Global Burden of Influenza as a Cause of Cardiopulmonary Morbidity and Mortality

William A. Fischer II*,†, Michelle Gong‡, Satish Bhagwanjee§, Jonathan Sevransky||

Chapel Hill, NC, USA; Bronx, NY, USA; Seattle, WA, USA; and Atlanta, GA, USA

ABSTRACT

Severe acute respiratory infections, 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% to 27% of all severe acute respiratory infections. The increased burden of disease in this setting is multifactorial and likely is the result of higher rates of comorbidities such as human immunodeficiency virus, decreased access to health care, including vaccinations and antiviral medications, and limited healthcare infrastructure, including oxygen therapy or critical care support. Improved global epidemiology of influenza is desperately needed to guide allocation of life-saving resources, including vaccines, antiviral medications, and direct the improvement of basic health care to mitigate the impact of influenza infection on the most vulnerable populations.

Severe acute respiratory infections (SARI) including influenza represent a leading cause of global morbidity and mortality. Each year, an estimated 5% to 10% of adults and 20% to 30% of children are infected with influenza, resulting in 3 to 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 healthcare infrastructure, and shortages of healthcare personnel. This includes poor availability of vaccinations and critical care support, and the high prevalence of comorbidities such as human immunodeficiency virus (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 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 spreading rapidly. The most severe pandemic occurred in 1918 when an influenza virus crossed over from birds to humans and killed an estimated 50 to 100 million people with a mortality rate of approximately 2% to 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 they 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 World Health Organization (WHO) launched the Global Agenda for Influenza Surveillance and Control in 2001, which prioritized influenza 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.

This work was supported by grants from the National Institutes of Health (#AG045088 [W.F.] and KL2TR001109), the Infectious Disease Society of America Young Investigator Award in Geriatrics (W.F.), the Association of Specialty Providers T. Franklin Williams Award (W.F.), and a Center for AIDS Research Award (W.F.). Dr. Gong has received research funding from the National Heart, Lung, and Blood Institute (HL10871203, HL12299801, HL12511901) and the Centers from Medicaid and Medical Services. The other authors report no relationships that could be construed as a conflict of interest.

From the *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; †The Center for Environmental Medicine, Asthma and Lung Biology, The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA; ‡Albert Einstein College of Medicine, Bronx, NY, USA; §Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA, USA; and the ||Division of Pulmonary, Allergy and Critical Care Medicine, Emory University, Atlanta, GA, USA. Correspondence: W. A. Fischer II (William_Fischer@med.unc.edu).

GLOBAL HEART

VOL. 9, NO. 3, 2014
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2014.08.004

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, 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 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 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.

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-income 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)." A total of 1,941 articles were identified and evaluated for content, including primary data related to sentinel surveillance of patients with influenza between 2009 and 2010. Of those, 1,823 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) [13–23].

North Africa

Morocco. Morocco is a country of 33 million people located in Northwest Africa [24]. In line with the WHO Global Agenda for Influenza Surveillance and Control, Morocco strengthened influenza sentinel surveillance in 2007. As a result, 3,102 respiratory samples were collected between 2007 and 2009 with 98 (3%) of these samples positive for influenza [20]. The emergence of the 2009 H1N1 pandemic led to increased surveillance resulting in the collection of 3,937 samples between June 2009 and February 2010 alone [15]. Of these, approximately 1,452 (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, which highlights the poor outcome of severe influenza in Morocco. Whereas severe disease was observed with similar frequency in all age groups (19% in children <5 years, 33% in children 5 to 14, 27% in those 15 to 24; 33% in those 25 to 59, and 25% in those >60), death occurred to a greater extent in adults between the ages of 25 and 59 years, which is 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% to 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 ≥1 case of 2009 H1N1 influenza, 75% of countries (12 of 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 of 98 (12%), 53 of 422 (13%), and 90 of 388 (23%) 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 2009); 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 WHO's African Region's Integrated Disease Surveillance and Response strategy [25]. Between 2009 and 2010, 2,803 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 patients (8%) tested