs), has led to a decrease in the influenza-associated mortality rate (Sugaya & Takeuchi, 2005). This experience with identifying genetic susceptibility for severe influenza illustrates the potential for successful intervention.

Hereditary predisposition to severe illness with avian A(H5N1) virus infection is suggested by some epidemiological observations, but specific mutations have not been reported to date.

**Unmet public health needs and research gaps 4.1.5**

There is a need for further validation of the contributions of the genetic variants reported to be associated with severe influenza. The range, frequency and importance of particular genetic risk factors is incompletely understood across populations. A deeper mechanistic understanding of the influence of genetic factors on influenza disease severity following infection could also lead to improved care of at-risk persons, and potentially to new treatments. Most pandemic and seasonal influenza virus infections are self-limited and not severe enough to require hospitalization; better understanding of possible protective host genetic factors might also lead to improved prevention strategies.

**Substream 4.2 Improve clinical management of patients**

**Research recommendation 4.2.1**

*Develop rapid, sensitive, affordable point-of-care diagnostic tests for detecting influenza virus.*

**Major Progress 4.2.1**

There have been improvements in the performance and reading of results for rapid antigen-based point-of-care (POC) influenza diagnostics. Traditional simple antigen-based POC tests have been read by eye, which can lead to variability in outcomes among users. Machine-based reading incorporated into several newer commercial POC tests, including the Becton Dickinson (BD) Veritor system and the Quidel Sofia, has improved the sensitivity of these assays compared with older visually read tests. The Veritor and Sofia tests had 93.8% and 95.8% positive agreement, respectively, compared with reverse transcriptase polymerase chain reaction (RT-PCR) for influenza A viruses in nasal wash specimens collected from children; this result was considerably better than the Binax POC test read by eye, which had a 79.2% positive agreement with RT-PCR (Dunn et al., 2014). However, the negative agreement of the Sofia test compared with RT-PCR was significantly lower than that of either Veritor or Binax (Dunn et al., 2014). Compared with real-time RT-PCR (rtRT-PCR) detection, the Sofia test showed 100% sensitivity but only 61.2% specificity among young Thai paediatric patients (Olsen et al., 2014).
Rapid antigen-based POC tests have typically only detected the influenza virus type level (A or B). A new assay, the GENEDIA Multi Influenza Ag Rapid Test (GENEDIA), is capable of also subtyping influenza A to H1, H3 or H5 subtypes (Jang et al., 2015). Compared with rtRT-PCR, the sensitivities of GENEDIA, SD Bioline Influenza Ag and Alere BinaxNow Influenza A&B Card were 73.0%, 57.0% and 58.0% for influenza A, respectively, and 68.5%, 65.8% and 57.5% for influenza B, respectively. Hence, the sensitivity of the GENEDIA assay is similar to other rapid antigen POC tests, which in general is at best moderate in adults. Multi-pathogen antigen-based POC systems have also been developed for detecting common respiratory viruses. The mariPOC® test (ArcDia) enables simultaneous detection of influenza A and B virus and several other respiratory virus antigens. The test method relies on fluorescent antibodies for viral antigens and detection of two-photon excited fluorescence from microsphere particles. The test provides a preliminary result in 20 minutes and a final result in 2 hours. However, this test proved to be insensitive for detecting influenza A virus compared with the nucleic acid amplification-based test (NAAT) based Alere I Influenza A&B assay, and was therefore unsuitable for individual patient diagnosis without confirmatory testing (Jokela et al., 2015).

In Japan, as many as 20 rapid antigen diagnostic tests are marketed, and they are considered core tools for determining whether to start NAI treatment. Almost all patients with ILI are tested with current influenza rapid diagnostic tests and, if positive, all of them are offered treatment with NAIs. The reliability of rapid test results seems to be higher in Japan than in other countries, possibly because most patients are tested within 48 hours of the onset of illness, when influenza viral load in the upper respiratory tract is high. The analytical detection sensitivity of the tests is 103 to 104 median tissue culture infective dose (TCID50)/100 µL (Sakai-Tagawa et al., 2014), such that much reduced sensitivity would be expected later in the course of illness. Whether this strategy is feasible and cost effective in other settings, especially when resources are limited, remains to be determined.

Progress has been made in developing rapid molecular POC diagnostics using cartridge-based NAATs. The Alere i Influenza A&B assay (Alere, USA) is a rapid isothermal NAAT based on the isothermal nicking endonuclease amplification reaction; the assay can provide detection and differentiation of influenza A and B viruses in 15 minutes. Compared to RT-PCR, the Alere i NAAT detected 77.8% of influenza A positive samples from adults with ILI versus 71.4% and 44.4% for the Quidel Sofia® Influenza A+B FIA and BinaxNOW® Influenza A&B assay, respectively (Hazelton et al., 2015). For influenza B, the Alere i NAAT detected 75% of those positive by RT-PCR, versus 33.3% and 25.0% for Sofia® and BinaxNOW®, respectively. Another study of inpatient adults and children reported that, compared with RT-PCR, the overall sensitivities for detection of influenza A and B viruses were 65.96% and 53.33%, respectively, with the Alere i NAAT, although this test has improved sensitivity compared with the antigen-based POC BinaxNOW® (Chiarella et al., 2016). Low sensitivity in detecting influenza B virus in nasopharyngeal specimens has been seen in other studies (Jokela et al., 2015). In comparison with the NAAT-based Xpert Flu/RSV assay, the overall sensitivity and specificity of the Alere i Influenza A&B assay was 95% and 100%, respectively, in a largely adult population presenting with ILI (Nguyen Van et al., 2016). The Cepheid Xpert® Flu (Cepheid, Sunnyvale, California, USA) requires minimal hands-on time, because it incorporates RNA extraction along with amplification and detection in a single process. It uses RT-PCR in an automated process run on the GeneXpert Dx system (Cepheid). The assay detects influenza A and B viruses in 1 hour, with differentiation of subtypes A(H1N1)pdm09 and A(H3N2). Sensitivity is higher than the antigen-based POC tests, but only marginally higher than that of the Alere i Influenza A&B assay. However, the costs of the platforms and reagents for these assays are high.
Unmet public health needs and research gaps 4.2.1

There is a continuing need for low-cost, sensitive POC assays for important respiratory viral pathogens including influenza viruses. Recent advances have seen an improvement in the performance of some antigen-based POC tests, such that they are approaching the clinical sensitivity of RT-PCR. The NAAT-based POCs are more sophisticated tests that have better performance but also greater cost than the earlier antigen-based POC tests. Thus, the performance of POC influenza tests has improved, but they remain expensive, and therefore still leave a need for a high-performing but more cost-effective POC test. Furthermore, these POC tests deliver only a diagnostic result on the type or subtype of influenza. Tests that can reliably detect and distinguish novel influenza A viruses from seasonal influenza A viruses are needed in at-risk countries, as are cost-effective multiplex assays that can detect other important respiratory pathogens.

The other diagnostic test of clinical utility would be a POC test for antiviral (specifically oseltamivir) susceptibility. Currently, there are no nucleic acid-based POC tests that detect common resistance mutations associated with loss of oseltamivir susceptibility (e.g. H275Y in N1 viruses). However, there is a novel POC phenotypic assay for oseltamivir susceptibility that can be performed directly on clinical samples. The Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, and the Melbourne WHO Collaborating Centre (CC) have been testing this machine-based assay being developed by BD. It incorporates two chemiluminescent signals and is unique in that the substrate is sensitive enough to enable a phenotypic assay to be conducted on influenza viruses in a clinical specimen, rather than there being a need to culture the virus before phenotypic susceptibility analysis. The assay is also rapid (completed in 30 minutes) and straightforward to perform, compared with the current enzyme-inhibition assays. Initial results indicate that the assay is effective at detecting viruses with reduced oseltamivir susceptibility, including mixtures of variant and wildtype viruses. A similar assay to that being developed by BD is the QFlu Combo Test, which is already available from Cellex, USA.1 Although these assays provide both detection of influenza virus and a read-out of oseltamivir susceptibility, they are not as easy to conduct as the other POC tests and therefore are unlikely to achieve Clinical Laboratory Improvement Amendments (CLIA)-waived status.

Research recommendation 4.2.2

Identify clinical markers and development of POC tools for the prognosis and management of influenza disease

Major Progress 4.2.2

One meta-analysis of 159 studies involving 26 commercial first-generation rapid antigen diagnostic tests reported an overall sensitivity of 62.3% compared with RT-PCR (Chartrand et al., 2012). Progress has been made in developing second-generation rapid antigen tests and rapid POC molecular tests, and multiple tests of this type are now commercially available (see above). While the newer machine-read antigen assays (also termed digital immunoassays) have improved sensitivity, they remain less sensitive than NAAT-based assays (Mese et al., 2016; Noh et al., 2015). Also, they have not been well validated with respect to performance in important target populations such as high-risk or hospitalized adults. POC molecular diagnostic technologies have greater sensitivity and can provide results in less than an hour with minimal operator training, although these technologies require costly equipment platforms.

1 http://cellex.us/qflu-combo-test/
Few studies have researched the use of dried blood spots or other simple technologies for collecting and storing samples for sero-epidemiological studies. Only one report on using dried blood spots for measuring oseltamivir carboxylate levels has been published (Hooff et al., 2011). However, the reliability and reproducibility of self-collected nasal swabs for virus detection has been demonstrated (Beigel et al., 2016; Ip et al., 2012), and has the potential to be used for both epidemiology and intervention studies. Furthermore, there is inconsistent performance and limited availability of assays to detect bacterial coinfections.

Unmet public health needs and research gaps 4.2.2
Rapid antigen and molecular diagnostic tests have generally been used for the initial virologic diagnosis, and studies are needed to assess their utility in monitoring the clinical course and responses to antiviral therapy in hospitalized influenza patients, especially in those who are severely ill. In general, newer rapid diagnostic technologies are expensive and have received limited assessment in low-resource settings. Increasing global availability would improve individual patient management and public health surveillance. Using rapid tests allows clinicians to diagnose influenza and prescribe an NAI with confidence, and might help to limit the use of antibiotics. Without rapid diagnostic testing, clinicians prescribe antibiotics more often than NAIs for influenza patients (Havers et al., 2014). Further study of the impact of the use of rapid tests on antibiotic use is needed.

There is uncertainty about the predictive value of detecting reduced NAI susceptibility in enzyme-inhibition assays or specific NA amino acid substitutions in genotypic assays, and lack of antiviral effectiveness in NAI-treated patients. This uncertainty is also likely to apply to newer antivirals such as polymerase inhibitors that are in advanced clinical development. Validation of assays that can rapidly detect clinically relevant antiviral resistance (or reduced susceptibility) are needed to help guide care of influenza patients, particularly for immunocompromised hosts and critically ill patients who are at higher risk of emergence of resistant variants.

Pneumonia and exacerbations of chronic bronchitis are leading causes of influenza hospitalizations. There is a lack of well-validated assays to determine when bacterial coinfection is present and hence to guide appropriate antibiotic therapy. Several less costly biomarkers such as PCT (Pfister et al., 2014; Rodriguez et al., 2016; Self et al., 2016) require further study, especially in resource-limited settings. The most promising approach of transcriptional profiling (Suarez et al., 2015) has not yet been fully validated, and is technically demanding and likely to prove costly.

Research recommendation 4.2.3
Optimize the effectiveness of current and novel antiviral treatments through development of new formulations, delivery routes or systems, and synergistic antiviral drug combinations.

Major Progress 4.2.3
Increasing evidence, primarily derived from observational studies in A(H1N1)pdm09 illness, indicates that timely initiation of NAI treatment can reduce influenza-related complications and mortality, even when administered beyond 2 days of illness (the time frame of illness specified in most licensed indications) (Louie et al., 2012; Venkatesan, 2016). However, underprescribing of antiviral drugs for influenza is common, even in high-risk or hospitalized patients in well-resourced countries, although use of such drugs has increased recently in the USA (Appiah et al., 2017; Havers et al., 2014; Stockmann et al., 2017). There is little information about the reasons for these prescribing patterns. Furthermore, antiviral drugs are not available in all countries, with only 65% of
countries in Africa having antiviral drugs available (Duque, McMorrow & Cohen, 2014). The reasons for lack of antiviral drug availability are unclear, especially since oseltamivir is now available in generic formulation.

Studies to optimize dose regimens of currently available NAIs have found no clear advantage to using higher NAI dose regimens. One RCT found no virological or clinical advantages with double-dose oseltamivir compared with standard dose in paediatric and adult patients hospitalized with serious influenza (South East Asia Infectious Disease Clinical Research, 2013). Other RCTs have not found greater antiviral or clinical effects with intravenous peramivir (currently approved in China, Japan, South Korea and the USA) or intravenous zanamivir compared to oral oseltamivir in hospitalized influenza patients (de Jong et al., 2014; Marty et al., 2017). The combination of two NAIs (oseltamivir and zanamivir) appeared inferior to oseltamivir monotherapy in an RCT in uncomplicated influenza, perhaps because of antiviral antagonism (Duval et al., 2010). Studies of convalescent plasma (Hung et al., 2011; Mair-Jenkins et al., 2015) and of hyperimmune globulin (Hung et al., 2013) combined with NAIs indicate improved mortality in critically ill influenza patients.

Recent clinical efficacy and safety data have been presented for several influenza polymerase inhibitors that are inhibitory for viruses resistant to currently approved classes of influenza antiviral drugs. In addition to Phase 3 studies of favipiravir (polymerase basic [PB] 1 inhibitor) in uncomplicated influenza (results pending), proof-of-concept clinical studies have given promising results with three novel polymerase inhibitors: JNJ-63623872 (VX-787) and ALS-794 in experimentally induced human influenza, and S-033188 in uncomplicated influenza. The PB2 inhibitor JNJ-872 inhibits a range of influenza A viruses in cell culture and has delayed therapeutic activity in lethal murine model of A/PR/8/34 (96 hours versus 24 hours for oseltamivir) (Byrn et al., 2015). In vitro passage has led to the selection of PB2 variants with more than 10-fold reductions in susceptibility; also, variants (specifically M431I) with more than 50-fold reduced susceptibility have been detected during experimental human infection. JNJ-872 shows synergy with oseltamivir, zanamivir and favipiravir in preclinical models; combination studies in outpatients and hospitalized patients are in progress. S-033188 is the oral prodrug of S-033447, a potent inhibitor of the CAP-dependent endonuclease (polymerase acidic [PA] inhibitor) of influenza A and B viruses (Uehara, 2016). In a sublethal mouse infection model, once-a-day dosing with S-033188 potently inhibited virus replication and resulted in more than 2 log10 TCID50/mL viral titre reduction compared with oseltamivir phosphate at clinically equivalent doses. S-033447 exhibits linear pharmacokinetics with prolonged plasma T1/2elim in humans, such that single doses may be adequate for treatment. In a Phase 2 study of uncomplicated influenza in Japan, single oral doses of S-033188 demonstrated favourable safety and dose-related virologic and clinical efficacy results. ALS-794 is the prodrug of ALS-033719, another PA inhibitor of influenza A and B viruses. In experimentally infected humans, oral AL-794 was associated with dose-related antiviral effects compared with placebo (Yogaratnam, 2016). Further clinical studies of these agents are in progress, and combination studies of NAIs in more serious influenza are of obvious interest. Arbidol (also termed umifenovir), an influenza haemagglutinin (HA) 2 inhibitor approved for use in China and the Russian Federation, has been reported to show promising clinical results in observational studies of hospitalized patients, and further trials in uncomplicated influenza are in progress (Leneva et al., 2016).
Unmet public health needs and research gaps 4.2.3
A continuing public health issue is underuse of current antiviral drugs and lack of timely administration in influenza patients who might benefit. Surveys of clinical practice guidelines and country-level availability for seasonal influenza treatment may provide insights about why this is the case. Also, development of more rigorous data on NAI effectiveness in preventing hospitalizations and mortality is needed to convince sceptics, and some experts think that it would be worth conducting placebo-controlled trials of oseltamivir and other NAIs in high-risk patient groups and hospitalized persons. Determining whether empirical antiviral therapy of CAP or SARI during periods of influenza virus circulation improves outcomes, particularly in low-resource settings, would be a valuable step. There is also a need to assess antiviral drug stockpiling quantities and strategies for rapid distribution for a major influenza outbreak and pandemic response.

Available clinical data indicate that alternative strategies to NAI monotherapy are needed to increase antiviral potency and improve clinical outcomes. In addition, combination therapies have the potential to reduce resistance emergence to oseltamivir and other NAIs. Several investigational antiviral drugs (PB1, PB2 and PA inhibitors; nitazoxanide; convalescent plasma; hyperimmune globulin; and anti-HA stem monoclonals) show enhanced antiviral activity in combination with NAIs (mainly oseltamivir) in preclinical models, and various combinations are being tested in RCTs (Koszalka, Tilmanis & Hurt, 2017; McKimm-Breschkin & Fry, 2016). A large clinical study comparing oseltamivir with a triple drug regimen (oseltamivir/ribavirin/amantadine) in high-risk outpatients has recently been completed, but preliminary results did not indicate greater clinical benefits (Beigel, 2016). In developing novel antiviral treatments, priority should be given to low-cost and easily delivered options that have novel mechanisms of action. More emphasis on the development of broad-spectrum antiviral products that might have activity against multiple viral agents causing ILI or SARI is also warranted.

Research recommendation 4.2.4
Develop novel and effective treatment strategies including adjunctive treatments (e.g. immunomodulators, immunoglobulin and natural products).

Major Progress 4.2.4
Preclinical and, in some instances, epidemiological or limited clinical studies of various immunomodulating agents (e.g. sirolimus, N-acetylcysteine, nitazoxanide, statins, fibrates, glitazones, cyclooxygenase 2 inhibitors, macrolides, mycophenolic acid, human mesenchymal stem cells, pamidronate and anti-C5a antibody) have suggested that such agents might offer benefit in treating influenza, but careful prospective clinical studies are needed (Chan et al., 2016; Hui, Lee & Chan, 2013; Kakeya et al., 2014; Lai et al., 2010; Martin-Loeches et al., 2013; Sun et al., 2015; Zheng et al., 2015). For example, one RCT in critically ill, influenza A(H1N1)pdm09 virus-infected patients requiring invasive mechanical ventilation (IMV) found that the addition of the mammalian target of rapamycin (mTOR) inhibitor sirolimus to a regimen of oseltamivir and prednisolone was associated with a higher frequency of liberation from IMV, a shorter duration of IMV, and more rapid clearance of virus without serious adverse effects compared with a group not given sirolimus (Wang et al., 2014b). An RCT in patients with sepsis-associated ARDS found that rosuvastatin did not improve clinical outcomes, and may have contributed to hepatic and renal organ dysfunction compared with placebo (Truwit et al., 2014). Statin treatment soon after influenza illness onset has not been rigorously studied, but an RCT of atorvastatin therapy in influenza patients is reportedly in progress (NCT02056340).
Systemic corticosteroids continue to be commonly used in critically ill influenza patients. A meta-analysis of multiple observational studies found that systemic corticosteroid use was associated with increased mortality (OR = 3.06, 95% CI: 1.58–5.92) in patients with severe influenza (Rodrigo et al., 2016). Two observational studies that used propensity scoring reported that corticosteroid treatment was associated with longer duration of mechanical ventilation and increased mortality (Brun-Buisson et al., 2011; Kim et al., 2011). However, a Canadian study of critically ill patients that used propensity scoring and adjustment for time-dependent between-group differences did not find an association between corticosteroid treatment and increased mortality (Delaney et al., 2016). Other serious adverse events – including opportunistic infections, prolonged virus replication and antiviral resistance emergence – have also been observed (Cao et al., 2016a; Cao et al., 2016b; Lee et al., 2015). However, a recent unpublished observational study found that in pneumonic influenza patients with PaO2/FiO2 of below 300 mmHg, low-to-moderate dose corticosteroid treatment was associated with significantly reduced mortality, but high-dose corticosteroid therapy yielded no benefits (Li, 2016). For patients with PaO2/FiO2 of 300 mmHg or more, corticosteroids (irrespective of dose) were associated with increased mortality and risk of invasive fungal infections.

**Unmet public health needs and research gaps 4.2.4**

Few prospective RCTs with immunomodulatory effects have been undertaken in serious influenza, and no adjunctive medical therapy has been proven to improve outcomes in severe influenza. Some commonly used interventions (e.g. high-dose systemic corticosteroids in influenza viral pneumonia and ARDS) appear to have adverse effects. Whether lower dose corticosteroids are beneficial in certain patient subgroups requires further study. Promising results have been reported with several interventions (e.g. macrolides, nonsteroidal anti-inflammatory drugs and mTOR inhibitors) in initial trials. One recent placebo-controlled study tested the effects of adding a 2-day regimen of oral naproxen and clarithromycin (both of which have wide availability, and potential immunomodulatory and influenza inhibitory effects in preclinical assays) to a standard 5-day regimen of oseltamivir in elderly adults hospitalized with influenza illness of short duration (Hung et al., 2016). The combination treatment was associated with lower 30-day mortality (1/107 versus 9/110), less frequent admission to ICU or high-dependency unit (HDU), shorter hospital stay and more rapid clearance of virus. Confirmation of these results and studies in patients treated at later stages of illness are needed. Clinical trials of CAP, including influenza-associated CAP, are ongoing with corticosteroids or anti-inflammatory agents; the results of these studies could benefit clinical care practices. The immunomodulatory agents selected for study in the future should be explored after independent preclinical studies have shown benefit, and the priority for human trials should be those agents that are known to be reasonably safe and well-tolerated (i.e. have a favourable risk–benefit in the target population), easily administered and low in cost.

Traditional Chinese medicines are commonly used for treatment of influenza and other acute respiratory viral infections. One type, called maxingshigan–yinqiaosan, was found to be comparable in clinical outcomes to oral oseltamivir in uncomplicated influenza (Zhao et al., 2014); another, named lianhuaqingwen, was reported to be superior (Zhao et al., 2014). However, their possible effectiveness in severe influenza is unclear, and the antiviral or immunomodulatory effects of individual components require study.

Probiotics have been reported to improve outcomes in critical illness (Manzanares et al., 2016) and have been administered in small numbers of A(H7N9)-infected patients. However, larger trials in patients with severe influenza are needed to assess whether they are beneficial (Hu et al., 2016).
Research recommendation 4.2.5

Optimizing management of persons at higher risk of, or presenting with, severe disease and/or disease complications, including intensive care practices that are applicable across a range of resource settings.

Major Progress 4.2.5

Large numbers of studies exist or are ongoing in critically ill patients, specifically related to supportive care interventions. Progress has been made in understanding the application and clinical usefulness of a range of supportive interventions in patients with critical SARI or ARDS, albeit largely in well-resourced settings and in adults. One single-centre RCT of adults admitted to the medical–surgical ICU found that a conservative oxygen therapy group (maintaining PaO2 70–100 mmHg or arterial oxyhaemoglobin saturation [SpO2] 94–98%) had lower mortality than a group receiving standard ICU practice (allowing PaO2 values up to 150 mmHg or SpO2 97–100%) (Girardis et al., 2016). Another study found that in patients with non-hypercapnic acute hypoxemic respiratory failure, treatment with high-flow oxygen through nasal cannula, standard oxygen or noninvasive ventilation did not result in significantly different intubation rates, but there was a significant 90-day mortality difference in favour of high-flow oxygen (Frat et al., 2015). In ARDS patients, other strategies that appear to reduce mortality include higher positive end-expiratory pressure (PEEP) levels (Briel et al., 2010), early administration of a neuromuscular blocking agent (Papazian et al., 2010) and prone positioning in severe ARDS (Guérin et al., 2013), whereas high-frequency oscillatory ventilation appears to be inferior to conventional ventilatory management (Ferguson et al., 2013; Young et al., 2013). An observational study on patients with influenza A(H1N1)pdm09 virus-associated pneumonia reported that noninvasive ventilation (NIV) was commonly used (40%), but was associated with avoidance of intubation in only 40% of NIV patients (Masclans et al., 2013). Studies in ARDS showed that NIV was associated with higher ICU mortality in patients with a PaO2/FiO2 lower than 150 mmHg. One RCT in non-selected patients with ARDS (Peek et al., 2009), and several observational studies (Beurtheret et al., 2012; Davies et al., 2009; Noah et al., 2011) in patients with influenza A(H1N1)pdm09-associated respiratory failure, have reported positive outcomes with extracorporeal membrane oxygenation (ECMO), but the value of and indications for this costly and invasive intervention are unclear.

Unmet public health needs and research gaps 4.2.5

Many aspects of the supportive care in the ICU are based on evidence from non-selected critically ill populations, and data regarding specific management of influenza patients are mainly observational. There may be clinically relevant differences between critical influenza illness and other causes of critical SARI that have therapeutic implications. For example, sedative and analgesic use was uniquely higher in critically ill patients with A(H1N1)pdm09 virus infection compared with patients with pneumonia of other infectious etiologies, especially if the patient was on ECMO (Nigoghossian et al., 2016; Olafson et al., 2012). This may be related to a combination of irritable airways and encephalopathy or encephalitis (or both). Myocardial dysfunction, including myocarditis, appears to be more common with severe influenza than in non-selected ARDS patients (Brown et al., 2011; Chacko et al., 2012). Consequently, there is a need for influenza-specific data from RCTs on most aspects of supportive care or management. Such data could be accrued in part by incorporating respiratory virus diagnostics into ongoing and future studies of ARDS interventions.
Development of appropriate strategies to improve supportive critical care in low-resource settings remains the long-term goal. Data on supportive management of serious influenza in resource-restricted settings are severely lacking. For example, in resource-restricted settings where timely access to mechanical ventilation is not available, aggressive fluid management of hypotension may be harmful, and clinical assessment of fluid responsiveness is important, along with quantification of ventricular size and function using echocardiography or dynamic minimally invasive cardiovascular monitoring, if available. At present, starting points could include conducting a systematic review to assess current best practices of supportive care applicable to management of critical influenza illness, and undertaking surveys of compliance with currently recognized best ICU practices, particularly in less well-resourced settings.

Substream 4.3
Health-care capacity and response

Research recommendation 4.3.1
Evaluate the effectiveness of global, national and local responses to pandemic, epidemic and zoonotic influenza, and development of new assessment tools.

Major Progress 4.3.1
WHO first published pandemic influenza preparedness guidance in 1999, with revised guidance issued in 2005 and in April 2009, just before the 2009 A(H1N1) pandemic. A checklist tool for pandemic planning was published by WHO in 2005 (World Health Organization, 2005). In 2013, WHO issued revised interim guidance, entitled “Pandemic influenza management”, partly based on lessons learned from the 2009 A(H1N1) pandemic (World Health Organization, 2013). This current version of the guidance applies the all-hazards emergency risk management for health that is used for disaster risk management in many countries for pandemic influenza risk management. The revised guidance introduces a risk-based approach and revised global phases of an influenza pandemic, and recommends that countries use national risk assessments to inform management decisions. In 2014, the CDC issued a revised framework for pandemic influenza preparedness planning in the USA (Holloway et al., 2014). The global response to the 2009 pandemic was suboptimal, and many lessons were learned that will improve future responses (Fineberg, 2014; Leung & Nicoll, 2010).

Few studies have reviewed the effectiveness of national pandemic plans in the response to the 2009 pandemic. One qualitative study reported that effective pandemic preparedness activities in Europe included political buy-in, cross-disciplinary approaches, expert technical input, use of exercises and simulations, staff training, public awareness and strong leadership; these factors contributed to a generally successful response to the 2009 pandemic, although a lack of flexibility of pandemic plans limited the response (Hashim et al., 2012). Six themes were identified as being essential elements of successful pandemic preparedness: communication, coordination, capacity building, adaptability and flexibility, leadership and mutual support. However, one study in 19 European countries reported no correlation between the overall completeness of national pandemic plans and ILI outcomes (Meeyai, Cooper & Coker, 2013). Another study of pandemic preparedness in 43 European countries identified many weaknesses in preparedness and planning
and the response to the 2009 pandemic, including inaccuracy of pandemic severity estimates, lack of flexibility of the response, lack of surge response by health-care facilities, inequitable distribution and use of pandemic vaccine, lack of use of antiviral drugs, poor sharing of clinical information with physicians, and late detection of adverse effects of the pandemic vaccine (Nicoll et al., 2012).

Before 2009, a metric was developed to evaluate 12 national core capacities for pandemic influenza preparedness and response: country planning, research and use of findings, communications, epidemiological capability, laboratory capability, routine influenza surveillance, national respiratory disease surveillance and reporting, outbreak response, resources for containment, community-based interventions to prevent the spread of influenza, infection control, and health sector response (MacDonald, Moen & St Louis, 2014). Using this tool before and after the 2009 pandemic, two international studies reported significant improvement in pandemic preparedness in nearly all countries assessed (Johnson et al., 2014; Moen et al., 2014). A further tool to assist in pandemic preparedness is the influenza risk assessment tool (IRAT) – an instrument to evaluate pandemic influenza threats worldwide – that has been used to prioritize novel influenza A viruses for candidate vaccine development (Cox, Trock & Burke, 2014; Trock, Burke & Cox, 2015). In 2014, a new framework was made available at the CDC, based on using transmissibility and disease severity to improve early and ongoing assessment of the severity of influenza pandemics (Reed et al., 2013). Both the IRAT and the novel framework for assessing pandemic influenza severity have been incorporated in the revised CDC preparedness and response framework to improve pandemic influenza response in the USA (Holloway et al., 2014).

Unmet public health needs and research gaps 4.3.1

Given that WHO issued revised pandemic influenza preparedness guidance in 2013, it would be useful to evaluate current national pandemic plans. Additionally, although the focus before 2009 was on the possibility of an influenza A(H5N1) virus pandemic, no metric or published reports were identified to assess national plans and policies and the response to zoonotic influenza. Highly pathogenic avian influenza A(H5N1) virus continues to have pandemic potential, with sporadic human infections in multiple countries; also, several other novel influenza A viruses have emerged to cause pandemic threats since 2009, especially A(H7N9) virus. However, the control of novel influenza A viruses is heavily dependent upon the agricultural sector, and upon prevention and control of avian influenza among poultry, and of swine influenza among pigs worldwide (e.g. surveillance, vaccination, stamping out or depopulating and disposal, closure of animal markets and disinfection of contaminated environments). It is difficult to assess the effectiveness of national or local plans to respond to sporadic human infections with novel influenza A viruses.

Assessing the effectiveness of the local and national response to seasonal influenza is daunting because the impact of seasonal influenza epidemics varies widely from year to year, country policies and actual use of medical countermeasures (i.e. vaccines and antiviral drugs) against influenza vary widely worldwide, and many countries lack national plans against seasonal influenza. Although the USA uses more seasonal influenza vaccines than all other countries combined, vaccine effectiveness is highly variable and is moderate at best. Few countries other than Japan use a high level of antiviral drugs for early treatment of seasonal influenza. However, strategies in national pandemic plans can be studied during moderate to severe seasonal influenza epidemics. Improving the ongoing health-care system response to seasonal influenza epidemics, and improving clinical management and infection prevention and control of seasonal influenza, will improve these responses to pandemic influenza. Consequently, it is currently not possible to evaluate the impact of national plans or
recommendations for seasonal influenza response. Similarly, the response to novel influenza A viruses is highly variable and depends more on agricultural practices than the public health response, meaning that it is difficult to evaluate the effectiveness of policies and responses to novel influenza A viruses.

Research recommendation 4.3.2
Conduct operational studies on surge capacity needs, including development of triage schemes in different health-care and resource settings, and surge planning to maintain adequate staffing.

Major Progress 4.3.2
There has been some work on facility-specific surge capacity and handling of overwhelming patient flows. In general, however, there is little evidence-based guidance on this topic. The issues raised in the 2009 recommendations remain a priority, particularly when compared to the local impact these questions have on day-to-day operations in health-care facilities. Consequently, many facilities have used the generic guidance as the basis for developing facility-specific guidance. If rapid POC tests for influenza with sufficient sensitivity and specificity (e.g. NAAT-based assays) were applied, this strategy might provide large-scale assistance in terms of helping facility leadership to place patients into cohorts (and also to not become overwhelmed with “rule-out” patients), and thus better handle resources that are sometimes limited. One study at a large maternity hospital could be used as a conceptual model and example for delineating use of limited resources (i.e. rationing) in an ethical manner, should that become necessary during an upcoming influenza pandemic (or any major infectious disease outbreak) (Beigi et al., 2010).

Unmet public health needs and research gaps 4.3.2
There is a need for stronger evidence-based guidance on surge capacity approaches, including triage and alternative models of care, to optimize patient and population health outcomes during a pandemic or major outbreak. One example is validating the use of a rapid POC diagnostic test to help triage patients presenting to health-care facilities; specifically, an assay that could be used on a large scale. Further development and testing of facility management algorithms during a major influenza event is also needed. Such data would allow facilities and public health authorities to handle surge in a more strategic and informed manner, minimizing nosocomial transmission and enabling more informed use of limited facility resources. Options for alternative health-care delivery sites during a pandemic or major outbreak are considered below in Recommendation 4.3.3.

Stronger evidence for the overall impact of both pharmaceutical and non-pharmaceutical interventions that can minimize the transmission of influenza viruses, both locally in a facility and on a population basis, would be helpful. One element is higher quality data on the effectiveness and safety of large-scale pharmaceutical prophylaxis against an influenza outbreak on an institutional basis. More broadly, investigation into tools enabling accurate and rapid assessment of the local and regional situation, including clinical data sharing across health-care entities, would help to improve regional population health practices.
Research recommendation 4.3.3
Research to develop alternative health delivery systems for care of patients including home care, community facilities other than hospitals and other venues.

Major Progress 4.3.3
During the 2009 pandemic, the most serious clinical management problem was the delay in starting antiviral treatment. In most countries, patients with mild influenza illness are not treated with NAIs due to cost and policy restrictions, and NAI treatment is often limited to patients with severe or progressive illness and hospitalized patients. However, influenza patients are often not hospitalized until 3–6 days after the onset of illness, when starting NAI therapy is much less effective. In Japan, almost all patients with ILI who seek medical care are tested early in the clinical course with an influenza rapid diagnostic test, and every patient who tests positive is offered treatment with an NAI (Sugaya et al., 2011). Although there were many influenza cases in Japan during the 2009 pandemic (20.7 million out of 128 million, or 16% of the total population), the low mortality in Japan was attributable to the near universal implementation of early NAI treatment (Sugaya et al., 2011). Almost all influenza patients sought care in the outpatient departments of hospitals and clinics, and these facilities became overcrowded. In contrast to the surge in numbers of patients treated in outpatient departments, there were no surges in the numbers of hospitalized patients or ICU patients because of influenza in Japan. If outpatient treatment with oseltamivir is based on the results of influenza rapid tests, it could be cost effective in well-resourced settings (Nshimyumukiza et al., 2016). However, this strategy depends on the performance characteristics and costs of the test, and is not currently applicable in resource-challenged settings.

Unmet public health needs and research gaps 4.3.3
There is a need to evaluate strategies to provide increased capacity for care during epidemics and pandemics in non-hospital locations, especially in resource-challenged settings. Sustainable strategies will depend on enhancing local capacities with international support, perhaps employing centralized or distributive models of care.

Home care is important for influenza patients, especially during pandemics, and patients can be managed at home with close follow-up and advice from influenza hotlines or other resources. However, home care without antiviral treatment often leads to delayed treatment, which was the most common cause of hospitalization and deaths during the 2009 pandemic. For a major influenza event, local pharmacies may be the best place to rapidly distribute NAIs to patients with mild influenza illness within 48 hours after the onset of illness. One 5-year study in New Zealand found that pharmacy-supplied oseltamivir distribution was feasible and did not increase antiviral resistance (Gauld et al., 2012). To implement early treatment with NAIs and help reduce pressure on hospitals and clinics when a pandemic or severe seasonal epidemic occurs, other public facilities (e.g. school gymnasiums, churches or convention centres) could be used (Levin et al., 2009). Pilot testing of alternative health-care delivery sites for patients during a major outbreak or other mass casualty event is needed. Careful evaluation of alternative health-care delivery systems is needed in both well-resourced and resource-restricted settings, to identify effective approaches that do not result in increased patient morbidity and mortality.

The use of rapid POC influenza diagnostic tests with high sensitivity is also important from the standpoint of reducing unnecessary or improper use of NAIs (Bouscambert, Valette & Lina, 2015). In addition to detection of seasonal influenza viruses, contemporary tests may be helpful as a means of initial detection of sporadic human infections by novel influenza A viruses of avian or swine
origin (Sakai-Tagawa et al., 2014), although most rapid antigen assays do not distinguish among influenza A virus subtypes. In a major outbreak situation, influenza rapid diagnostic tests could be performed at pharmacies or potentially by patients themselves at home, but these strategies require validation.

**Research recommendation 4.3.4**
*Conduct studies to develop best practices that provide protection of health-care workers and other care-givers in different health-care and resource settings.*

**Major Progress 4.3.4**
Health-care workers have a higher risk of acquiring influenza than the general population because of the nature of their work. While there has been some progress in increasing influenza vaccination among health-care workers, the coverage levels remain suboptimal and vary widely (2–99%) across countries, in part because of policy differences and attitudes of health-care workers (Black et al., 2016; Little et al., 2015).

The appropriate level of personal protective equipment (PPE) for health-care workers caring for influenza patients is an area of active research and debate (Bessesen et al., 2013; Bin-Reza et al., 2012). One large RCT in China randomized health-care workers to medical masks, N95 respirators or targeted use of N95 respirators while doing high-risk procedures or barrier nursing. The frequency of respiratory illness was found to be highest in the medical mask arm (17%), followed by the targeted N95 arm (11.8%) and the routine N95 arm (7.2%; P <0.05) (MacIntyre et al., 2011). Confirmation of these results with influenza-specific data in other settings is needed. With the limited availability of PPE for influenza control programmes in lower resourced settings, questions have been raised about whether home-made masks can be used. One RCT found that simple cloth masks were significantly less effective than medical masks in protecting health-care workers from ILI and other respiratory virus infections (MacIntyre et al., 2015).

**Unmet public health needs and research gaps 4.3.4**
There is a lack of data, especially in less well-resourced settings, from longitudinal studies involving both vaccinated and non-vaccinated health-care workers, about the incidence and severity of influenza among both the health-care workers and their patient contacts. Such data are needed to determine impacts on the health-care workforce, patients and the health system. Few surveys of knowledge, attitudes and practices (KAP) have been conducted in health-care workers to assess the main factors leading to low vaccine uptake other than in well-resourced settings. Major remaining research gaps include both understanding the barriers to vaccine uptake (e.g. concerns about vaccine efficacy and safety, and cost) and determining effective policies to overcome these barriers (e.g. ward-based immunization, cost-free vaccine and policies such as mandatory receipt) (Black et al., 2016; Costantino et al., 2016; Little et al., 2015). A specific policy that increases coverage is mandatory influenza vaccination of health-care workers (De Serres et al., 2017), although this approach raises important ethical and legal questions (Ottenberg et al., 2011).

Questions also remain about the indications and use of antiviral chemoprophylaxis (e.g. duration and target groups, and use of full therapeutic doses among close contacts of patients with novel influenza A virus infection), and the appropriate application of non-pharmaceutical interventions (e.g. mask versus respirators, face shields versus goggles, other PPE and patient isolation procedures) in prevention and control of nosocomial influenza (Cowling et al., 2010; Wizner et al., 2010; Little et al., 2015).
2016). Other areas of uncertainty are the operational effectiveness – taking compliance and cost issues into account – of medical masks compared with N95 respirators (or equivalent), of different types of eye protection, and of gowns and gloves in preventing infection in health-care workers.

**Research recommendation 4.3.5**

*Studies to identify evidence-driven clinical care pathways and principles that optimize healthcare delivery in a range of resource settings.*

**Major Progress 4.3.5**

No major studies have been published since 2009 that addressed this recommendation.

**Unmet public health needs and research gaps 4.3.5**

There is a public health need to validate evidence-driven, context-appropriate clinical care pathways, and to share this knowledge in a community of practice with optimized delivery in a range of settings. The Surviving Sepsis Campaign\(^1\) and many other situations have shown the fallacy of widely adopting pathways to improve care based on evidence generated in specific resource contexts. Guidelines should be crafted with local experts, and should be linked to treatment protocols. Also, there is a need to evaluate care-seeking behaviours that may be relevant to adoption of clinical care pathways for influenza, and to evaluate care-giving cultures that are relevant for providing best clinical care.

Ongoing surveillance for influenza should be coupled with trigger tools and simple protocols for instituting therapy of proven value based on resources and setting. A simple environmental scan document to judge resources and readiness to implement the tools would also be useful. Simple outcome measures should be incorporated, so that the impact of interventions can be evaluated and adapted in real time to improve care processes and outcomes. Ultimately, clinical trials and rigorous quality improvement studies to assess the effect of implementing evidence-based clinical guidelines and pathways on patient health outcomes will be required.

**Research recommendation 4.3.6**

*Studies to develop principles and practices for rapid assessment and introduction of new interventions during health emergencies, including systems for clinical data collation, sharing and assessment in real time.*

**Major Progress 4.3.6**

Substantial attention has been given to the principles and practices for rapid assessment and introduction of new interventions during health emergencies, including the development of clinical data collection and sharing platforms, systems for clinical data collation and assessment in real time. Such assessment takes the form of, for example, published observational studies (case series and cohort) conducted during the 2009 pandemic, perspective pieces and recommendations from the international clinical research community, and funded SARI surveillance and rapid clinical research networks. Few interventional RCTs were undertaken during the 2009 pandemic, and most of these were under-enrolled. A general point is that the groups making early contributions with respect to the pathogenesis and clinical management of severe A(H1N1)pdm09 illness were those

\(^1\) [http://www.survivingsepsis.org/Pages/default.aspx](http://www.survivingsepsis.org/Pages/default.aspx)
conducting related research during the inter-pandemic period. Recent examples of progress in relation to rapid clinical research responses to new infectious diseases events include funding and initiation of inter-pandemic clinical trials by groups within the Platform for European Preparedness Against (Re)emerging Epidemics\(^1\) and coordination of funding efforts through the formation of the Global Research Collaboration for Infectious Disease Preparedness.\(^2\)

**Unmet public health needs and research gaps 4.3.6**

A recurring theme of SARI outbreaks and influenza pandemics has been that there is little pre-existing coordinated national and international capacity for rapid clinical assessment and introduction of new interventions during health emergencies, including systems for clinical data collation, sharing and assessment in real time (Dunning et al., 2014; Fowler et al., 2010). The usual process of conducting observational and interventional research – including development of research protocols, data collection tools, research ethics assessment, data-sharing agreements and research funding; establishing contracts; and conducting, analysing and disseminating research findings – is usually insufficiently rapid and nimble to start before an influenza outbreak or season peaks across various geographical regions. The consequences are that few observational studies or interventional trials begin before an influenza outbreak or season has passed. Additionally, research efforts have traditionally been focused on high-resource settings with pre-existing research infrastructure and ongoing studies, with substantial data collection requirements. Also, they have been focused on interventions that may not be applicable to resource-challenged health-care settings – regions suffering the highest burden of morbidity and mortality often have the least ability to undertake rapid assessment and introduction of new interventions (Duggal et al., 2016).

Other practical steps to address unmet needs would include greater integration of national and international surveillance systems for influenza and other SARIs to enable expanded or focused capacities during periods of heightened risk (e.g. during outbreaks of existing or new and evolving pathogens) and establishing in-waiting funding mechanisms for outbreak and pandemic-related clinical research with pre-existing triggers, allowing rapid mobilization of resources across a broad range of health systems.

\(^1\) https://www.prepare-europe.eu/
\(^2\) http://www.glopid-r.org/
References


