NIH Public Access
Author Manuscript
Glob Heart. Author manuscript; available in PMC 2015 October 31.

Published in final edited form as:
Glob Heart. 2014 September ; 9(3): 325–336. doi:10.1016/j.gheart.2014.08.004.

Global burden of Influenza: Contributions from Resource Limited and Low-Income Settings

William A. Fischer II[1,2], **Michelle Gong**[3], **Satish Bhagwanjee**[4], and **Jonathan Sevransky**[5]

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, The University of North Carolina at Chapel Hill School of Medicine – Chapel Hill, NC/USA

[2]The Center for Environmental Medicine, Asthma and Lung Biology, The University of North Carolina at Chapel Hill School of Medicine – Chapel Hill, NC/USA 27599

[3]Albert Einstein College of Medicine, Bronx, NY/USA 10461

[4]Department of Anesthesiology and Pain Medicine, University of Washington, 1959 NE Pacific Street, Seattle, WA/USA 98195

[5]Division of Pulmonary, Allergy and Critical Care Medicine, Emory University, Atlanta, GA/USA 30322

Abstract

Severe acute respiratory infections (SARI), including influenza, are a leading cause of cardiopulmonary morbidity and mortality worldwide. Until recently the epidemiology of influenza was limited to resource-rich countries. Emerging epidemiological reports characterizing the 2009 H1N1 pandemic however suggest that influenza exerts an even greater toll in low-income resource constrained environments where it is the cause of 5–27% of all SARI. The increased burden of disease in this setting is multifactorial and likely is the results of higher rates of comorbidities such as HIV, decreased access to healthcare including vaccinations and antiviral medications, and limited healthcare infrastructure including oxygen therapy or critical care support. Improved global epidemiology of influenza is desperately needed in order to guide allocation of life saving resources including vaccines, antiviral medications, and direct the improvement of basic health care in order to mitigate the impact of influenza infection on the most vulnerable populations.

Keywords

Influenza; 2009 H1N1 Pandemic; Low-income; Resource-constrained; Cardiopulmonary complications; Intensive care unit

© 2014 World Heart Federation (Geneva). Elsevier Ltd. All rights reserved.

Corresponding Author/Institution: William A. Fischer II, University of North Carolina at Chapel Hill School of Medicine, CEMALB, 104 Mason Farm Road, Chapel Hill, NC 27599-7310, William_Fischer@med.unc.edu, Phone: 919 843-9108, Fax: 919 966-9863.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Introduction

Severe acute respiratory infections (SARI) including influenza represent a leading cause of global morbidity and mortality. Each year, an estimated 5–10% of adults and 20–30% of children are infected with influenza, resulting in 3–5 million cases of severe disease and approximately 1 million deaths worldwide (1). Until recently, the epidemiology of influenza has been primarily derived from resource-rich settings. Emerging data from the 2009 H1N1 pandemic, however, suggests that influenza exerts an even greater toll on patients in resource-limited environments due to decreased access to health care, limited health care infrastructure and shortages of health care personnel. This includes poor availability of vaccinations and critical care support, and the high prevalence of co-morbidities such as HIV infection and malnutrition.

Influenza is a respiratory virus that, despite the availability of vaccines and effective antiviral medications, exerts a substantial toll on global morbidity and mortality every year. Seasonal influenza is often clinically mild, recognized by a constellation of symptoms including fever and cough or sore throat, which is classified as “influenza-like-illness” (ILI) in the absence of a known cause other than influenza (2). More severe influenza infections can occur and are further classified as severe acute respiratory infections (SARI) if the patient with ILI has shortness of breath (3). Pandemics occur when a novel influenza virus enters into the human population and is capable of rapid spread. The most severe pandemic occurred in 1918 when an influenza virus crossed over from birds to humans and killed an estimated 50–100 million people with a mortality rate of ~2–2.5% (4). Recently a number of influenza viruses (H5N1 and H7N9) have emerged with pandemic potential and even greater mortality rates of up to 60% but have not yet reached sustained transmission in humans (5, 6). In April 2009, a novel strain of H1N1 influenza jumped from swine into humans and infected over 200 million people globally resulting in the first influenza pandemic of the 21st century. Despite a wealth of information about influenza from resource-rich countries, very little is known about influenza’s epidemiology and sequelae in resource-limited countries.

Given the global impact of influenza and the paucity of data for many countries, this review represents an initial step to better characterize the burden of influenza including epidemiology, sequelae of severe influenza infection, and strategies to improve supportive care and virus-specific therapy in resource limited, low-income settings. The review will examine the available epidemiology in resource-limited countries with a specific focus on the first year of the 2009 H1N1 pandemic as well the known risk factors for influenza in these settings. The most prominent sequelae of infection including cardiopulmonary complications will then be reviewed. Finally it will consider treatment and remaining barriers to improving influenza care globally.

SENTINEL SURVEILLANCE OF 2009 PANDEMIC H1N1 INFLUENZA IN LOW AND LOW-MIDDLE INCOME COUNTRIES

Since the outbreak of avian H5N1 influenza in 1997 there has been growing recognition of the need for improved global surveillance of influenza. In response, the WHO launched the Global Agenda for Influenza Surveillance and Control in 2001, which prioritized influenza

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

surveillance as part of a comprehensive strategy to reduce morbidity and mortality from annual influenza epidemics (7). Despite the implementation of basic influenza surveillance systems across the globe very little was reported about seasonal influenza in resource-limited areas.

The global spread of pandemic H1N1 in 2009 represented the first influenza pandemic of the 21st century. Within a year cases were reported in more than 214 countries, overseas territories, and communities (8). On June 11, 2009, the World Health Organization (WHO) raised the pandemic alert to a level 6, the highest level, indicating evidence of sustained human-to-human transmission and global spread of this virus. In the United States alone, there were an estimated 59 million illnesses, 265,000 hospitalizations, and 12,000 deaths as of February 2010 (9). The pandemic was declared over in August 2010 but not before an estimated 200 million people were infected (8). Approximately 18,500 laboratory-confirmed deaths due to H1N1 were reported to the WHO. However, these numbers are likely a gross underrepresentation of the true burden of global influenza due to a lack of standardized case reporting or access to health care (10). Early reports of high morbidity and mortality from Mexico, an upper-middle income country according to the World Bank, suggested that an excess in mortality and life years lost occurs in more resource-limited settings (11). Furthermore, of the 18,500 2009 pandemic H1N1 (pH1N1) influenza deaths reported to the WHO, only 168 (0.9%) were from Africa despite its being home to 12% of the world's population (12). The juxtaposition between the large numbers of people living in low income countries and the small numbers of infections and deaths due to 2009 pH1N1 influenza in these settings highlighted the gap in the current understanding of the global burden of influenza.

In order to better characterize the effect of influenza infection in resource-limited or low income areas, we performed a comprehensive search of articles related to the 2009 H1N1 pandemic influenza in low and lower-middle income countries using the following combined search terms: "(swine or H1N1) and (flu or influenza or virus or outbreak or pandemic) and (Africa or Southeast Asia or India or Eastern Europe or resource limited or low income)." One thousand nine hundred and forty one articles were identified and evaluated for content including primary data related to sentinel surveillance of patients with influenza between 2009 and 2010. One thousand eight hundred and twenty three studies were excluded, as they did not contain primary data relevant to this study. The remaining 118 were reviewed and 97 were excluded as they did not report data from low-income countries or included only pediatric populations. We analyzed the subsequent 21 articles to characterize the sentinel surveillance of the 2009 H1N1 influenza pandemic in low-income countries (Table 1) (13–22).

NORTH AFRICA

MOROCCO

Morocco is a country of 33 million people located in Northwest Africa (23). In line with the WHO Global Agenda for Influenza Surveillance and Control, Morocco strengthened influenza sentinel surveillance in 2007. As a result 3102 respiratory samples were collected between 2007–2009 with 98 (3%) of these samples positive for influenza (20). The

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

emergence of the 2009 H1N1 pandemic led to increased surveillance resulting in the collection of 3937 samples between June 2009 and February 2010 alone (15). Of these, approximately 1452 (37%) tested positive for 2009 pandemic H1N1 influenza. Approximately 40% of patients who presented with ILI and 27% with SARI were positive for 2009 pH1N1 (15). The largest number of patients with ILI and SARI occurred in children under 15 (56% and 51% respectively) (15, 19). Sixty-four patients (19%) admitted with SARI died highlighting the poor outcome of severe influenza in Morocco. While severe disease was observed with similar frequency in all age groups (19% in children <5, 33% in children 5–14, 27% 15–24; 33% 25–59, and 25% in those >60), death occurred to a greater extent in adults between the ages of 25–59, similar to that found in the United States and Europe. Influenza in Morocco was seasonal with peak transmission between October and April (20). Influenza vaccination was reported in only 2–4% of patients presenting with ILI or SARI (20). The high proportion of patients presenting with ILI and SARI due to influenza suggests that influenza may be a leading cause of vaccine preventable respiratory infection and mortality in North Africa.

WEST AFRICA

GUINEA, MALI, AND NIGER

Despite the fact that by December 2009 approximately 92% of countries worldwide had reported at least one case of 2009 H1N1 influenza, 75% of countries (12/16) in West Africa had yet to report a single case (18). In an attempt to understand the transmission of 2009 pandemic H1N1 in Africa, surveillance data was obtained from 10 countries during the 2009 pandemic (18). Between May 4, 2009 and April 3, 2010, a total of 10,203 respiratory samples were tested of which 25% were positive for H1N1 pandemic influenza (18). Between May 2009 and April 2010, 12/98 (12%), 53/422 (13%), and 90/388 (23%) of samples were positive for influenza in Guinea, Mali and Niger respectively. The 2009 pandemic H1N1 virus was first detected in Cape Verde and Cote d'Ivoire in June 2009 followed by Ghana and Cameroon (August 2009), Mauritania, Guinea, and Senegal (December), Mali (January 2010) and finally Niger in February 2010 (18). Only 14% of samples tested through the end of December 2009 were positive for the 2009 H1N1 pandemic strain indicating that the belated detection of cases in Mauritania, Guinea, Senegal, Mali and Niger truly represented a delayed spread of the 2009 H1N1 influenza virus in West Africa (18).

NIGERIA

As the most populous country in Africa (173 million people), Nigeria only expanded influenza sentinel surveillance in 2008, building on a foundation established as part of the WHO's African Region's Integrated Disease Surveillance and Response strategy (24). Between 2009 and 2010, 2803 samples were obtained from patients presenting with ILI or SARI (412 were unclassified as either ILI or SARI) from 4 sentinel sites (16). Of these, 217 (8%) patients tested positive for influenza of which 167 (77%) presented with ILI and 17 (8%) with SARI (16). In contrast to reports from elsewhere in Africa, influenza accounted for a lower percentage of ILI and SARI cases in Nigeria with 8.1% and 5% respectively. An overwhelming majority of ILI and SARI occurred in children under 5 (67.8 and 71.6

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

respectively) concerning for reporting bias or a skewed utilization of healthcare resources. While individuals presenting with ILI due to pandemic H1N1 were most commonly between the ages of 5–17, SARI due to pH1N1 was most frequently detected in individuals over the age of 65 (16). Seasonality of influenza in Nigeria was less pronounced but peak influenza activity between 2009 and 2010 occurred during November 2009 and March 2010.

SUBSAHARAN AFRICA

Influenza is often confused with other febrile illnesses in Sub-Saharan Africa and thus the epidemiology remains poorly defined in this area. Additionally, influenza surveillance in this region has been limited due to financial constraints, limited public health infrastructure and competing health priorities such as tuberculosis, malaria, and HIV (21).

RWANDA

Rwanda, a Sub-Saharan country of almost 12 million people, initiated an influenza sentinel surveillance program in collaboration with the US Centers for Disease Control and Prevention (CDC) in 2008 (25). Between October 2009 and May 2010 the Rwandan National Reference Laboratory tested 2,045 samples from patients meeting the WHO case definition for pandemic H1N1 (22). Five hundred and thirty two (26%) tested positive for influenza, 93% of which were 2009 H1N1. Similar to Morocco, laboratory confirmed cases of influenza during this pandemic period were highest in children under the age of 15. Overall the 2009 H1N1 pandemic was reportedly mild in Rwanda with 70% of cases presenting as ILI and 30% as SARI. Approximately 12% of patients required hospitalization, of which 69% received Oseltamivir therapy, and there were no deaths reported (22, 26). Chronic respiratory problems followed by cardiac disease were the most common comorbid conditions associated with influenza infection in this population (22). Although influenza was detected year-round in Rwanda, peaks of disease were noted between February-March and October-November coinciding with the rainy seasons (26).

KENYA

In 2006, with support from the Centers for Disease Control and Prevention-Kenya, a national sentinel surveillance system was established. Between July 1, 2007 and June 30, 2013 almost 40, 000 samples (0.09% of Kenya’s population) were obtained from patients with ILI and SARI (21). Influenza was confirmed in 15% (1030/6712) of patients presenting with ILI and 11% (962/8975) of those admitted with SARI in 2009–2010. Less than 3% of SARI patients were of adult age concerning for either a surveillance bias or perhaps due to a disparity in the utilization of healthcare resources between pediatric and adult populations. Influenza transmission was detected each month; however peak disease activity was detected between July and November. Influenza vaccination was reported in 1.6% of patients with ILI and 1.5% of patients SARI highlighting the lack of access to potentially life saving public health interventions (21).

DEMOCRATIC REBULIC OF CONGO

Beginning in 2007, the Democratic Republic of Congo, home to approximately 67 million people, implemented sentinel surveillance for influenza in the capital Kinshasa in response

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

to the growing threat of avian influenza (27). In 2009, 1311 samples were collected from 1048 patients presenting with ILI and 263 with SARI (17). Influenza was confirmed in 208 (20%) of the ILI cases and 41 (16%) of the SARI cases (17). Similar to other African countries cases of SARI peaked in children under the age of 14. Influenza activity appears to circulate most commonly between January and March however, but peaked in October during the 2009 H1N1 pandemic (17).

INDIA, SOUTHEAST ASIA AND MONGOLIA

INDIA

In 2004, the Indian Council of Medical Research established a systematic influenza surveillance network to characterize the prevalence and burden of influenza in India, the second most populous country in the world (>1.2 billion people) (28, 29). Between May 2009 and April 2010 2,588 samples were tested for influenza and 699 (27%) were positive. The 2009 H1N1 virus accounted for 80% (557/699) of influenza positive infections. Influenza was detected in 35% of patients presenting with ILI and 18% of those with SARI in India consistent with other lower-middle income countries. 2009 pandemic H1N1 was detected in all ages but peaked in the age range 5–15 for those presenting with ILI.

BANGLADESH

Bangladesh is a low-income country of 156 million people located east of India that experienced approximately 6000 2009 H1N1-related deaths with an estimated 6.1 million US dollars in direct medical costs (13)((30). In collaboration with the government of Bangladesh, the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDRB) initiated a hospital based influenza surveillance network to better characterize the epidemiology of influenza in Bangladesh. From 2009 to 2010, 2377 samples at ICDDRB were collected of which 391 (16%) were positive for influenza (13). Laboratory confirmed influenza was detected in 17% and 16% of patients presenting with ILI and SARI respectively. Only 1% of 495 SARI patients over the age of 5 had underlying pulmonary comorbidities compared with 3% of patients presenting with ILI (13). Influenza infection was detected each month between May 2008 and September 2010 consistent with other tropical countries. The limited access to healthcare and vaccines in addition to a lack of antiviral drugs and pervasive malnutrition were reported as likely contributors to the increased mortality associated with influenza in Bangladesh.

BHUTAN

Bhutan, located just north of Bangladesh and east of India, has a population of approximately 650,000 people and is considered a lower-middle income country by the World Bank. In collaboration with the Department of Virology, Armed Force Research Institute for Medical Sciences (AFRIMS) based in Bangkok, Thailand, Bhutan launched an influenza surveillance system in 2008. Initially diagnostics were performed in Thailand, as PCR-based domestic influenza diagnostics were not available until April 2010 (14). Between June 2009 and August 2010, 2149 samples were collected of which 711 (33%) were positive for influenza. Of these 487 (69%) were found to be the 2009 pandemic H1N1 virus. As in other low to lower middle income countries, the most common age group

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

infected with the 2009 H1N1 virus was 6–20 years (57%) with very few above the age of 50 (<2%). Approximately 22 deaths were attributed to influenza and/or pneumonia during the pandemic however none of these had samples obtained for laboratory confirmation further suggesting that the true burden of influenza in under-resourced areas is unknown due to a lack of standardized diagnostic testing.

LAO PEOPLE'S DEMOCRATIC REPUBLIC (Lao PDR)

Influenza-like illness accounts for a significant proportion (50,390/509,313 or 10%) of all outpatient and emergency room visits in Lao PDR from 2008–2010 (31). Lao PDR is a lower-middle income country of 6.7 million people located in between Thailand and Vietnam (32). The Lao PDR national influenza surveillance network was established in response to emerging strains of influenza including the H5N1 avian strain and the 2009 H1N1 pandemic virus. Between 2008 and 2010, 523 (22%) cases of influenza were confirmed in 2,338 patients presenting with ILI. Influenza activity was highest in children between the ages of 5 and 17 (33%) followed by 18–64 (28%). Strangely, influenza was not detected in the 19 individuals older than 65 years of age that were tested. Although Lao PDR crosses both tropical and semi-tropical zones, influenza was detected year-round typical and displayed peak activity between August and November. Similar to most under-resourced areas, seasonal and pandemic influenza vaccines are not routinely available.

PHILLIPINES

The Philippines is an archipelago that is home to over 98 million people and located north east of Malaysia (33). Since 2004, the Research Institute for Tropical Medicine has established the National Influenza Center in the Philippines consisting of two sentinel sites in 12 of the 17 administrative regions. Of the 4,178 respiratory samples collected from patients with ILI between January 2009 and December 2010, 1068 (26%) were positive for influenza, 48% of which were pandemic H1N1 (34). Although the seasonal strains of H1N1 and H3N2 more commonly occurred in children under 5, the 2009 pandemic H1N1 predominantly infected individuals between the ages of 5 and 14. Between April 2009 and December 2011, 1438 patients were admitted with SARI and 152 (11%) were confirmed to have been infected with influenza. Similar to other tropical countries influenza was detected year round but appeared to peak from February to March and June to September coinciding with the rainy season.

MONGOLIA

The increased burden of influenza in resource-limited areas is not geographically isolated to Africa, India or Southeast Asia. Although the first case of 2009 H1N1 pandemic influenza did not occur in Mongolia until October 2009, a community based serological study in the Selenghe province suggests that once introduced, this virus infected approximately 30% of the Mongolian population during in the first wave of the pandemic. The low population density of Mongolia, in comparison to more developed or urban nations, may explain the late appearance of this global pathogen. More than half of the influenza infections during this time period occurred in individuals under 20 years of age (35). Although influenza is often a vaccine-preventable illness, 93.9% of patients in this study did not receive an influenza seasonal vaccine in the year prior. Unfortunately the 2009 H1N1 pandemic

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

vaccine was not available prior to January 2010 highlighting the limited access to public health preventative strategies.

2009 PANDEMIC H1N1 MORTALITY

Influenza infection results in a substantial burden of illness in resource-limited settings and is the etiology of 5–27% of all cases of severe acute respiratory infections (Table 1). Mortality attributable to influenza in these settings is difficult to determine as case fatality rates in many of these countries are not regularly reported. The lack of epidemiologic data surrounding influenza-associated mortality in low-income countries is highlighted by the fact that although Africa and Southeast Asia account for 38% of the world's population, only 12% of the 2009 H1N1 deaths were reported from these regions. Limited studies from low and low-middle income countries, such as those from India and Kenya, demonstrate markedly elevated influenza-related mortality rates in hospitalized patients ranging from 4 to 68% (Table 2) (36–44). Additionally a recent meta-analysis of the global burden of severe influenza in pediatric populations reported that 99% of SARI in children younger than 5 occur in low and middle-income countries, 13% of which are due to influenza (45, 46).

Modeling studies have estimated a disproportionate burden of influenza in resource-limited settings. Using data derived from symptomatic attack rates and case fatality rates modified by a respiratory disease-related mortality multiplier, Dawood et al. found an estimated 201,200 (105,700-395,600) respiratory-related deaths associated with 2009 H1N1 influenza occurred globally (47). This is more than 15 times the reported number of laboratory deaths from the 2009 H1N1 provided to the WHO. Furthermore, 51% of these deaths were estimated to have occurred in Africa and Southeast Asia with an estimated 2.4 fold increase in mortality in Africa and a 1.4 fold increase in Southeast Asia compared with resource-rich countries; the true burden of global influenza appears to reside in the most impoverished and under-resourced nations (10, 47).

These estimates were supported by the Global Pandemic Mortality (GLaMOR) study, which used global and regional estimates of pandemic H1N1 influenza deaths, to also highlight the disproportionate burden of influenza morbidity and mortality in resource-limited settings. The GLaMOR study, however, found differences in the regional distribution of influenza-related mortality compared to the aforementioned modeling study. Whereas the highest mortality rates were estimated to occur in the Americas by the GLaMOR study, Dawood et al. projected the greatest mortality in Africa, India, and Southeast Asia. Importantly, neither study had reliable influenza-related mortality data from Africa. In the case of the GLaMOR study, data was derived from South Africa, an upper-middle income country that is vastly different from many other African countries in terms of access to and quality of healthcare (48). In contrast, Dawood et al. based its conclusions of increased influenza-related mortality in Africa, India, and Southeast Asia on increased respiratory-related mortality multipliers proportional to case fatality rates from all respiratory related illness in these areas. Though this variance in regional burden of disease underscores the deficient epidemiology, it supports the growing understanding of the disproportionate burden of influenza-associated morbidity and mortality in resource-constrained environments.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

SPECIFIC RISK FACTORS FOR SEVERE INFLUENZA IN RESOURCE-LIMITED SETTINGS

Since the start of the 2009 H1N1 pandemic, WHO and member states have collected patient information in an attempt to understand which conditions predispose influenza-infected patients to severe outcomes. Data from 70,000 patients hospitalized in 19 countries or administrative regions with H1N1 influenza revealed that age, cardiorespiratory disease, diabetes and pregnancy are leading risk factors associated with severe disease (49). Despite the low level of infection seen in developed countries among older adults, mortality was highest among those 50–64 years old and over 65 (RR = 1.5 and 1.6 respectively compared to the general population) (49). Only one country however (Madagascar) was defined as low income; the rest were among upper-middle and high income countries including Argentina, Australia, Canada, Chile, China, France, Germany, Hong Kong SAR, Japan, Mexico, the Netherlands, New Zealand, Singapore, South Africa, Spain, Thailand, the United States and the United Kingdom. Recent studies have identified other risk factors that may be playing a role in predisposing individuals from low-income countries to more severe disease such as HIV and malnutrition (50).

Cardiopulmonary comorbidities in particular have been associated with poor outcomes especially in resource-constrained environments. Patients with more severe influenza including viral pneumonia were more likely to have underlying cardiac disease. In Morocco, cardiovascular comorbidities, including hypertension, were associated with an increased risk of death with an adjusted odds ratio of 28.2 (CI 2–398.7; p = .013) (20, 51, 52). Cardiac disease was also identified as a leading risk factor for ICU admission and death from influenza, with a RR of 8 for severe disease in India (40, 49).

Chronic infections such as tuberculosis (TB) and HIV, more prevalent in low-income settings, are also associated with severe disease. In South Africa individuals with HIV accounted for 20% of deaths due to 2009 H1N1 pandemic influenza, which is notably higher than the 10% HIV prevalence in the general population (53). After controlling for age, influenza infection of HIV positive individuals was noted to carry a five-fold risk of severe acute respiratory infection (RR 5.3 95% CI 4–6.9) compared with HIV negative individuals (54–56). The increased association between HIV infection and severe influenza disease was greatest in the adults between the ages of 25 and 44 (56). HIV infected individuals were also noted to have increased rates of bacterial co-infection (58%) compared with HIV negative patients (44%) whereas only 10–30% of hospitalized patients in Argentina or the US were found to have bacterial co-infection (57–59).

Malnutrition has long been suspected of predisposing individuals to infection through its role in affecting the immune response but studies have provided conflicting results. Both micro- and macro-nutrient deficiency have been implicated in the development of immunodeficiency in general and specifically in increasing the susceptibility to influenza in animal models (60, 61). Additionally, malnutrition was associated with a poor response to influenza vaccination in one study of elderly adults (62). Yet, another study among pediatric patients found no association between malnutrition and influenza (63). Given the conflicting results, absence of sufficient data, and the fact that 95.9% of the 826 million undernourished

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

people live in resource-limited settings globally, the role of malnutrition as a risk factor for severe influenza requires further investigation (64).

INFLUENZA-ASSOCIATED SEVERE DISEASE

RESPIRATORY COMPLICATIONS OF INFLUENZA

Influenza infection typically results in a mild, self-limiting upper respiratory tract infection with fever, cough, sore throat, myalgia, rhinorrhea, conjunctivitis and shortness of breath. Severe influenza, defined by more severe organ involvement or complications, is most commonly associated with pulmonary complications including primary viral pneumonia, secondary bacterial infection and exacerbations of underlying lung disease and more often seen in older adults or those with other high risk conditions (65). Additionally, influenza can progress to acute respiratory distress syndrome (ARDS). Influenza infects respiratory epithelial cells including alveolar epithelial cells resulting in flooding of the alveolar lumen with protein-rich fluid, blood and inflammatory cells limiting oxygen gas exchange and resulting in severe hypoxic respiratory failure. The pathogenesis of influenza-induced ARDS has been reviewed previously (66). The 2009 pandemic H1N1 virus led to ARDS in 30–80% of patients admitted to an intensive care unit with increased percentages associated with lower-income countries (Table 3) (11, 42, 57, 58, 67–72).

Bacterial co-infection was first recognized as a major complication of influenza during the 1918 epidemic that resulted in the death of over 50 million individuals. Autopsy reports suggest that close to 95% of severe illness and death were associated with bacterial co-infection (73). Infection with the 2009 H1N1 pandemic strain was also associated with secondary bacterial infection in approximately 20–40% of ICU patients in most studies (Table 3) (57, 58, 67). The pathogenesis underlying influenza-bacterial co-infection is likely multifactorial and involves changes to both the airway defense including decreased mechanical clearance of invading bacteria through deficient ciliary movement and breakdown of the airway epithelium. Epithelial damage from influenza infection is thought to be an important step in the pathogenesis of secondary bacterial pneumonia by facilitating bacterial adherence (74). Additionally influenza-associated depletion of alveolar macrophages and alterations to the innate immune response reduces the ability to fight invading bacteria.

CARDIOVASCULAR COMPLICATIONS OF INFLUENZA

Although influenza is traditionally associated with respiratory complications, cardiac sequelae are increasingly recognized. In fact an additional 83,300 (range 46,000–179,900) cardiovascular related deaths worldwide have been attributed to infection with the 2009 pandemic H1N1 virus suggesting that the already substantial global mortality burden of influenza is likely under-estimated due to unrecognized cardiopulmonary complications in influenza-infected individuals worldwide (47).

The relationship between influenza and increased cardiac morbidity and mortality was initially recognized in epidemiologic studies demonstrating peaks of influenza activity and cardiac related deaths coinciding during winter months (75). Increases in cardiovascular deaths during influenza epidemics, further suggest an influenza-specific causal association.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

The cardiovascular complications of influenza range from asymptomatic ECG abnormalities to acute myocardial infarction. In a study of 30 adults with clinical evidence of influenza infection, 53% had abnormal ECGs on day 1 and 23% on day 11 although serum troponin levels and echocardiographic studies were unremarkable (76). More severely, 15% of influenza infected army recruits had evidence of myocarditis with increased levels of cardiac enzymes and echocardiographic evidence of wall motion abnormalities (77).

More recently, studies have demonstrated myocardial dysfunction during infection with the 2009 H1N1 pandemic influenza virus. An echocardiographic study of 28 patients presenting with ILI to a hospital in Turkey revealed a global myocardial performance index (sum of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET); higher values correspond to increased cardiac dysfunction) that was significantly higher in 2009 H1N1 infected patients as compared to patients with non-influenza related ILI (78). Similarly, a Belgian study using echocardiography to evaluate the incidence and hemodynamic consequences of right and left ventricular dysfunction in critically ill patients with 2009 H1N1 infection found that 72% of the 39 patients evaluated displayed abnormal ventricular function; forty-six percent (n=13) had isolated left ventricular dysfunction, 39% (n=11) had isolated right ventricular abnormalities and 14% (n=4) had biventricular dysfunction (79). Interestingly, while left ventricular function normalized after an initial decline, right ventricular abnormalities tended to worsen over the course of illness.

Influenza infection has also been associated with acute myocardial infarction (80, 81). The most compelling evidence comes from influenza vaccination trials, which demonstrate a 67% reduction in the risk of myocardial infarction and a decrease in cardiovascular mortality from 8% in unvaccinated subjects to 2% among the vaccinated (RR 0.25 (95% CI 0.07–0.86; p = 0.01) (82, 83). The protective effect of influenza vaccines has been most pronounced in older adults with a 19% reduced risk of hospitalization for heart disease, 23% reduction in cerebrovascular accidents and a 50% reduction in all cause mortality during influenza seasons (84, 85). Additionally a recent meta-analysis found that influenza vaccination was associated with a lower risk of composite cardiovascular events (RR .64 [95%CI, 0.48–0.86, p=.003] (86). Despite the current recommendation for patients with underlying cardiovascular disease to receive influenza vaccination coverage, coverage remains insufficient in the resource-rich settings globally; in resource-limited environments, vaccines are very rarely available at all(87).

2009 H1N1 INTENSIVE CARE UNIT CARE AND OUTCOMES

Severe influenza requiring intensive care unit admission is associated with significant morbidity and mortality. In the United States between April 2009 and April 2010 an estimated 61 million people were infected with the 2009 H1N1 virus resulting in over 250,000 hospitalizations and 12,500 deaths (71). An estimated 23–34% of hospitalized patients required admission to an intensive care unit (71). While ICU admissions globally are associated with underlying co-morbidities, pregnancy, and/or a delay in antiviral therapy, very little is known about critical care management and outcomes in resource limited settings. Recent studies from India and Syria suggest that influenza-related critical

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

illness in low-income countries is associated with substantially greater mortality than in high-income countries (Table 3).

A multi center study from three intensive care units in South India reported 106 (106/464; 22.8%) patients with 2009 H1N1 required admission to an intensive care unit (42). Of these, 18 (17%) required invasive mechanical ventilation and 16 (15.1%) needed dialysis. Intensive care unit mortality in South India was reported as 49%. Despite lower severity of illness scores (Acute Physiology and Chronic Health Evaluation (APACHE II) or Sequential Organ Failure Assessment (SOFA) scores where higher scores are worse) among these patients, this ICU case fatality rate is approximately 2–3 fold higher than that reported in ICUs in the United States, Canada, New Zealand, or Australia (Table 3) (58).

Outcomes in ICUs located in Syria were also worse than in high-resource areas. In a retrospective review of 80 patients admitted to four ICUs in Damascus, Syria, 58 (72.5%) had acute lung injury or ARDS and 59 (73.7%) were mechanically ventilated (67). APACHE II and SOFA scores reported in Syria were similar to those in South India (15.2 and 5 respectively) and ICU mortality was similarly elevated at 51% (42).

As suggested by the data in Syria and India, despite markedly lower SOFA and APACHE II scores in resource-limited countries, there is higher mortality in these settings (Table 3) (42, 67). Further, mortality rates from ICUs in upper-middle income countries, including Mexico and Tunisia, suggest that resource-availability is linked to outcomes in severe disease there as well. Mortality rates in both countries were in-between those from lower- and higher-income countries (Table 3) (11, 42, 57, 58, 67–72). Disparities in access to critical care resources may partly explain some of the pandemic influenza mortality differences reported among high and low-income countries. However, additional factors such as lack of available trained staff, or even travel time to facilities, cost of treatment for patients and families, and delays in presentation likely also contribute. For example, a recent study showed that patients presenting to ICUs in India arrived on average 6 days after the onset of symptoms versus patients in high-income countries who presented 3–4 days after (42).

DISPARITY IN ACCESS TO TREATMENT IN RESOURCE-CONSTRAINED AREAS

The 2009 H1N1 influenza pandemic revealed the limitations of current critical care capacity in all countries but no more so than in resource limited regions. Notable barriers to treatment in resource-constrained locations included lack of influenza diagnostics, vaccinations, antiviral medications and even basic monitoring devices such as blood pressure cuffs or pulse oximeters. Additionally, many countries lacked basic supportive treatment such as oxygen let alone more advanced critical care support such as mechanical ventilation or cardiopulmonary monitoring (88, 89).

Influenza vaccination remains the best defense against seasonal influenza and may play a role in reducing the severity of disease(90, 91). Unfortunately, the populations in low-income countries, which bear a disproportionate burden of disease, are least likely to have access to vaccination. In a 2012 survey of 14 African countries, only four (29%) reported availability of seasonal influenza vaccines (92). However, within these countries, less than 2% of the population that had access were actually vaccinated. Reports from Morocco,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Mongolia, Kenya and Lao PDR suggest a similar deficiency in seasonal vaccine coverage with only 2–6% of the population being vaccinated (20, 21, 31, 35). Although data supporting vaccine efficacy in low-income areas are limited, a recent prospective controlled trial of maternal influenza immunization in Bangladesh demonstrated not only reliable immunogenicity of the inactivated vaccine in pregnant woman but also decreased infection in their newborn child (93–95).

Antiviral neuraminidase inhibitors (NAIs) are the mainstay of pharmacological treatment for influenza; the principal NAI used is oseltamivir. Access to antivirals, however, has been identified as a major barrier to delivery of effective care in resource poor environments, due to poor availability or high cost. Data from Argentina demonstrated an increased severity of disease in patients who received antiviral therapy greater than 48 hours from the onset of symptoms compared to those treated earlier, including increased risk of pneumonia (66.6% vs. 33.3% p = .006), ICU admission (68% vs. 32%; p = .01), prolonged hospitalization (11 vs. 7 days), need for oxygen (61.7% vs. 38.2% p=. 0001) and mechanical ventilation (68.2% vs. 31.8% p=.002) (53). In a survey of 40 countries about the availability of NAIs, only 65% of respondents (19/31) reported these drugs being available (92).

Early initiation of antiviral therapy correlates with improved outcomes however there are significant disparities in the dispensing of these drugs (96). The increased use of NAIs in Japan correlated with decreased mortality (0.15 per 100,000 people) in contrast to the conservative distribution in Argentina, which experienced higher mortality rates (1.73 per 100,000) (97). Recently, a study demonstrated a 1.6% reduction of H1N1 mortality with each 10% increase in kilograms of oseltamivir distributed (97). While use of and timing of NAIs in ICUs found in low-income countries was not regularly reported, it is worth noting only 29–43% of patients admitted to ICUs in high-income countries received NAI within 48 hours of symptom onset (70, 71). Improved education and awareness of the efficacy and protocols for NAIs may help. Early initiation of antiviral therapy was reported to improve in Ukraine following a WHO mission there, suggesting that real time WHO guidance can affect clinical management in the middle of a pandemic (53).

Supportive care including mechanical ventilation, cardiopulmonary monitoring, and other invasive support is essential in the management of critically ill influenza patients. Mechanical ventilation was required by approximately 40–80% of patients admitted to an ICU in both low and high-income countries (Table 3) (11, 42, 57, 58, 67–72). However, many resource-constrained environments lack intensive care unit capabilities. Moreover, even many upper-middle income countries have limited healthcare infrastructure, which can be quickly overwhelmed and unable to meet the surge demand of a pandemic; in these cases, such as in Mexico, critically ill patients may be managed outside of intensive care units (11). Similar strains on resources have been identified in Chile where critical care beds and mechanical ventilators were identified as limited resources (98). Possible solutions may be to develop experienced referral centers where outcomes of patients with ARDS are improved; regionalizing critical care services may improve outcomes in pandemic disease especially in areas where these resources are already limited (99).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

A significant number of patients in high-income countries receive salvage oxygenation therapies including prone positioning, extracorporeal membrane oxygenation (ECMO), and/or neuromuscular blockade for severe influenza; these therapies require experience and expertise which likely contributes to the disparity in mortality between resource-rich and poor countries. Use of prone positioning may be a viable option for severe lung injury and/or ARDS resulting from influenza in resource-limited countries given that expensive technology is not required. Prone positioning has been shown to improve oxygenation, and more recently, mortality in patients with severe ARDS (100). It was reported as used in 3–8% of critically patients in South Korea and the Canada (58, 70, 100). In Mexico, a more resource-challenged country, prone position was implemented in 6.9% of patients admitted to ICUs in Mexico (Table 3) (11). Prone positioning has not been mentioned in any reports from resource-limited countries, but should be considered as inexpensive salvage therapy with appropriate education and training for patients with refractory hypoxia. The use of ECMO has increased in many ICU settings following improved outcomes documented in the 2009 CESAR trial. Approximately 4–7% of patients in high-income countries were treated with the use of ECMO (74). There are no reported cases of use in low-income countries. Neuromuscular paralysis has been reported in Syria and India where its use is more frequent (58.5–79.7%) compared with high-income countries such as South Korea and Canada (28–43%); this may indicate both a need for and a lack of available rescue oxygenation modalities in such settings (Table 3) (42, 58, 67, 70).

Precluding even advanced technology, some resource-limited countries report a lack of even basic supportive treatments including, for example, oxygen (68). Oxygen is considered an essential medicine by the WHO and is on the WHO's essential medicines list to guide resource-limited countries on a basic formulary. Pulse oximeters and appropriate use of oxygen therapy can reduce mortality in resource-limited environments (101). However, despite this priority, it has been cited as "never available" in 11% of hospitals in low- and middle-income countries (89). Similarly in hospitals that reported having oxygen, it was "sometimes available" 33% of the time and only "always available" 21% of the time (89). Oxygen availability in sub-Saharan Africa represents a significant challenge; while 44% (99/231) of health facilities in 12 Sub-Saharan countries surveyed in a 2007–2009 study reported access to oxygen, only 34% (75/231) reported access to relevant, needed supplies such as face masks or tubing (88).

SUMMARY

The first pandemic of the 21st century, 2009 H1N1, exposed significant gaps in the current understanding of the global burden of influenza. Lack of robust influenza epidemiology in the world's most populous and under-resourced regions heralds a major deficiency in our understanding of the true burden of influenza. Though this burden remains poorly characterized and underestimated, there is growing recognition that resource limited countries bear a disproportionate burden of morbidity and mortality from influenza globally. The difference in mortality between high- and low-resource countries is likely attributable in part to the increased prevalence of underlying high-risk comorbidities such as untreated cardiopulmonary disease, HIV and malnutrition as well as limited availability of antivirals, vaccines and or supportive care resources such as oxygen, mechanical ventilators and

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

salvage technologies such as ECMO. Influenza is a preventable and treatable cause of severe respiratory illness but resources that exist in high-income countries will need to reach patients in resource-limited countries where the burden is highest. Hopefully, improved epidemiology of influenza can help further guide allocation of preventative and supportive interventions such as vaccines, antiviral medications, and improved basic health care in order to mitigate the impact of influenza infection on these most vulnerable populations.

Abbreviations

AFRIMS	Armed Force Research Institute for Medical Sciences
APACHE II	acute physiology and chronic health evaluation
ARDS	acute respiratory distress syndrome
CDC	centers for disease control and prevention
DRC	Democratic Republic of Congo
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
GLaMOR	global pandemic mortality study
HIV	human immunodeficiency virus
ICU	intensive care unit
ILI	influenza like illness
pH1N1	pandemic H1N1 influenza virus
PCR	polymerase chain reaction
RR	relative risk
SARI	severe acute respiratory infection
SOFA	sequential organ failure assessment
TB	tuberculosis
WHO	World Health Organization

Works Cited

1. WHO. Vaccines against influenza WHO position paper - November 2012. Weekly epidemiological record. 2012; 87:461–476. [PubMed: 23210147]
2. Prevention CfDCa. [cited 2014 July 25] Available from: http://www.cdc.gov/flu/weekly/overview.htm.
3. Organization WH. [cited 2014 7/25/14] WHO surveillance case definitions for ILI and SARI 2014. Available from: http://www.who.int/influenza/surveillance_monitoring/ili_sari_surveillance_case_definition/en/.
4. Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. Emerg Infect Dis. 2006; 12(1):15–22. PubMed PMID: 16494711; PubMed Central PMCID: PMC3291398. [PubMed: 16494711]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

5. Mei ZLS, Wu X, Shao L, Hui Y, Wang J, et al. Avian influenza A (H7N9) virus infections, Shanghai, China [letter]. Emerging Infectious Diseases. 2013

6. Prevention CfDCa. [cited 2014 July 26] Highly Pathogenic Avian Influenza A (H5N1). 2014. Available from: http://www.cdc.gov/flu/avianflu/h5n1-people.htm.

7. Stohr K. The global agenda on influenza surveillance and control. Vaccine. 2003; 21(16):1744–1748. PubMed PMID: 12686087. [PubMed: 12686087]

8. Girard MP, Tam JS, Assossou OM, Kieny MP. The 2009 A (H1N1) influenza virus pandemic: A review. Vaccine. 2010; 28(31):4895–4902. PubMed PMID: 20553769. [PubMed: 20553769]

9. Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw M, Uyeki TM, Zaki SR, Hayden FG, Hui DS, Kettner JD, Kumar A, Lim M, Shindo N, Penn C, Nicholson KG. Writing Committee of the WHOCoCAoPI. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. The New England journal of medicine. 2010; 362(18):1708–1719. PubMed PMID: 20445182. [PubMed: 20445182]

10. Garcia-Basteiro AL, Llupia A, Mena G, Bayas JM, Trilla A. Quantifying the efficacy of influenza vaccines. The Lancet infectious diseases. 2012; 12(9):657–658. author reply 60-1. PubMed PMID: 22917095. [PubMed: 22917095]

11. Dominguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, Poblano-Morales M, Baltazar-Torres JA, Bautista E, Martinez A, Martinez MA, Rivero E, Valdez R, Ruiz-Palacios G, Hernandez M, Stewart TE, Fowler RA. Critically Ill patients with 2009 influenza A(H1N1) in Mexico. JAMA : the journal of the American Medical Association. 2009; 302(17):1880–1887. PubMed PMID: 19822626.

12. Viboud C, Simonsen L. Global mortality of 2009 pandemic influenza A H1N1. The Lancet infectious diseases. 2012; 12(9):651–653. PubMed PMID: 22738892. [PubMed: 22738892]

13. Azziz-Baumgartner E, Alamgir AS, Rahman M, Homaira N, Sohel BM, Sharker MA, Zaman RU, Dee J, Gurley ES, Al Mamun A, Mah EMS, Fry AM, Widdowson MA, Bresee J, Lindstrom S, Azim T, Brooks A, Podder G, Hossain MJ, Rahman M, Luby SP. Incidence of influenza-like illness and severe acute respiratory infection during three influenza seasons in Bangladesh, 2008–2010. Bulletin of the World Health Organization. 2012; 90(1):12–19. PubMed PMID: 22271960; PubMed Central PMCID: PMC3260571. [PubMed: 22271960]

14. Wangchuk S, Thapa B, Zangmo S, Jarman RG, Bhoomiboonchoo P, Gibbons RV. Influenza surveillance from November 2008 to 2011; including pandemic influenza A(H1N1)pdm09 in Bhutan. Influenza and other respiratory viruses. 2013; 7(3):426–430. PubMed PMID: 22813389. [PubMed: 22813389]

15. Barakat A, Ihazmad H, El Falaki F, Tempia S, Cherkaoui I, El Aouad R. 2009 Pandemic influenza A virus subtype H1N1 in Morocco, 2009–2010: epidemiology, transmissibility, and factors associated with fatal cases. The Journal of infectious diseases. 2012; 206(Suppl 1):S94–S100. PubMed PMID: 23169979; PubMed Central PMCID: PMC3572880. [PubMed: 23169979]

16. Dalhatu IT, Medina-Marino A, Olsen SJ, Hwang I, Gubio AB, Ekanem EE, Coker EB, Akpan H, Adedeji AA. Influenza viruses in Nigeria, 2009–2010: results from the first 17 months of a national influenza sentinel surveillance system. The Journal of infectious diseases. 2012; 206(Suppl 1):S121–S128. PubMed PMID: 23169957. [PubMed: 23169957]

17. Muyembe Tamfum JJ, Nkwembe E, Bi Shamamba SK, Bankoshi F, Ilunga BK, Katz KA, Cohen AL, Kabamba J, Wemankoy EO. Sentinel surveillance for influenzalike illness, severe acute respiratory illness, and laboratory-confirmed influenza in Kinshasa, Democratic Republic of Congo, 2009–2011. The Journal of infectious diseases. 2012; 206(Suppl 1):S36–S40. PubMed PMID: 23169969. [PubMed: 23169969]

18. Nzussouo NT, Michalove J, Diop OM, Njouom R, Monteiro Mde L, Adje HK, Manoncourt S, Amankwa J, Koivogui L, Sow S, Elkory MB, Collard JM, Dalhatu I, Niang MN, Lafond K, Moniz F, Coulibaly D, Kronman KC, Oyofo BA, Ampofo W, Tamboura B, Bara AO, Jusot JF, Ekanem E, Sarr FD, Hwang I, Cornelius C, Coker B, Lindstrom S, Davis R, Dueger E, Moen A, Widdowson MA. Delayed 2009 pandemic influenza A virus subtype H1N1 circulation in West Africa, May 2009-April 2010. The Journal of infectious diseases. 2012; 206(Suppl 1):S101–S107. PubMed PMID: 23169954. [PubMed: 23169954]

19. Radin JM, Katz MA, Tempia S, Talla Nzussouo N, Davis R, Duque J, Adedeji A, Adjabeng MJ, Ampofo WK, Ayele W, Bakamutumaho B, Barakat A, Cohen AL, Cohen C, Dalhatu IT, Daouda

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

C, Dueger E, Francisco M, Heraud JM, Jima D, Kabanda A, Kadjo H, Kandeel A, Bi Shamamba SK, Kasolo F, Kronmann KC, Mazaba Liwewe ML, Lutwama JJ, Matonya M, Mmbaga V, Mott JA, Muhimpundu MA, Muthoka P, Njuguna H, Randrianasolo L, Refaey S, Sanders C, Talaat M, Theo A, Valente F, Venter M, Woodfill C, Bresee J, Moen A, Widdowson MA. Influenza surveillance in 15 countries in Africa, 2006–2010. The Journal of infectious diseases. 2012; 206(Suppl 1):S14–S21. PubMed PMID: 23169960. [PubMed: 23169960]

20. Barakat A, Ihazmad H, Benkaroum S, Cherkaoui I, Benmamoun A, Youbi M, El Aouad R. Influenza surveillance among outpatients and inpatients in Morocco, 1996–2009. PloS one. 2011; 6(9):e24579. PubMed PMID: 21931764; PubMed Central PMCID: PMC3169614. [PubMed: 21931764]
21. Katz MA, Muthoka P, Emukule GO, Kalani R, Njuguna H, Waiboci LW, Ahmed JA, Bigogo G, Feikin DR, Njenga MK, Breiman RF, Mott JA. Results from the first six years of national sentinel surveillance for influenza in kenya, july 2007-june 2013. PloS one. 2014; 9(6):e98615. PubMed PMID: 24955962; PubMed Central PMCID: PMC4067481. [PubMed: 24955962]
22. Wane J, Nyatanyi T, Nkunda R, Rukelibuga J, Ahmed Z, Biedron C, Kabeja A, Muhimpundu MA, Kabanda A, Antara S, Briet O, Koama JB, Rusanganwa A, Mukabayire O, Karema C, Raghunathan P, Lowrance D. 2009 pandemic influenza A (H1N1) virus outbreak and response--Rwanda, October, 2009-May, 2010. PloS one. 2012; 7(6):e31572. PubMed PMID: 22745652; PubMed Central PMCID: PMC3383749. [PubMed: 22745652]
23. Bank, TW. [cited 2014 July 28] Morocco. 2014. Available from: http://www.worldbank.org/en/country/morocco.
24. Bank, TW. [cited 2014 July 28] Nigeria. 2014. Available from: http://data.worldbank.org/country/Nigeria..
25. Bank, TW. [cited 2014 July 28] Rwanda. 2014. Available from: http://data.worldbank.org/country/rwanda.
26. Nyatanyi T, Nkunda R, Rukelibuga J, Palekar R, Muhimpundu MA, Kabeja A, Kabanda A, Lowrance D, Tempia S, Koama JB, McAlister D, Mukabayire O, Wane J, Raghunathan P, Katz M, Karema C. Influenza sentinel surveillance in Rwanda, 2008–2010. The Journal of infectious diseases. 2012; 206(Suppl 1):S74–S79. PubMed PMID: 23169976. [PubMed: 23169976]
27. Bank, TW. [cited 2014 July 28] Democratic Republic of Congo. 2014. Available from: http://data.worldbank.org/country/congo-dem-rep.
28. Chadha MS, Broor S, Gunasekaran P, Potdar VA, Krishnan A, Chawla-Sarkar M, Biswas D, Abraham AM, Jalgaonkar SV, Kaur H, Klimov A, Lal RB, Moen A, Kant L, Mishra AC. Multisite virological influenza surveillance in India: 2004–2008. Influenza and other respiratory viruses. 2012; 6(3):196–203. PubMed PMID: 21955356. [PubMed: 21955356]
29. Bank, TW. [cited 2014 July 28] India. 2014. Available from: http://data.worldbank.org/country/india.
30. Bank, TW. [cited 2014 July 28] Bangladesh. 2014. Available from: http://data.worldbank.org/country/bangladesh.
31. Khamphaphongphane B, Ketmayoon P, Lewis HC, Phonekeo D, Sisouk T, Xayadeth S, Ongkhammy S, Vongphrachanh P, Tsuyuoka R, Moen A, Corwin A. Epidemiological and virological characteristics of seasonal and pandemic influenza in Lao PDR, 2008–2010. Influenza and other respiratory viruses. 2013; 7(3):304–311. PubMed PMID: 22716289. [PubMed: 22716289]
32. Bank, TW. [cited 2014 July 28] Lao PDR. 2014. Available from: http://data.worldbank.org/country/lao-pdr.
33. Bank, TW. [cited 2014 July 28] Philippines. 2014. Available from: http://data.worldbank.org/country/philippines.
34. Tallo VL, Kamigaki T, Tan AG, Pamaran RR, Alday PP, Mercado ES, Javier JB, Oshitani H, Olveda RM. Estimating influenza outpatients' and inpatients' incidences from 2009 to 2011 in a tropical urban setting in the Philippines. Influenza and other respiratory viruses. 2014; 8(2):159–168. PubMed PMID: 24393336. [PubMed: 24393336]
35. Burmaa A, Tsatsral S, Odagiri T, Suzuki A, Oshitani H, Nymadawa P. Cumulative incidence of pandemic influenza A (H1N1) 2009 by a community-based serological cohort study in Selenghe

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Province, Mongolia. Influenza and other respiratory viruses. 2012; 6(6):e97–e104. PubMed PMID: 22329794. [PubMed: 22329794]

36. Osoro EM, Munyua P, Muthoka P, Gikundi S, Njenga MK, Lifumo S, Achilla R, Waiboci L, Nzioka C, Omolo J, Feikin DR, Breiman RF, Katz MA. Hospitalized patients with pandemic (H1N1) 2009, Kenya. Emerg Infect Dis. 2011; 17(9):1744–1746. PubMed PMID: 21888810; PubMed Central PMCID: PMC3322052. [PubMed: 21888810]
37. Siddharth V, Goyal V, Koushal VK. Clinical-Epidemiological Profile of Influenza A H1N1 Cases at a Tertiary Care Institute of India. Indian journal of community medicine : official publication of Indian Association of Preventive & Social Medicine. 2012; 37(4):232–235. PubMed PMID: 23293437; PubMed Central PMCID: PMC3531016. [PubMed: 23293437]
38. Jagannatha Rao SR, Rao MJ, Swamy N, Umapathy BL. Profile of H1N1 infection in a tertiary care center. Indian journal of pathology & microbiology. 2011; 54(2):323–325. PubMed PMID: 21623082. [PubMed: 21623082]
39. Allam RR, Murhekar MV, Tadi GP, Udaragudi PR. Descriptive epidemiology of novel influenza A (H1N1), Andhra Pradesh 2009–2010. Indian journal of public health. 2013; 57(3):161–165. PubMed PMID: 24125931. [PubMed: 24125931]
40. Mathur S, Dubey T, Kulshrestha M, Agarwal H, Mathur G, Mathur A, Mathur S, Prakash P, Rajpurohit V, Gehlot G, Tak P. Clinical profile and mortality among novel influenza A (H1N1) infected patients: 2009–2010 Jodhpur, Rajasthan pandemic. The Journal of the Association of Physicians of India. 2013; 61(9):627–632. PubMed PMID: 24772700. [PubMed: 24772700]
41. Mehta AA, Kumar VA, Nair SG, F KJ, Kumar G, Singh SK. Clinical Profile of Patients Admitted with Swine-Origin Influenza A (H1N1) Virus Infection: An Experience from A Tertiary Care Hospital. Journal of clinical and diagnostic research : JCDR. 2013; 7(10):2227–2230. PubMed PMID: 24298482; PubMed Central PMCID: PMC3843408. [PubMed: 24298482]
42. Ramakrishna K, Sampath S, Chacko J, Chacko B, Narahari DL, Veerendra HH, Moorthy M, Krishna B, Chekuri V, Raju RK, Shanmugasundaram D, Pichamuthu K, Abraham AM, Abraham O, Thomas K, Mathews P, Varghese GM, Rupali P, Peter JV. Clinical Profile and Predictors of Mortality of Severe Pandemic (H1N1) 2009 Virus Infection Needing Intensive Care: A Multi-Centre Prospective Study from South India. Journal of global infectious diseases. 2012; 4(3):145–152. PubMed PMID: 23055645; PubMed Central PMCID: PMC3459431. [PubMed: 23055645]
43. Chudasama RK, Patel UV, Verma PB, Amin CD, Savaria D, Ninama R, Fichadiya N. Clinico-epidemiological features of the hospitalized patients with 2009 pandemic influenza A (H1N1) virus infection in Saurashtra region, India (September, 2009 to February, 2010). Lung India : official organ of Indian Chest Society. 2011; 28(1):11–16. PubMed PMID: 21654979; PubMed Central PMCID: PMC3099502. [PubMed: 21654979]
44. Moorthy M, Samuel P, Peter JV, Vijayakumar S, Sekhar D, Verghese VP, Agarwal I, Moses PD, Ebenezer K, Abraham OC, Thomas K, Mathews P, Mishra AC, Lal R, Muliyil J, Abraham AM. Estimation of the burden of pandemic(H1N1)2009 in developing countries: experience from a tertiary care center in South India. PloS one. 2012; 7(9):e41507. PubMed PMID: 22957015; PubMed Central PMCID: PMC3434194. [PubMed: 22957015]
45. Ortiz JR, Jacob ST, West TE. Clinical care for severe influenza and other severe illness in resource-limited settings: the need for evidence and guidelines. Influenza and other respiratory viruses. 2013; 7(Suppl 2):87–92. PubMed PMID: 24034491. [PubMed: 24034491]
46. Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, Simmerman JM, Gordon A, Sato M, Howie S, Krishnan A, Ope M, Lindblade KA, Carosone-Link P, Lucero M, Ochieng W, Kamimoto L, Dueger E, Bhat N, Vong S, Theodoratou E, Chittaganpitch M, Chimah O, Balmaseda A, Buchy P, Harris E, Evans V, Katayose M, Gaur B, O'Callaghan-Gordo C, Goswami D, Arvelo W, Venter M, Briese T, Tokarz R, Widdowson MA, Mounts AW, Breiman RF, Feikin DR, Klugman KP, Olsen SJ, Gessner BD, Wright PF, Rudan I, Broor S, Simoes EA, Campbell H. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011; 378(9807):1917–1930. PubMed PMID: 22078723. [PubMed: 22078723]
47. Dawood FS, Iuliano AD, Reed C, Meltzer MI, Shay DK, Cheng PY, Bandaranayake D, Breiman RF, Brooks WA, Buchy P, Feikin DR, Fowler KB, Gordon A, Hien NT, Horby P, Huang QS, Katz MA, Krishnan A, Lal R, Montgomery JM, Molbak K, Pebody R, Presanis AM, Razuri H, Steens

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

A, Tinoco YO, Wallinga J, Yu H, Vong S, Bresee J, Widdowson MA. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. The Lancet infectious diseases. 2012; 12(9):687–695. PubMed PMID: 22738893. [PubMed: 22738893]

48. Simonsen L, Spreeuwenberg P, Lustig R, Taylor RJ, Fleming DM, Kroneman M, Van Kerkhove MD, Mounts AW, Paget WJ, Teams GLC. Global mortality estimates for the 2009 Influenza Pandemic from the GLaMOR project: a modeling study. PLoS medicine. 2013; 10(11):e1001558. PubMed PMID: 24302890; PubMed Central PMCID: PMC3841239. [PubMed: 24302890]
49. Van Kerkhove MD, Vandemaele KA, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, Carlino LO, Owen R, Paterson B, Pelletier L, Vachon J, Gonzalez C, Hongjie Y, Zijian F, Chuang SK, Au A, Buda S, Krause G, Haas W, Bonmarin I, Taniguichi K, Nakajima K, Shobayashi T, Takayama Y, Sunagawa T, Heraud JM, Orelle A, Palacios E, van der Sande MA, Wielders CC, Hunt D, Cutter J, Lee VJ, Thomas J, Santa-Olalla P, Sierra-Moros MJ, Hanshaoworakul W, Ungchusak K, Pebody R, Jain S, Mounts AW. Infection WHOWGfRFfSHNp. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS medicine. 2011; 8(7):e1001053. PubMed PMID: 21750667; PubMed Central PMCID: PMC3130021. [PubMed: 21750667]
50. Gessner BD, Shindo N, Briand S. Seasonal influenza epidemiology in sub-Saharan Africa: a systematic review. The Lancet infectious diseases. 2011; 11(3):223–235. PubMed PMID: 21371656. [PubMed: 21371656]
51. Sertogullarindan B, Ozbay B, Gunini H, Sunnetcioglu A, Arisoy A, Bilgin HM, Mermit Cilingir B, Duran M, Yildiz H, Ekin S, Baran A. Clinical and prognostic features of patients with pandemic 2009 influenza A (H1N1) virus in the intensive care unit. African health sciences. 2011; 11(2): 163–170. PubMed PMID: 21857845; PubMed Central PMCID: PMC3158518. [PubMed: 21857845]
52. Yavarian J, Naseri M, Shadab A, Shafiei Jandaghi NZ, Mokhtari Azad T. Epidemiological aspects of pandemic influenza A(H1N1) virus from 2009 to 2011 in Iran. Influenza and other respiratory viruses. 2012; 6(6):e74–e76. PubMed PMID: 22487173. [PubMed: 22487173]
53. WHO. WHO Global Influenza Programme Report: Clinical managemet of influenza and other acute respiratory illness in resource limited settings: learning from the influenza pandemic (H1N1). 2009. 2011 [July 20, 2014]. Available from: http://www.who.int/influenza/patient_care/clinical/858-WHOGIPReport_A4_WEB_FA.pdf.
54. Cohen AL, Hellferscee O, Pretorius M, Treurnicht F, et al. Epidemiology of Influenza Virus Types and Subtypes in South Africa, 2009-2012. Emerging Infectious Diseases. 2014; 20(7):1162–1169. Epub July 2014. doi: http://dx.doi.org/10.3201/eid2007.131869. [PubMed: 24960314]
55. Archer B, Cohen C, Naidoo D, Thomas J, Makunga C, Blumberg L, Venter M, Timothy G, Puren A, McAnerney J, Cengimbo A, Schoub B. Interim report on pandemic H1N1 influenza virus infections in South Africa, April to October 2009: epidemiology and factors associated with fatal cases. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2009; 14(42) PubMed PMID: 19883549.
56. Cohen C, Moyes J, Tempia S, Groom M, Walaza S, Pretorius M, Dawood H, Chhagan M, Haffejee S, Variava E, Kahn K, Tshangela A, von Gottberg A, Wolter N, Cohen AL, Kgokong B, Venter M, Madhi SA. Severe influenza-associated respiratory infection in high HIV prevalence setting, South Africa, 2009–2011. Emerg Infect Dis. 2013; 19(11):1766–1774. PubMed PMID: 24209781; PubMed Central PMCID: PMC3837669. [PubMed: 24209781]
57. Investigators AI, Webb SA, Pettila V, Seppelt I, Bellomo R, Bailey M, Cooper DJ, Cretikos M, Davies AR, Finfer S, Harrigan PW, Hart GK, Howe B, Iredell JR, McArthur C, Mitchell I, Morrison S, Nichol AD, Paterson DL, Peake S, Richards B, Stephens D, Turner A, Yung M. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. The New England journal of medicine. 2009; 361(20):1925–1934. PubMed PMID: 19815860. [PubMed: 19815860]
58. Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, Stelfox T, Bagshaw S, Choong K, Lamontagne F, Turgeon AF, Lapinsky S, Ahern SP, Smith O, Siddiqui F, Jouvet P, Khwaja K, McIntyre L, Menon K, Hutchison J, Hornstein D, Joffe A, Lauzier F, Singh J, Karachi T, Wiebe K, Olafson K, Ramsey C, Sharma S, Dodek P, Meade M, Hall R, Fowler RA. Canadian Critical Care Trials Group HNC. Critically ill patients with 2009 influenza A(H1N1) infection in Canada.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

JAMA : the journal of the American Medical Association. 2009; 302(17):1872–1879. PubMed PMID: 19822627.

59. Rice TW, Rubinson L, Uyeki TM, Vaughn FL, John BB, Miller RR 3rd, Higgs E, Randolph AG, Smoot BE, Thompson BT, Network NA. Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. Critical care medicine. 2012; 40(5):1487–1498. PubMed PMID: 22511131; PubMed Central PMCID: PMC3653183. [PubMed: 22511131]
60. Beck MA, Nelson HK, Shi Q, Van Dael P, Schiffrin EJ, Blum S, Barclay D, Levander OA. Selenium deficiency increases the pathology of an influenza virus infection. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2001; 15(8):1481–1483. PubMed PMID: 11387264. [PubMed: 11387264]
61. Taylor AK, Cao W, Vora KP, De La Cruz J, Shieh WJ, Zaki SR, Katz JM, Sambhara S, Gangappa S. Protein energy malnutrition decreases immunity and increases susceptibility to influenza infection in mice. The Journal of infectious diseases. 2013; 207(3):501–510. PubMed PMID: 22949306. [PubMed: 22949306]
62. Bellei NC, Carraro E, Castelo A, Granato CF. Risk factors for poor immune response to influenza vaccination in elderly people. The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases. 2006; 10(4):269–273. PubMed PMID: 17293910.
63. Adegbola RA, Falade AG, Sam BE, Aidoo M, Baldeh I, Hazlett D, Whittle H, Greenwood BM, Mulholland EK. The etiology of pneumonia in malnourished and well-nourished Gambian children. The Pediatric infectious disease journal. 1994; 13(11):975–982. PubMed PMID: 7845751. [PubMed: 7845751]
64. Katona P, Katona-Apte J. The interaction between nutrition and infection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2008; 46(10): 1582–1588. PubMed PMID: 18419494. [PubMed: 18419494]
65. Rothberg MB, Haessler SD, Brown RB. Complications of viral influenza. The American journal of medicine. 2008; 121(4):258–264. PubMed PMID: 18374680. [PubMed: 18374680]
66. Short KR, Kroeze EJ, Fouchier RA, Kuiken T. Pathogenesis of influenza-induced acute respiratory distress syndrome. The Lancet infectious diseases. 2014; 14(1):57–69. PubMed PMID: 24239327. [PubMed: 24239327]
67. Alsadat R, Dakak A, Mazlooms M, Ghadhban G, Fattoom S, Betelmal I, Abouchala N, Kherallah M. Characteristics and outcome of critically ill patients with 2009 H1N1 influenza infection in Syria. Avicenna journal of medicine. 2012; 2(2):34–37. PubMed PMID: 23210019; PubMed Central PMCID: PMC3507075. [PubMed: 23210019]
68. Bai L, Gu L, Cao B, Zhai XL, Lu M, Lu Y, Liang LR, Zhang L, Gao ZF, Huang KW, Liu YM, Song SF, Wu L, Yin YD, Wang C. Clinical features of pneumonia caused by 2009 influenza A(H1N1) virus in Beijing, China. Chest. 2011; 139(5):1156–1164. PubMed PMID: 20864615. [PubMed: 20864615]
69. Nicolay N, Callaghan MA, Domegan LM, Oza AN, Marsh BJ, Flanagan PC, Igoe DM, O'Donnell JM, O'Flanagan DM, O'Hora AP. Epidemiology, clinical characteristics and resource implications of pandemic (H1N1) 2009 in intensive care units in Ireland. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2010; 12(4):255–261. PubMed PMID: 21143086. [PubMed: 21143086]
70. Hong SB, Choi EY, Kim SH, Suh GY, Park MS, Lee MG, Lim J, Lee HK, Kim SC, Kim SJ, Kim KU, Kwak SH, Koh Y. Korean Society of Critical Care Medicine HNC. Epidemiological analysis of critically ill adult patients with pandemic influenza A(H1N1) in South Korea. Epidemiology and infection. 2013; 141(5):1070–1079. PubMed PMID: 22853817. [PubMed: 22853817]
71. Bramley AM, Dasgupta S, Skarbinski J, Kamimoto L, Fry AM, Finelli L, Jain S, Pandemic Influenza AVHIT. Intensive care unit patients with 2009 pandemic influenza A (H1N1pdm09) virus infection - United States, 2009. Influenza and other respiratory viruses. 2012; 6(6):e134–e142. PubMed PMID: 22672249. [PubMed: 22672249]
72. Damak H, Chtara K, Bahloul M, Kallel H, Chaari A, Ksibi H, Chaari A, Chelly H, Rekik N, Ben Hamida C, Bouaziz M. Clinical features, complications and mortality in critically ill patients with 2009 influenza A(H1N1) in Sfax, Tunisia. Influenza and other respiratory viruses. 2011; 5(4):230–240. PubMed PMID: 21651733. [PubMed: 21651733]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

73. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. The Journal of infectious diseases. 2008; 198(7):962–970. PubMed PMID: 18710327; PubMed Central PMCID: PMC2599911. [PubMed: 18710327]
74. McCullers JA. The co-pathogenesis of influenza viruses with bacteria in the lung. Nature reviews Microbiology. 2014; 12(4):252–562. PubMed PMID: 24590244.
75. Madjid M, Miller CC, Zarubaev VV, Marinich IG, Kiselev OI, Lobzin YV, Filippov AE, Casscells SW 3rd. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. European heart journal. 2007; 28(10):1205–1210. PubMed PMID: 17440221. [PubMed: 17440221]
76. Ison MG, Campbell V, Rembold C, Dent J, Hayden FG. Cardiac findings during uncomplicated acute influenza in ambulatory adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2005; 40(3):415–422. PubMed PMID: 15668866. [PubMed: 15668866]
77. Karjalainen J, Nieminen MS, Heikkila J. Influenza A1 myocarditis in conscripts. Acta medica Scandinavica. 1980; 207(1–2):27–30. PubMed PMID: 7368969. [PubMed: 7368969]
78. Erden I, Erden EC, Ozhan H, Basar C, Yildirim M, Yalcin S, Aydin LY, Dumlu T. Echocardiographic manifestations of pandemic 2009 (H1N1) influenza a virus infection. The Journal of infection. 2010; 61(1):60–65. PubMed PMID: 20430056. [PubMed: 20430056]
79. Fagnoul D, Pasquier P, Bodson L, Ortiz JA, Vincent JL, De Backer D. Myocardial dysfunction during H1N1 influenza infection. Journal of critical care. 2013; 28(4):321–327. PubMed PMID: 23566732. [PubMed: 23566732]
80. Dong M, Liu T, Li G. Association between acute infections and risk of acute coronary syndrome: a meta-analysis. International journal of cardiology. 2011; 147(3):479–482. PubMed PMID: 21296437. [PubMed: 21296437]
81. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. The Lancet infectious diseases. 2009; 9(10):601–610. PubMed PMID: 19778762. [PubMed: 19778762]
82. Naghavi M, Barlas Z, Siadaty S, Naguib S, Madjid M, Casscells W. Association of influenza vaccination and reduced risk of recurrent myocardial infarction. Circulation. 2000; 102(25):3039–3045. PubMed PMID: 11120692. [PubMed: 11120692]
83. Gurfinkel EP, de la Fuente RL, Mendiz O, Mautner B. Influenza vaccine pilot study in acute coronary syndromes and planned percutaneous coronary interventions: the FLU Vaccination Acute Coronary Syndromes (FLUVACS) Study. Circulation. 2002; 105(18):2143–2147. PubMed PMID: 11994246. [PubMed: 11994246]
84. Mamas MA, Fraser D, Neyses L. Cardiovascular manifestations associated with influenza virus infection. International journal of cardiology. 2008; 130(3):304–309. PubMed PMID: 18625525. [PubMed: 18625525]
85. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. The New England journal of medicine. 2003; 348(14):1322–1332. PubMed PMID: 12672859. [PubMed: 12672859]
86. Udell JA, Zawi R, Bhatt DL, Keshtkar-Jahromi M, Gaughran F, Phrommintikul A, Ciszewski A, Vakili H, Hoffman EB, Farkouh ME, Cannon CP. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. JAMA : the journal of the American Medical Association. 2013; 310(16):1711–1720. PubMed PMID: 24150467.
87. Singleton JA, Wortley P, Lu PJ. Influenza vaccination of persons with cardiovascular disease in the United States. Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital. 2004; 31(1):22–27. PubMed PMID: 15061622; PubMed Central PMCID: PMC387428.
88. Belle J, Cohen H, Shindo N, Lim M, Velazquez-Berumen A, Ndihokubwayo JB, Cherian M. Influenza preparedness in low-resource settings: a look at oxygen delivery in 12 African countries. Journal of infection in developing countries. 2010; 4(7):419–424. PubMed PMID: 20818088. [PubMed: 20818088]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

89. Kushner AL, Cherian MN, Noel L, Spiegel DA, Groth S, Etienne C. Addressing the Millennium Development Goals from a surgical perspective: essential surgery and anesthesia in 8 low- and middle-income countries. Archives of surgery. 2010; 145(2):154–159. PubMed PMID: 20157083. [PubMed: 20157083]

90. Catania J, Que LG, Govert JA, Hollingsworth JW, Wolfe CR. High intensive care unit admission rate for 2013–2014 influenza is associated with a low rate of vaccination. American journal of respiratory and critical care medicine. 2014; 189(4):485–487. PubMed PMID: 24512430; PubMed Central PMCID: PMC3977724. [PubMed: 24512430]

91. Fischer WA, Hayden F. Georgiev KW, John McGowan. Antivirals for Influenza: Novel Agents and Approaches. Vassil St. National Institute of Allergy and Infectious Diseases, NIH Frontiers in Research2008. :179–192.

92. Duque J, McMorrow ML, Cohen AL. Influenza vaccines and influenza antiviral drugs in Africa: are they available and do guidelines for their use exist? BMC public health. 2014; 14:41. PubMed PMID: 24433304; PubMed Central PMCID: PMC3898391. [PubMed: 24433304]

93. Ortiz JR, Englund JA, Neuzil KM. Influenza vaccine for pregnant women in resource-constrained countries: a review of the evidence to inform policy decisions. Vaccine. 2011; 29(27):4439–4452. PubMed PMID: 21550377. [PubMed: 21550377]

94. Steinhoff MC, Omer SB, Roy E, Arifeen SE, Raqib R, Altaye M, Breiman RF, M BBSK. Influenza immunization in pregnancy--antibody responses in mothers and infants. The New England journal of medicine. 2010; 362(17):1644–1646. PubMed PMID: 20427817. [PubMed: 20427817]

95. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, Omer SB, Shahid NS, Breiman RF, Steinhoff MC. Effectiveness of maternal influenza immunization in mothers and infants. The New England journal of medicine. 2008; 359(15):1555–1564. PubMed PMID: 18799552. [PubMed: 18799552]

96. 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. The Journal of infectious diseases. 2013; 207(4):553–563. PubMed PMID: 23204175; PubMed Central PMCID: PMC3549600. [PubMed: 23204175]

97. Miller PE, Rambachan A, Hubbard RJ, Li J, Meyer AE, Stephens P, Mounts AW, Rolfes MA, Penn CR. Supply of neuraminidase inhibitors related to reduced influenza A (H1N1) mortality during the 2009–2010 H1N1 pandemic: an ecological study. PloS one. 2012; 7(9):e43491. PubMed PMID: 22984431; PubMed Central PMCID: PMC3439456. [PubMed: 22984431]

98. Ugarte S, Arancibia F, Soto R. Influenza A pandemics: clinical and organizational aspects: the experience in Chile. Critical care medicine. 2010; 38(4 Suppl):e133–e137. PubMed PMID: 19935412. [PubMed: 19935412]

99. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. The New England journal of medicine. 2006; 355(1):41–50. PubMed PMID: 16822995. [PubMed: 16822995]

100. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L, Group PS. Prone positioning in severe acute respiratory distress syndrome. The New England journal of medicine. 2013; 368(23):2159–2168. PubMed PMID: 23688302. [PubMed: 23688302]

101. Duke T, Wandi F, Jonathan M, Matai S, Kaupa M, Saavu M, Subhi R, Peel D. Improved oxygen systems for childhood pneumonia: a multihospital effectiveness study in Papua New Guinea. Lancet. 2008; 372(9646):1328–1333. PubMed PMID: 18708248. [PubMed: 18708248]

102. Bank, TW. Country and Lending Groups. [cited 2014 July 29] Data. 2014. Available from: http://data.worldbank.org/about/country-and-lending-groups.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Highlights

- The epidemiology of influenza is largely based on data from resource-rich countries
- Emerging data indicate that influenza is the etiology of 8–40% of influenzalike-illness and 5–27% of severe acute respiratory illness in low-income countries
- The lack of access to healthcare and adequate healthcare infrastructure portends a disproportionate burden of influenza disease in resource-constrained environments
- Cardiopulmonary comorbidities are important risk factors for severe influenza
- Improved influenza surveillance is needed to guide resource allocation and basic healthcare infrastructure development

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 1

Influenza sentinel surveillance in low and lower-middle income countries during the first year of the 2009 H1N1 influenza pandemic

Country (Region)	Income	Population (millions) #	Date of Surveillance	Total Samples	Influenza Positive [n(%)]	ILI P ositive for Influenza [n(%)]	SAR I Positive for Influenza [n(%)]
North Africa							
Morocco	Lower middle	33	June 2009 - Feb 2010	3937	1452 (37%)*	1056 (40%)*	342 (27%)*
West Africa							
Guinea	Low	12	May 2009-April 2010	98	12 (12%)	**NR**	**NR**
Mali	Low	15	May 2009-April 2010	422	53 (13%)	**NR**	**NR**
Niger	Low	18	May 2009-April 2010	388	90 (23%)	**NR**	**NR**
Nigeria	Lower middle	174	April 2009 - August 2010	2803	217 (8%)	167 (8%)	17 (5%)
Sub-Saharan Africa							
Rwanda	Low	12	2009–2010	2552	369 (15%)	273 (25%)	96 (7%)
Kenya	Low	44	2009–2010	15687	1992 (13%)	1030 (15%)	962 (11%)
Democratic Republic of Congo	Low	66	January 2009-December 2009	1311	249 (19%)	208 (20%)	41 (16%)
Tanzania	Low	49	2009–2010	1810	154 (9%)	97 (9%)	57 (8%)
Asia							
India (South)	Lower middle	1,252	May 2009-April 2010	2588	699 (27%)	489 (35%)	210 (18%)
India (Andhra Pradesh)	Lower middle	1,252	May 2009–2010	6527	1480 (23%)	**NR**	**NR**
Bangladesh	Low	157	2009–2010	2377	391 (16%)	273 (17%)	118 (16%)
Bhutan	Lower middle	<1	2009–2011	2149	711 (33%)	**NR**	**NR**
Laos PDR	Lower middle	7	January 2008-December 2010	2338#	523 (22%)	523 (22%)	**NR**
Philipines	Lower middle	98	January 2009- December 2010	5,616	1220 (22%)	1068 (26%)	152 (11%)

NR- Not recorded; ILI - Influenza-like illness; #ILI only; pH1N1 - 2009 pandemic H1N1;

*pH1N1 only Income status as defined by the World Bank (102).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2

Mortality of hospitalized patients with influenza in low and lower-middle income countries during th

Country (Region)	Income level	Date of Surveillance	Hospitalized [n]	Case Fatality Rate [%]
India (South)	Lower middle	May 2009-April 2010	50	68%
India	Lower middle	May 2009 - April 2010	54	55%
India (Jodhpur Rajasthan)	Lower middle	2009–2010	221	36%
India (Kerala)	Lower middle	June 2009-December 2011	88	7%
India (Saurashtra)	Lower middle	September 2009 - February 2	274	25%
India	Lower middle	August 209-April 2010	20	25%
India (Andhra Pradesh)	Lower middle	2009–2010	1480	7%
India (Western)	Lower middle	August 2009 - February 2010	63	22%
Kenya	Low	June 2009 - Nov 2009	88	4%

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 3

Intensive Care Unit demographics, therapies and outcomes in lower-middle, upper-middle, and high-income levels

Country	Income Level	Study Date	Number of Patients [n]	Women [n(%)]	ARDS [n(%)]	Mechanical Ventilator [n(%)]	Vasopressors [n(%)]	Paralysis [n(%)]	Prone [n(%)]	HFOV [n(%)]	ECMO [n(%)]	SOFA	APACHE II	Mortality [n(%)]
India	Lower middle	September 2009-December 2009	106	64 (60%)	85 (80%)	18 (17%)	NR	62 (59%)	NR	NR	NR	5.5	14.4	49%
Syria	Lower middle	2009	80	32 (40%)	58 (73%)**	59 (74%)	NR	47 (80%)	NR	NR	NR	5	15.2	51%
Mexico	Upper Middle	2009	58	31 (53%)	NR	48 (82.7%)	34 (59%)	NR	4 (7%)	1 (2%)	0	9	20.1	35%*
Tunisia	Upper Middle	November 2009 - Jan 2010	32	14 (44%)	21 (34%)	15 (46.9%)	7 (22%)	NR	NR	NR	NR	4	NR	9 (28%)
South Korea	High	September 2009-February 2010	245	111 (45%)	136 (56%)	162 (66.1%)	88 (36%)	106 (43%)	21 (9%)	NR	12 (5%)	7.7	19.1	80 (33%)
Ireland	High	July 2009 - June 2010	77	37 (49%)	47 (62%)	50 (64.9%)	39 (51%)	NR	NR	17 (22%)	4 (7%)	5.9	NR	14 (18%)
Canada	High	2009	168	113 (67%)	73%	128 (76.2%)	55 (33%)	47 (28%)	5 (3%)	10 (12%)	7 (4%)	6.8	19.7	14%
Australia/New Zealand	High	2009	722	376 (52%)	336 (49)%	64.60%	NR	NR	NR	NR	53/706 (8%)	NR	NR	14%
US	High	2009	154	23 (50%)	48 (38%)	58%	NR	NR	NR	NR	NR	NR	NR	24%
US	High	May - June 2009	47	27 (57%)	30 (64%)	NR	NR	NR	NR	NR	NR	7	21	17%

** ALI or ARDS

Glob Heart. Author manuscript; available in PMC 2015 October 31.