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Role of Influenza among Adult Respiratory Hospitalizations: a Systemic Review

Melissa Whaley

Abstract

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Role of Influenza among Adult Respiratory Hospitalizations: a Systematic Review
(Under the direction of Dr. Lisa Casanova, faculty member)

With the threat of avian influenza, influenza laboratory testing and surveillance capacity has increased globally. Data from global surveillance activities have been used to identify circulating influenza strains for vaccine policy decisions, and have provided evidence of influenza disease among various populations. A recent meta-analysis, which includes findings from these surveillance efforts, has shown that influenza contributes to 10% of pediatric respiratory hospitalizations. Although statistical models indicate a high burden of influenza-associated morbidity among older adults and pandemic studies reveal an increase in hospitalizations among young adults, the global burden of seasonal influenza among adults remains unknown. In order to estimate the global burden of seasonal influenza among adult respiratory hospitalizations, we conducted a systematic review of the published literature, and identified 48 eligible articles published between January 1996 and June 2012 that met our inclusion criteria. We combined these published datasets with 29 eligible, unique datasets from year-round, influenza hospital-based surveillance. These combined data covered 50 countries with varying income and vaccine policies. Extracting numbers tested and positive for influenza, we calculated crude median positive proportions and evaluated potential differences in crude proportions among variables using Kruskal-Wallis non-parametric tests. We observed differences by data source and country development status when we included the 2009 pandemic year. With the exclusion of the 2009 pandemic year, we then generated adjusted pooled estimates using the log binomial model. We found 11% of cases from adult respiratory hospitalizations worldwide were laboratory-confirmed for influenza. This pooled estimate was independent of age but increased as country development or income level decreased. Our findings suggest that influenza is an important contributor to severe acute respiratory illness among both young and older adult populations. For countries without reliable influenza data, we provide an estimate that they may use in planning and allocating resources for the control and prevention of influenza.

ROLE OF INFLUENZA AMONG ADULT RESPIRATORY HOSPITALIZATIONS: A SYSTEMATIC REVIEW

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Chapter I Introduction

1.1 Background

Respiratory diseases remain the second leading cause of deaths globally. Influenza contributes to this global mortality (Ferkol & Schraufnagel, 2014). According to the World Health Organization (WHO), an estimated 200,000 to 500,000 deaths and 3 to 5 million hospitalizations annually are attributable to influenza (WHO, 2014b). This burden is due in part to the mutable nature of the influenza virus, which causes seasonal epidemics and potentially pandemics (CDC, 2012, 2013). The only current means of influenza prevention is through vaccination (CDC, 2012, 2013; Fiore, Bridges, & Cox, 2009). Although influenza vaccination and other interventions have been associated with reductions in influenza disease many countries do not have sufficient evidence on the burden of influenza to support the implementation of such interventions (Bresee et al., 2013; Partridge & Kieny, 2013; Radin et al., 2012).

High-income, developed countries have found evidence of the high influenza disease burdens among young children and older adults, through modeling approaches and hospital-based surveillance (W. W. Thompson, Shay, Weintraub, & et al., 2004; Zhou et al., 2012). The recent advancement and expansion of both approaches has afforded developing countries and countries with complicated influenza seasons the ability to monitor influenza disease (Savy et al., 2013; Simmerman & Uyeki, 2008) (Gessner, Shindo, & Briand, 2011; Mmbaga et al., 2012; Radin et al., 2012; Savy et al., 2013). Combining the data from these advancements and from a systematic review, two meta-analyses have estimated the global burden of seasonal influenza in pediatric respiratory hospitalizations (Lafond et al., 2014; Nair et al., 2011). The meta-analyses revealed substantial morbidity among the pediatric population globally (~1 million cases of severe acute lower respiratory infections, 374,000 to 870,000 hospitalizations), with school-aged children bearing the highest burden (Lafond et al., 2014; Nair et al., 2011).

While global burden is not known for adults, certain adult populations are at higher risk of disease. Adults who care for ill children or patients are at an increased risk of influenza disease (Kuster et al., 2011; Dena L. Schanzer, Langley, & Tam, 2008a; Mauskopf, Klesse, Lee, & Herrera-Taracena, 2013). Complications as a result of disease have been observed in individuals with underlying conditions (C. Cohen et al., 2012; Gessner et al., 2011; Mauskopf et al., 2013; Dena L. Schanzer et al., 2008a). The increased risk of influenza disease and complications associated with disease is especially high during pandemics (CDC, 2013; N. J. Cox & Subbarao, 2000; F. S. Dawood et al., 2012; Kuster et al., 2011; Dena L. Schanzer et al., 2008a). Similarly to previous pandemics, an estimated 65% of deaths associated with the 2009 pandemic H1N1 influenza virus was observed globally among adults <65 years old (N. J. Cox & Subbarao, 2000; F. S. Dawood et al., 2012).

In preparation for future pandemics, WHO is working with country officials and stakeholders to increase vaccine supply and to encourage influenza vaccine research and development (Friede et al., 2011). With sufficient supply of effective influenza vaccines, countries across the global will potentially reduce case-fatalities and prevent the breakdown of health and social services (Friede et al., 2011). Research and development will lead to improved treatment options, prevention strategies, and diagnostics (Stohr, 2003; Yu et al., 2014).

Due to competing priorities and limited resources, many countries have not implemented policies to control and prevent influenza disease (Ayele et al., 2012; Samaan, McPherson, & Partridge, 2013) leaving their populations susceptible to influenza disease (Friede et al., 2011; Partridge & Kieny, 2013). Middle and low income countries without established influenza vaccine policies report the largest burden of influenza morbidity and mortality within Asia, Africa, and Latin America and the Caribbean, and among the pediatric population worldwide (Gessner et al., 2011; Lafond et al., 2014; Nair et al., 2011; Savy et al., 2013; Simmerman & Uyeki, 2008). These high burden estimates, obtained from hospital-based surveillance and summed through meta-analyses, may provide the needed evidence to advocate for investments in influenza control and prevention measures, which will in turn improve the global pandemic

preparedness and response (Friede et al., 2011; Gordis, 2009; Schoub, 2010; WHO, 2005).

Although current systematic reviews and meta-analyses shed light on the high influenza burdens in developing countries and within the global pediatric population, little is known about the global burden of influenza among the adult populations (Gessner et al., 2011; Kuster et al., 2011; Dena L. Schanzer et al., 2008a). A recent publication suggests higher incidences of respiratory failure due to influenza among hospitalized adults than among pediatric patients (Ortiz et al., 2013). Through this systematic review of published and unpublished influenza-associated hospitalization datasets, we provide an estimate for the global burden of influenza among adult respiratory hospitalizations. This estimate may be used to guide influenza policy, assisting the needs assessment for interventions, in countries without reliable influenza data, and to support global programs that establish and sustain influenza surveillance, laboratory testing, and vaccine manufacturing capacity.

1.2 Purpose of study

The purpose of this study is to estimate the global proportion of influenza in adult acute respiratory hospitalizations through a systematic review.

1.3 Research questions:

1. What is the estimated global proportion of adult (≥18 years old) acute respiratory hospitalizations due to seasonal influenza?
2. Of these hospitalizations, is a higher influenza-positive proportion observed among older adults (≥65 years old) than younger adults (18-64 years old)?
3. Do influenza positive proportions differ by WHO regions?
4. Do the positive proportions vary by country income levels and/or developmental status?
5. Due to the variability of laboratory tests (differences in sensitivity and specificity between different laboratory tests) and clinical presentations, do the test performance and/or case definitions impact the positive proportions?
6. How does the pandemic H1N1 data impact the positive proportions?

Chapter II Literature Review

Influenza has caused morbidity and mortality throughout the centuries globally. The first documented influenza pandemic was in 1580 (CDC, 2012). An estimated 20-30 million or more deaths resulted from the Spanish influenza pandemic in 1918 (CDC, 2012). In 2009, approximately 60 million cases of pandemic influenza A (H1N1) were reported in the United States alone (CDC, 2012). Of these cases, 270,000 were hospitalized and 12,500 died (CDC, 2012). Other influenza pandemics occurred in 1957 (H2N2) and 1968 (H3N2, WHO 2005). During non-pandemic years, "seasonal" influenza viruses contribute to morbidity and mortality worldwide (L. Simonsen et al., 1997). Viboud *et al.* estimated that 1 million annual deaths worldwide are attributable to influenza (Cécile Viboud, Alonso, & Simonsen, 2006).

2.1 Influenza Viruses

Influenza is a single-stranded RNA virus of the Orthomyxovirus family (CDC, 2012). Three types of influenza cause disease in humans—type A, B, and C (CDC, 2012). Type C is thought to be the least virulent, typically causing subclinical infections in children and young adults (CDC, 2012; Greenbaum, Morag, & Zakay-Rones, 1998; White & Fenner, 1994). Greenbaum *et al* and others report sporadic cases of influenza type C during influenza types A and B outbreaks (Greenbaum et al., 1998; Taylor, 1951).

In recent years, the burden of influenza type B illness has reportedly increased in the United States and the United Kingdom (W.P. Glezen, Schmier, Kuehn, Ryan, & Oxford, 2013). Type B viruses are divided into two genetic lineages, Victoria and Yamagata (CDC, 2012, 2013). These lineages may co-circulate (CDC, 2013). *In vitro* analysis suggests that type B is a more stable virus, with a slower mutation rate than type A (CDC, 2013; W.P. Glezen et al., 2013); the same lineage (Victoria) included in the trivalent vaccine for last 10 years (CDC, 2013). Five of those ten years, the vaccine lineage was predominant (CDC, 2013). While lineage is the same, the vaccine strain

changes similarly to type A subtypes (WHO, 2014c). Generally, type B infections are primarily found in children (CDC, 2013).

Type A is categorized into subtypes by surface antigens, hemagglutinin (HA) and neuraminidase (NA) (CDC, 2012, 2013; White & Fenner, 1994). HA (H1-16) promotes viral attachment to host cell, while NA allows the virus to penetrate the cell (CDC, 2012, 2013; White & Fenner, 1994). HA in human flu viruses are genetically similar to those isolated from birds and pigs (CDC, 2013). In 2013, human cases of H7N9, resulting from a triple assortment, were identified and thought to be associated with open markets selling birds (Liu et al., 2014).

Influenza viruses undergo frequent antigenic change during viral replication (CDC, 2013). Small changes occur within the genes coded for the antigen-binding sites of the virus, known as antigenic drift (CDC, 2012, 2013). Antigenic drift may lead to epidemics, since these changes may result in a new, unrecognizable virus to the host's immune system (CDC, 2012). Epidemics are reported annually for types A and B (CDC, 2012, 2013; W.P. Glezen et al., 2013). In the United States, annual influenza epidemics account for 114,000 hospitalizations and 20,000 deaths (Brammer et al., 2002). Type A viruses experience antigenic drift more frequently and more rapidly than types B (CDC, 2013). Type A viruses may also undergo recombination events, where not seen before surface antigens arise (CDC, 2012, 2013; White & Fenner, 1994). This phenomenon is known as antigenic shift (CDC, 2012, 2013; White & Fenner, 1994). Antigenic shift promotes the greatest change potentially resulting in pandemics where little or no pre-existing immunity exists and when the new virus effectively transmits from human to human (CDC, 2013). Antigenic shifts are thought to occur approximately every 20 years, while antigenic drifts occur all the time (CDC, 2012). Pandemics have higher attack rates than epidemics (CDC, 2012, 2013). Gordan *et al* found attack rates doubled for pandemic H1N1 (20.1%) in comparison to the 2007 seasonal influenza (11.7%) among children in Nicaragua (Gordon et al., 2010). While severe disease during annual epidemics often disproportionately affects certain age groups (<5 and ≥65 years old) and individuals with comorbidities, pandemics have a wider impact across age groups and health statuses, including healthy young individuals (CDC, 2012; WHO, 2012a). However, seasonal epidemics can occasionally cause spikes in severe respiratory illness

in young, healthy individuals as well, as observed in the 2003-2004 season (CDC, 2014a; WHO Collaborating Center for Surveillance et al., 2004).

2.2 Transmission, Clinical Presentations, and Diagnosis

The main mode of influenza transmission is through direct or indirect, via contaminated object, contact with respiratory droplets from an infected individual (Weinstein, Bridges, Kuehnert, & Hall, 2003). One to four days after contact, newly infected individuals may exhibit the classic influenza symptoms: abrupt onset of fever, myalgia, sore throat, nonproductive cough, and/or headache (CDC, 2012). These symptoms are often used to describe other pathogenic infections (CDC, 2012; Harper et al., 2009; Weinstein et al., 2003). Influenza infections are generally self-limiting and can be asymptomatic (Harper et al., 2009). In fact, 50% of influenza-infected individuals present symptoms (CDC, 2012). The clinical course of influenza infections depend on the individual's health as well as on the circulating influenza strain (CDC, 2012). Influenza infections may progress to severe pneumonia, primary influenza pneumonia or secondary bacterial pneumonia (Bader & McKinsey, 2005; CDC, 2012). Influenza was identified as one of the leading causes of community acquired pneumonia hospitalizations among adults in Vietnam and acute respiratory illness case-fatalities among adults in Guatemala (Takahashi et al., 2013; Verani et al., 2013). Influenza infections have led to the exacerbations of underlying medical conditions, such as myocarditis and chronic pulmonary diseases (CDC, 2012; Harper et al., 2009; Dena L. Schanzer, Langley, & Tam, 2008b).

As influenza illness presents similarly to many other respiratory pathogens and cannot be diagnosed by clinical presentation alone, infection needs to be confirmed through laboratory testing (Weinstein et al., 2003). These laboratory tests may include viral culture, direct or indirect immunofluorescence, serology (such as antigen complement fixation assay, hemagglutination inhibition assay, and enzyme-linked immunosorbent assays), single or multiplex polymerase chain reaction (PCR), and rapid antigen tests (Kumar & Henrickson, 2012; Talbot & Falsey, 2010). Laboratory tests vary in required technical skills and/or specialized equipment, turnaround times, as well as sensitivity and specificity for influenza detection (Kumar & Henrickson, 2012; Talbot &

Falsey, 2010). Despite these differences, all tests are limited in their ability to detect influenza virus by the time from illness onset to of specimen collection as peak shedding occurs early in infection, and by the handling and storage of specimen (Lau et al., 2010) (Carrat et al., 2008; Kumar & Henrickson, 2012).

2.3 General Epidemiology

Circulation of influenza viruses

The dominant circulating influenza type and/or subtype may change from year to year and vary in disease severity. Prior to pandemic H1N1, higher influenza-associated mortality rates were reported when type A H3N2 predominately circulated than when type A H1N1 or type B predominately circulated (CDC, 2010; Kyncl et al., 2005; L. Simonsen et al., 1997; W. W. Thompson et al., 2009). Following the pandemic H1N1 in 2009, in 2010, influenza B was the virus type in eastern Asia, and northern and eastern Europe (WHO, 2010). In Southeast Asia and in Africa, pandemic type A (H1N1) remained predominant with type B and type A H3N2 co-circulating (WHO, 2010).

Influenza peaks during the winter months in temperate regions (November through March in the northern hemisphere and April through September in the southern hemisphere); these periods are marked by an increase in medical visits for classic influenza-like symptoms (fever and cough and/or sore throat) (CDC, 2012; N. J. Cox & Subbarao, 2000). This may be due to the fact that the influenza virus survives longer outside of the host in cold and dry weather (Cécile Viboud et al., 2006; WHO, 2014b). Peaks of influenza occur year-round in tropical and subtropical regions (CDC, 2012; N. J. Cox & Subbarao, 2000; Cécile Viboud et al., 2006).

Risk factors associated with severe outcomes due to seasonal influenza

Influenza viruses cause disease in all ages (CDC, 2013). Illness due to influenza, as described earlier, is generally mild, not requiring medical attention (CDC, 2012, 2013). Some cases, however, do lead to severe outcomes, such as hospitalization and/or death. From influenza mortality and morbidity rates, studies have shown that certain age groups and people with comorbidities are at an increased risk of severe influenza-associated outcomes (CDC, 2012, 2013).

During a typical influenza season, a U-shaped distribution curve is observed among the age groups, where the highest number of influenza-attributable hospitalizations and deaths are reported for children <5 years old and adults ≥65 years old (CDC, 2013; C. Viboud et al., 2004). Functionality of the host immune system may play a role; young children lack immunity while older adults are unable to mount adequate protective immune response against the circulating influenza virus (CDC, 2013; Haq & McElhaney, 2014; Sambhara & McElhaney, 2009). Immune functionality is further decreased in children and adults with underlying medical conditions (CDC, 2013).

Medical conditions, such as chronic cardiovascular disease and chronic respiratory disease, may worsen when individuals become ill due to influenza (Madjid, Aboshady, Awan, Litovsky, & Casscells, 2004; Mauskopf et al., 2013; Dena L. Schanzer et al., 2008a; Siriwardena, 2012). Within 3 days of influenza infection, individuals with cardiovascular disease are 4-times more likely to experience myocardial infarction and stroke (Smeeth et al., 2004). Influenza infections increase the incidence of secondary bacterial infections in patients with chronic obstructive pulmonary disease (COPD), leading to longer hospitalization stays and greater lung impairment (Mallia & Johnston, 2007). Influenza infections exacerbate wheezing and asthma in young children (Patria, Tenconi, & Esposito, 2012). Neurological diseases, diabetes, chronic renal disease, morbid obesity, and compromised or suppressed immune systems due to HIV, transplants, or chemotherapy have also been linked to influenza-related complications (CDC, 2013; C. Cohen et al., 2012; Mauskopf et al., 2013).

Pregnant or recently pregnant women have also shown to be at increased risk of complications due influenza infections (CDC, 2013; Laibl & Sheffield, 2005; WHO, 2012a). Secondary bacterial infections are common among pregnant women in their third trimester and postpartum women within 4 weeks after delivery (Laibl & Sheffield, 2005). Some studies report increased delivery complications in pregnant women hospitalized for influenza infection (CDC, 2013).

Due to the nature of their job, healthcare workers are at an increased risk of influenza infections (CDC, 2013; Kuster et al., 2011). Kuster et al calculated this risk as a 2.5 fold increase in healthcare workers compared to adults not working in the

healthcare field (Kuster et al., 2011). Healthcare workers may also spread influenza to vulnerable patients (Kuster et al., 2011).

Prevention

Although good hygiene assists in preventing influenza transmission, the only and most effective method of influenza prevention is through vaccination (CDC, 2010, 2013; Fiore et al., 2009). Current vaccines available in the United States are the inactivated influenza vaccine (administered to anyone ≥6months without contradictions); live, attenuated, cold adapted influenza vaccine (LAIV, administered via nasal spray to only children 2-8 without aspirin-regiments or respiratory conditions (asthma or wheezing)); the inactivated influenza vaccine with a higher dose of hemagglutinin (available as another option for adults >65 years old); and trivalent recombinant influenza vaccine and cell-based inactivated influenza vaccine (as options for individuals with an egg allergy) (Fiore et al., 2009; Grohskopf et al., 2014). Inactivated influenza vaccines may be formulated to protect against three (trivalent) or four (quadrivalent) different influenza viruses (CDC, 2014b; Grohskopf et al., 2014). Vaccine effectiveness is not 100%; it depends on age, immune status, and the antigenic similarity between the circulating and vaccine strains (Harper et al., 2009). Reduction in vaccine effectiveness has been reported in older adults, >65 years old, with or without comorbidities, and immunocompromised patients (Jansen, Sanders, Hoes, van Loon, & Hak, 2007; Lenglet et al., 2007; Mauskopf et al., 2013; Sambhara & McElhaney, 2009). Despite the reduced effectiveness, studies have shown that immunizing older adults reduced influenza-associated hospitalizations (Jansen et al., 2007; Jefferson et al., 2010). This effectiveness is only seen when vaccine strains antigenically match the strains in circulation (Fiore et al., 2009). Due to the constant antigenic changes that influenza viruses undergone, one or more strains included in the vaccine change annually (CDC, 2012, 2013).

Treatment

Although treatment is not usually recommended for self-limited influenza infection, antivirals are available and recommended for influenza-infected individuals who are at high risk of developing complications (Harper et al., 2009). Early treatment, within 48 hours of onset, with antivirals has shown to reduce severity and duration of

influenza infections (CDC, 2010; Harper et al., 2009). Current antivirals target viral infection, the release of viral particles and viral replication (Gu, Liu, & Wei, 2013; Michiels, Van Puyenbroeck, Verhoeven, Vermeire, & Coenen, 2013). Neuraminidase inhibitors, oseltamivir and zanamivir, are the only antivirals available in the United States (CDC, 2012). Studies show that oseltamivir and zanamivir are effective against influenza types A and B (CDC, 2012; Harper et al., 2009). Their effectiveness against type A viruses may be subtype-specific (Harper et al., 2009). M2 proton channel inhibitors, amantadine and rimantadine, have been used in the past to treat non-pandemic A (H1N1viruses) (Harper et al., 2009). Since strains circulating in the United States and worldwide have shown resistance to amantadines and rimantadines, these antivirals are not currently recommended (CDC, 2012). The decision to use antivirals for the prophylaxis or treatment of influenza-like-illness often depends on if the benefits outweigh the risks (virus strain resistance, side-effects, and financial costs) (Michiels et al., 2013).

2.4 Burden of Influenza Disease

Burden of disease is the measure of impact that a pathogen has on a population (Gordis, 2009). This impact includes morbidity and mortality—from the very mild disease to severe disease to death (Gordis, 2009). Different methods and tools are used to quantify this impact (Gordis, 2009; Lozano et al., 2012; Parashar, Hummelman, Bresee, Miller, & Glass, 2003).Quantifying the burden allows leaders to see if efforts or additional efforts are needed in developing interventions (Gordis, 2009; Lozano et al., 2012; Parashar et al., 2003).

Influenza disease severity varies. Most often, influenza disease is self-limiting and does not require medical attention (CDC, 2012; Harper et al., 2009). To capture these mild cases, epidemiologists issue household or serum surveys (CDC, 2012). Sudden increases in outpatient visits usually coincide with annual influenza epidemics (CDC, 2012, 2013; N. J. Cox & Subbarao, 2000; W. P. Glezen, Payne, Snyder, & Downs, 1982). Surveillance systems may be developed to systematically collect, analyze, and interpret outpatient, inpatient, and mortality data (CDC, 2012; Gordis, 2009). From the synthesis of the influenza surveillance data, epidemiologists calculate the estimates of excess

influenza-associated mortality, influenza-associated hospital morbidity, and direct and indirect costs associated with medical care and/or loss time due to influenza infections (CDC, 2012).

Excess influenza-associated mortality

Influenza infections may go untested, undiagnosed, and underreported for various reasons (Azziz-Baumgartner et al., 2013). Testing can be resource intensive (Layne, 2006; Schoub, 2010). When testing is completed, the results are not always available for clinical management, and a positive test may not alter the treatment plan, especially for mild cases (Azziz-Baumgartner et al., 2013). Due to incomplete identification and varying severity of influenza infections, epidemiologists rely on statistic modeling for estimating disease burden of influenza (CDC, 2010; Lopez-Cuadrado, de Mateo, Jimenez-Jorge, Savulescu, & Larrauri, 2012; L. Simonsen et al., 1997). This approach was introduced by William Farr during the 1847-1848 influenza epidemic in London (L. Simonsen et al., 1997). Early epidemiologists, such as William Farr, calculated simple excess mortality estimates as differences in the number of deaths between time periods where influenza is present and where influenza is absent (L. Simonsen et al., 1997). Initially, these modeling techniques were limited to regions with defined influenza seasons and countries with established vital statistics (Cécile Viboud et al., 2006). Since influenza often circulates throughout the year in tropical and subtropical regions, it is more difficult to establish a baseline, a period of non-influenza activity, which is essential for this approach (Cécile Viboud et al., 2006). Influenza-associated deaths are obtained from deaths coded for pneumonia or influenza by the International Classification of Diseases, ICD-10: J00-J99 for instance (Gordis, 2009; D. L. Schanzer, Sevenhuysen, Winchester, & Mersereau, 2013), although alternative approaches also include deaths due to respiratory and circulatory diseases, and in some cases, all-cause deaths accounting for severe influenza infections complicated by underlying conditions and secondary bacterial infections. Vital registration records, however, do not capture all the deaths (Lozano et al., 2012). In 2005, 18.8 million of 51.7 million deaths were recorded (Lozano et al., 2012). Coding regulations and categories change often, which may lead to inaccurate estimations of influenza-associated deaths (Barker & Mullooly, 1981; W. P. Glezen et al., 1982).

Since 1889, the United States and Western Europe have been tracking influenza-associated mortality (Monto, 2004). Earlier modeling techniques did not account for deaths due to co-circulating pathogens, such as respiratory syncytial virus, and lacked confirmation of influenza infection (Yang, Chiu, et al., 2011). With advancements in diagnostics, surveillance networks were established and reliable influenza activity became available (Lopez-Cuadrado et al., 2012; Yang, Chiu, et al., 2011). Serfling regression, poisson regression, negative binomial regression, and generalized linear regression are models used to calculate influenza-associated mortality (Lopez-Cuadrado et al., 2012; W. W. Thompson et al., 2009). The Poisson or generalized linear regression models allowed epidemiologists to account for changes in population size, to incorporate other factors (such as temperature or co-circulating pathogens), and to assess disease severity by virus type and/or subtype (Freitas et al., 2013; Lopez-Cuadrado et al., 2012; W. W. Thompson, Comanor, & Shay, 2006; W. W. Thompson et al., 2009). These advanced statistical models require consistent, robust weekly viral surveillance data and at least 5 years of mortality data (W. W. Thompson et al., 2009). The quality and quantity of available mortality data and influenza surveillance data vary by region and country (Gordis, 2009; D. L. Schanzer et al., 2013; W. W. Thompson et al., 2009). Other statistical models, such as rate difference and autoregressive integrated moving average (ARIMA), do not require virological data or manually setting baselines (W. W. Thompson et al., 2009). Rate difference and ARIMA may serve as options for countries with limited viral surveillance and complex influenza seasons (W. W. Thompson et al., 2009). In a comparison of four different models using the same data, Thompson et al found that annual influenza-associated death estimates were similar among the models except for summer-season rate difference model and ARIMA, which were consistently higher (W. W. Thompson et al., 2009). Schanzer *et al* found that different models of Poisson regression (multiplicative, additive, negative binomial distribution) produced almost identical results (D. L. Schanzer et al., 2013). Influenza-associated mortality estimates from various models and regions are listed in the table below.

Table of Influenza-associated Excess Mortality

Country	**Study period**	**Statistical Method**	**Underlying pneumonia/ influenza (per 100,000 person-years)**	**Underlying respiratory/ circulatory deaths (per 100,000 person-years)**	**All-cause deaths**
Southern Brazil (Freitas et al., 2013)	1980-2008	Serfling regression model using monthly number of deaths	All ages: 1.4 ≥60yr: 10.0	All ages: 9.2 ≥60yr: 86.6	
Singapore (Chow, Ma, Ling, & Chew, 2006)	1996-2003	Negative binomial regression using monthly number of deaths and monthly proportion of influenza-positive test result	All ages: 2.9 ≥65yr: 46.9	All ages: 11.9 ≥65yr: 155.4	
Hong Kong (C.-M. Wong, Chan, Hedley, & Peiris, 2004)	1996-1999	Poisson regression model using weekly number of deaths and weekly proportion of influenza-positive test result	All ages: 4.1 ≥65yr: 39.3	All ages: 12.4 ≥65yr: 102.0	
USA (CDC, 2010)	1976-2007	Poisson regression model using weekly number of deaths and weekly influenza-positive proportion	All ages: 2.4 <19yrs: 0.1 19-64yrs: 0.4 ≥65yr: 17.0	All ages: 9.0 <19yrs: 0.2 19-64yrs: 1.5 ≥65yrs: 66.1	
South Africa (Cheryl Cohen et al., 2010)	1998-2003	Serfling regression model using monthly number of deaths	≥65yr: 42.0		
Argentina (Azziz-Baumgartner et al., 2013)	2002-2009	Linear regression model/Serfling using deaths	All ages: 6.0 men≥65yr: 37 women ≥65yr: 36 men <65yr: 2 women <65yr: 1 2009 H1N1, <65: 8 (compared to seasonal periods, 3)	All ages: 21.4 men≥65yr: 171 women ≥65yr: 136 men <65yr: 4 women <65yr: 2 2007 (H3N2), all ages: 34 flu A (H1N1) or flu B seasons, all ages: 11.4 to 23.4	
East and Southeast Asia (Guangzhou, Hong Kong, and Singapore)(Yang, Ma, et al., 2011)	2004-2006	Poisson regression model using weekly number of deaths (natural spline smoothing function of time, temperature, and relative humidity)	Guangzhou All ages: 1.0 Hong Kong All ages: 4.6 Singapore All ages: 2.8	Guangzhou All ages: 9.8 >65yr: 104.1 Hong Kong All ages: 9.5 >65yr: 78.7 Singapore All ages: 5.3 >65yr: 46.0	

Country	Study period	Statistical Method	Underlying pneumonia/ influenza (per 100,000 person-years)	Underlying respiratory/ circulatory deaths (per 100,000 person-years)	All-cause deaths
Canada (D. L. Schanzer et al., 2013)	1992-2009	Poisson regression model using weekly deaths (vital statistics) and hospitalization discharge records	All ages: 11.3 (fluA H3N2, H1N1, and pH1N1) Only pH1N1 All ages: 1.7 <65 yrs: 0.9 65+ yrs: 0.6		
Canada (Dena L. Schanzer et al., 2008a)	1994 – 2000	Poisson regression model using weekly death (vital statistics) and hospital discharge/ admission records and database (identified individuals with comorbidities)			All ages: 14 <50yrs: 0.3 50-54yrs: 3 55-59yrs: 4 60-65yrs:10 65-69yrs: 2 70-74yrs: 34 75-79yrs: 89 80-84yrs: 175 85-89yrs: 387 90+yrs: 831 65+yrs: 96
Spain (Lopez-Cuadrado et al., 2012)	1999 – 2005	Serfling using only national vital statistics; Poisson regression model using vital statistics and viral surveillance	Serfling >44yrs:2.68 45-64yrs: 0.33 >64yrs: 15.25 GLM >44yrs:1.08 45-64yrs: 0.18 >64yrs: 6.00		Serfling >44yrs:30.42 45-64yrs: 3.77 >64yrs: 164.10 GLM >44yrs:10.97 45-64yrs: 2.31 >64yrs: 57.05
USA (W. W. Thompson et al., 2003)					All ages: 19.6
Portugal (Nunes et al., 2011)	1980 – 2004		All ages: 1.45		All ages: 13
Czech Republic (Kyncl et al., 2005)	1982 – 2000	Serfling with poisson distribution using weekly number of deaths (vital statistics) and viral surveillance data			All ages: 25.99
Italy (Rizzo et al., 2007)	1969 – 2000		All ages: 3		

Influenza-associated excess mortality rates vary by age and health status. The highest influenza-associated excess mortality rates are observed among adults older than

65 years of age. In fact, 90% of influenza-associated deaths reported in the United States were identified in the older age group (CDC, 2010).Singapore also reported an 11.3 times higher risk for influenza-related mortality in older adults than in the general population (Simmerman & Uyeki, 2008). Schanzer *et al* found that age as well as underlying conditions, especially chronic lung or heart disease, contributed independently to elevate risks of influenza-associated mortality (Dena L. Schanzer et al., 2008a). Estimated excess influenza-associated mortality were also elevated in individuals infected with human immunodeficiency (C. Cohen et al., 2012), 94-146/100,000 estimated excess influenza-associated mortality compared to 0.9-1.0 in general population between 25-64 years of age and 64-70 deaths in adults ≥65 years old (CDC, 2010).

Influenza-associated hospital morbidity

Mortality only accounts for a small portion of severe influenza cases (Lenglet et al., 2007; Lone Simonsen, Fukuda, Schonberger, & Cox, 2000). Hospitalizations make up an important component of influenza disease burden, and these individuals may present atypical influenza symptoms and therefore are not tested for influenza (Lenglet et al., 2007; W. W. Thompson et al., 2004; Yang, Chiu, et al., 2011; Zhou et al., 2012). Since testing for influenza is not routine, even hospitalized patients with influenza symptoms may not be tested for influenza (Wang et al., 2012; Yang, Chiu, et al., 2011; Zhou et al., 2012). In attempts to overcome these limitations and indirectly estimate the burden of influenza hospitalizations, modeling approaches similar to those used to estimate excess influenza-associated mortality, can be used (Kim, Kilgore, Lee, Nyambat, & Ki, 2011; Yang, Chiu, et al., 2011). The total number of hospitalizations during and outside of an influenza season can be obtained from hospital or health insurance discharge databases (Gordis, 2009; Kim et al., 2011). These databases are usually unavailable in lower-middle and low income countries (Gordis, 2009). Since hospital discharge records utilize a similar international coding system as death certificates, they are subject to the same coding changes, possible misclassifications, and differences in usage by various healthcare systems (Jansen, Sanders, Hoes, van Loon, & Hak, 2007; Kim et al., 2011; Perrotta, Decker, & Glezen, 1985). Records may be incomplete in the description of patient conditions, excluding underlying conditions, possible co-infections, and vaccine status (Gordis, 2009; Kim et al., 2011; Zhou et al., 2012). To limit underestimations of

influenza-associated hospitalizations as a result of incomplete records, some models expanded the list of codes used to define an influenza-associated hospitalization, 'pneumonia and influenza' to 'respiratory and circulatory diseases' for example. These models and other models may have included viral surveillance data for confirming influenza seasons and for taking into account co-circulating viruses (Kim et al., 2011; Jansen, Sanders, Hoes, van Loon, & Hak, 2007). The table below presents influenza-associated hospitalization rates resulting from these various models.

Table of Influenza-associated Hospitalizations

Country (source)	**Study Period**	**Data Source**	**Method**	**Estimated Hospitalization Rates**
Hong Kong (C. M. Wong et al., 2009)	1996-2000	Hospital discharge diagnoses from 14 acute hospitals	Poisson regression weekly counts (control for RSV)	29.3 excess pneumonia & influenza per 100,000 (all age groups) 11.6% of all hospitalizations Excess influenza-associated hospitalizations coded as acute respiratory disease 0-14yrs: 163.3 (135.2, 189.7) 15-39yrs: 6.0 (2.7, 8.9) 40-64yrs: 14.9 (10.7, 18.8) 65-74yrs: 83.8 (61.2, 104.2) 75+ yrs: 266 (198.7, 330.2) All: 60.6 (52.8, 67.2)
Hong Kong (C. M. Wong et al., 2012)	2005-2010	Electronic hospital discharge records from 41 hospitals	quasiPoisson regression models	Seasonal rates of excess influenza-associated hospitalizations Pneumonia/influenza Acute Respiratory 0-5yrs: 23% 12.8% 6-17yrs: 18.3% 15.5% 18-39yrs: 9.5% 10.4% 40-64yrs: 6.8% 8.3% 65-74yrs: 6.3% 7.1% 75+yrs: 6.2% 6.7% All ages: 8.5% 8.8%
United States (W. W. Thompson et al., 2004)	1979 - 2001	National Hospital Discharge Survey data and WHO Collaborating Labs influenza Surveillance data	Poisson regression	Excess pneumonia & influenza hospitalizations 8.6% of all hospitalizations <5yrs: 18.5/100,000 5-49yrs: 6.8/100,000 50-64yrs: 37.9/100,000 65-74yrs: 97.3/100,000 75+yrs: 344.1/100,000 All ages: 36.8/100,000 Excess influenza-associated hospitalizations coded for respiratory and circulatory diseases <5yrs: 107.5/100,000 5-49yrs: 20.8/100,000 50-64yrs: 83.3/100,000 65-69yrs: 189.7/100,000 70-74yrs: 321.2/100,000 75-79yrs: 431.1/100,000

Country (source)	Study Period	Data Source	Method	Estimated Hospitalization Rates
United States (W. W. Thompson et al., 2004)	1979 - 2001		Poisson regression	80-84yrs: 686.1/100,000 85+yrs: 1194.9/100,000 All ages: 88.4/100,000
United States (Lone Simonsen et al., 2000)	1970 - 1995	National Hospital Discharge Survey Data		~3 million excess P&I hospitalizations ≥65yrs: 174/100,000 <65yrs: 33/100,000
United States (Zhou et al., 2012)	1993 - 2008	Statewide hospital discharge database (13 states, 40% of population); influenza and RSV viral surveillance data	Negative binomial regression model weekly	Excess influenza-associated respiratory and circulatory hospitalizations <1yrs: 151/100,000 1-4yrs: 38.8/100,000 5-49yrs: 16.8/100,000 50-64yrs: 65.6/100,000 65+yrs: 309.1/100,000 All ages: 63.5/100,000
Netherlands (Jansen, Sanders, Hoes, van Loon, & Hak, 2007)	1997-2003	hospitalization discharge (viral surveillance for flu and RSV)	Rate-difference models	Rates of hospitalizations for influenza-associated all-cause mortality 0-17yrs: 14% 18-49yrs: 12% 50-64yrs: 23% 65yrs+: 51% (H3N2 most seasons, 2000/01 H1N1)
Finland (Jacks, Ollgren, Ziegler, & Lyytikainen, 2012)	1996-2009	Annual national discharge register (including weekly reports of seasonality, RSV, M. pna)	Negative binomial regression model	Rates = "pneumonia & influenza coded"/100,000 of age group pop/week 2009 Pre-pandemic (1996-2009) 0-4yrs: 16.6 15.2 5-24yrs: 3.5 2.3 25-64yrs: 6.7 5.1 ≥65yrs: 46.5 47.3 All ages: 13.4 11.5
South Korea (Kim et al., 2011)	2002-2005	National health insurance databases	Rate-difference models	Rates of hospitalizations coded for pneumonia & influenza per year (all ages groups): 4.61% (2002), 4.47% (2003), 4.46% (2004), 4.64% (2005) Per 1000 2002: 2003: 2004: <5yrs: 36.7 41.2 45.8 5-14yrs: 3.3 5 3.2 15-49yrs: 0.9 0.9 0.9 50-64yrs: 3.1 3 3.5 65-74yrs: 8.4 8.4 10.4 ≥75yrs: 15.6 16.9 21.6 All ages: 4.6 5.1 5.3
Spain (Lenglet et al., 2007)	2000-2004	Hospitalization discharge	Poisson regression model	Influenza-associated hospitalization for all-caused mortality All ages by season: 2001/02: 24.7/100,000 2002/03: 18/100,000 2003/04: 17.7/100,000

Country (source)	Study Period	Data Source	Method	Estimated Hospitalization Rates
Canada (Dena L. Schanzer et al., 2008b)	1994-2000	Hospitalization database including clinical diagnostics	Poisson regression model	Hospitalizations coded for influenza & pneumonia 20-49yrs: 1-2/100,000 50-64yrs: 5-7/100,000 65+yrs: 37-36/100,000 20+yrs: 6-8/100,000
Canada (D. L. Schanzer et al., 2013)	1992-2009	Hospitalization discharge records	Poisson regression model	Hospitalizations coded for influenza & pneumonia Seasonal average due to H3N2, H1N1, pH1N1 All ages: 39.5/100,000
Argentina (Azziz-Baumgartner et al., 2013)	2005-2008	Government-operated hospital discharge forms	Serfling model (P/I) Linear regression model (R/C)	Hospitalizations coded for influenza & pneumonia (P/I) All ages: 2.0 Hospitalizations coded for respiratory and circulatory disease (R/C) All ages: 5.7/100,000 2007 (H3N2), all ages: 8.4/100,000

From the studies included in the summary table above, the highest rates of influenza-associated hospitalizations were commonly observed among older adults (>65 years of age) and young children, <5 years of age. Severity of disease was dependent on type or subtype; hospitalization rates increased when multiple influenza types or subtype H3N2 were in circulation (Azziz-Baumgartner et al., 2013; Dao et al., 2010; W. W. Thompson et al., 2004). To validate these influenza-associated hospitalization rates, Zhou *et al* suggested conducting large studies testing hospitalized patients prospectively using PCR (Zhou et al., 2012).

In recent years, laboratory-testing capacity has grown globally (Mmbaga et al., 2012; Nair et al., 2011; WHO, 2013). The number of countries in Africa completing influenza surveillance using PCR has increased from 5 to 15 from the year 2006 to 2011 (Radin et al., 2012). This increased capacity has improved the understanding of influenza epidemiology, allowing for the establishment of influenza seasonality and detection of novel influenza circulating strains with pandemic potential (WHO, 2011b). The increased capacity has also increased the recognition of influenza infections among children and adults in developing countries, adding to the evidence of disease worldwide (Nair et al., 2011; Takahashi et al., 2013; Verani et al., 2013). Along with increased laboratory capacity, the Global Influenza Hospitalization Surveillance Network was recently established to evaluate influenza burden among hospitalized patients matching a

standardized case definition, to quantify virus type and subtype distribution, and to measure vaccine effectiveness (Puig-Barbera et al., 2014). With the expansion of laboratory capacity and support of network surveillance, countries have calculated laboratory-confirmed influenza-associated hospitalization rates (Chadha et al., 2013; Dao et al., 2010; Yu et al., 2014) examples of rates are seen in the following table.

Country-specific, laboratory-confirmed influenza-associated hospitalization rates

Country	**Influenza Seasons**	**Overall estimates**	**Age-group specific estimates**			
USA (Dao et al., 2010)[1]	2005-2006 2006-2007 2007-2008 Mean	9.9/100,000 4.8/100,000 18.7/100,000	18-49yrs 3.6/100,000 2.5/100,000 7.3/100,000 4.5/100,000	50-64yrs 7.8/100,000 4.2/100,000 14.8/100,000 8.9/100,000	65-74yrs 22.9/100,000 10.6/100,000 37.6/100,000 23.7/100,000	75+yrs 65.1/100,000 22.3/100,000 116.6/100,000 68/100,000
China (Yu et al., 2014)	2010-2011 2011-2012				65+yrs 141/100,000 89/100,000	
India (Chadha et al., 2013)[2]	Entire study 2009-2010 2010-2011	44.1/10,000	15-29yrs 67.1/10,000 58.3/10,000	30-44yrs 25.2/10,000 23.3/10,000	45-59yrs 18.3/10,000 28.8/10,000	60+ 11.6/10,000 18.7/10,000

[1]Dao et al study population represents 7% of US population ≥18 years old and from only urban hospitals.
[2]Chadha et al study may not reflect the typical influenza season, since it includes pandemic H1N1.

As seen in the above table, estimated rates based on laboratory-confirmed influenza hospitalizations are generally lower than rates estimated by models discussed earlier. Models may account for severe influenza cases, especially those with atypical symptoms, not tested for influenza, where laboratory-confirmed influenza surveillance does not. Depending on the sources used, models may underestimate or overestimate influenza associated hospitalizations, either by not accounting for influenza hospitalizations due to not fully developed or widespread use of hospital administrative databases or including hospitalizations not confirmed for influenza and potentially caused by other co-circulating pathogens (Azziz-Baumgartner et al., 2013). In attempt to overcome the limitations of earlier models and by laboratory-confirmed surveillance, Reed, Biggerstaff, and colleagues have created the multiplier model for estimating local influenza morbidity (Biggerstaff et al., 2013; Reed et al., 2009). The multiplier model adjusts the laboratory-confirmed cases for the portion of population with influenza who did not seek care or provide a specimen, for specimens not sent to the public health laboratory or tested for influenza, and for mishandled specimens and/or the delay in collection of specimens (Biggerstaff et al., 2013; Reed et al., 2009). These adjustments

rely on prior knowledge of population health-seeking behaviors, and influenza testing procedures and policies (Biggerstaff et al., 2013; Reed et al., 2009).

In addition to modeling, systematic reviews provide an assessment of the available knowledge to estimate influenza-associated morbidity and mortality (Gessner et al., 2013; W.P. Glezen et al., 2013; Savy et al., 2013; Simmerman & Uyeki, 2008). Gessener et al summarized literature findings on seasonal influenza in sub-Saharan Africa from 1980 to 2009 (Gessner et al., 2013). Gessner and colleagues found that influenza viruses contribute substantially to respiratory infection morbidity and mortality for all ages, although little was reported about children older than five years old and adults (Gessner et al., 2013). They also noted an eight times greater risk of influenza mortality and morbidity when a child was co-infected with the human immunodeficiency virus (Gessner et al., 2013). Savy *et al* completed a similar literature review for Latin America and the Caribbean (Savy et al., 2013). According to literature from 1980 to 2008, Savy *et al* also found substantial morbidity and mortality due to seasonal influenza infections (Savy et al., 2013). Although the percentage of specimens received by testing centers was low during this time period, 4.7 to 15.4%, Savy *et al* calculated 36,080 influenza-like illnesses per 100,000 annually with a mean hospital stay of 5.8 to 12.9 days and a mean direct cost of $575 US dollars per confirmed case (Savy et al., 2013). Savy *et al* noted low vaccine uptake in the region (Savy et al., 2013). Low vaccine uptake was also observed in East and Southeast Asia, according Simmerman and Uyeki who summarized literature findings for this region from 1980 to 2006 (Simmerman & Uyeki, 2008). Due to high variability between studies, using different case definitions and data collection methods, they were unable to aggregate data and calculate estimates (Simmerman & Uyeki, 2008). Simmerman and Uyeki, however, found evidence of influenza disease throughout the region (Simmerman & Uyeki, 2008). Middle and high income countries, with improved and sustained laboratory capacity and surveillance, reported the largest burden of influenza morbidity and mortality (Simmerman & Uyeki, 2008). Higher proportions of the known influenza burden were observed in young children and adults >65 years old (Simmerman & Uyeki, 2008).

To explore the role of influenza in pediatric respiratory hospitalizations globally, Nair *et al* and Lafond *et al* completed meta-analyses of published and surveillance data

(Lafond et al., 2014; Nair et al., 2011). Nair *et al* estimated 1 million cases of hospitalized severe acute respiratory infections in children under five-years-old were attributed to influenza each year (Nair et al., 2011). Using the rate-based approach, they estimated 28,000 to 111,000 annual influenza-associated deaths (Nair et al., 2011). Lafond *et al* calculated pooled estimates and found that 9.5% of pediatric respiratory hospitalizations were due to seasonal influenza infections during the 1996 to 2012 time period (Lafond et al., 2014). A higher proportion of influenza associated hospitalizations were observed in school-age children (16%) compared to children <5 years-old (6%) (Lafond et al., 2014). During seasonal influenza epidemics, adults also experience severe outcomes from influenza-related respiratory infections (CDC, 2013; N. J. Cox & Subbarao, 2000; F. Dawood et al., 2012). Although Dawood *et al* found 65% of pandemic H1N1 deaths globally were adults 18 to 64 years old in 2009, no global estimates for seasonal influenza currently exist for adults (F. Dawood et al., 2012; Kuster et al., 2011; Dena L. Schanzer et al., 2008a).

Economic impact of influenza infections

After estimating excess mortality and hospital morbidity, a cost analysis associated with the disease burden of influenza and with the impact of the targeted interventions can be conducted (Azziz-Baumgartner et al., 2013; Szucs, 1999). Influenza disease has direct and indirect costs (CDC, 2010; Molinari et al., 2007; Monto, 2004; Ott et al., 2013; Peasah, Azziz-Baumgartner, Breese, Meltzer, & Widdowson, 2013; Ryan, Zoellner, Gradl, Palache, & Medema, 2006; Szucs, 1999). Physician visits and hospital admissions due to influenza infections contribute to high direct costs (Szucs, 1999). In France, the use of healthcare services for influenza infections totaled appropriately $300 million in 1989; the United States reported higher annual direct costs with totals of $1-3 billion (Szucs, 1999). A larger price tag, however, was observed for indirect costs among high income countries (Peasah et al., 2013; Szucs, 1999). Indirect costs, such as productivity losses and school or work absenteeism, due to influenza infections totaled $2.3 billion in France and $10-15 billion per year in the United States (Szucs, 1999). Indirect costs were 50% less than direct costs in Hong Kong and Thailand (Peasah et al., 2013). Influenza accounts for 10-12% of all sick-related absentees among workers (Ryan et al., 2006; Szucs, 1999). An average of 3.7 to 5.9 working days were lost due to

laboratory-confirmed influenza infections among healthy working adults (Karve, Misurski, Meier, & Davis, 2013; Keech & Beardsworth, 2008). The magnitude of direct and indirect costs sharply increases among high risk groups. Influenza infections among older adults, for an example, contribute to 64% of the economic burden due to seasonal influenza in the United States (Menec, Black, MacWilliam, & Aoki, 2003; Molinari et al., 2007). School or work absenteeism was reported highest among closely living communities with young children (Szucs, 1999). Individuals with comorbidities experience severe influenza outcomes, hospitalizations and deaths, more frequently than healthy adults (Dena L. Schanzer et al., 2008a; Szucs, 1999). Interventions, specifically influenza vaccination programs, targeting high risk groups have shown to be cost-effective in the United States and China (Ott et al., 2013; Ryan et al., 2006; Szucs, 1999). Vaccinating older adults reduced rates of influenza disease severity (Szucs, 1999). After vaccinating healthy adults, rates of absenteeism decreased by 43% and 25% less upper respiratory infections were reported (Szucs, 1999).

Many factors contribute to the cost-effectiveness of influenza vaccination. As previously mentioned, vaccine effectiveness varies among age groups and from year to year (Fiore et al., 2009; Ott et al., 2013). The timing of vaccination, location of vaccine administration, and duration of vaccine protection also impact cost-effectiveness and cost-benefit analyses (Ott et al., 2013). Influenza vaccination has been shown to be most cost-effective when administrated early in the season (Ott et al., 2013). Due to vaccine limitations, lower efficacy in older adults and antigenic differences between vaccine and circulating strains, other interventions, such as antivirals, may need to be considered (Szucs, 1999).

Influenza infections have a substantial economic impact (Karve et al., 2013; Szucs, 1999). Cost analyses of influenza burden and the impact of its interventions aid in policy decisions (Ott et al., 2013; Peasah et al., 2013). High income, temperate-climate countries have provided the majority of currently available cost evaluations (Ott et al., 2013; Peasah et al., 2013). A few publications on cost analysis come from middle income countries (Ott et al., 2013; Peasah et al., 2013). Evaluations in lower middle income and low income countries are lacking (Ott et al., 2013; Peasah et al., 2013). Since cost analyses are lacking despite the evidence of substantial influenza disease burden, middle

and low income countries do not have sufficient evidence to support the establishment of influenza vaccine policies or recommendations (Ott et al., 2013; Peasah et al., 2013) (Samaan et al., 2013).

Applications of influenza burden estimates

Burden estimates provide evidence of disease and improve the understanding of influenza epidemiology. Prior to the expansion of surveillance and laboratory capacity, many developing countries were unaware of the impact of influenza (Katz et al., 2012; Muyembe Tamfum et al., 2012; Nyatanyi et al., 2012; Schoub, 2010; Steffen et al., 2012). Influenza, in fact, may have been misdiagnosed as malaria or as other diseases with nonspecific symptoms (Muyembe Tamfum et al., 2012; Schoub, 2010). Using laboratory diagnostics has confirmed the presence of influenza in circulation and as a cause of morbidity and mortality for all ages worldwide (Layne, 2006; Nyatanyi et al., 2012; WHO, 2011b).

One key aspect of influenza epidemiology is seasonality and timing of virus circulation each year. A peak of influenza confirmed cases may occur during the same time period for multiple years in a particular region or country (L. Simonsen et al., 1997). Studying this trend or occurrence may reveal the seasonality of influenza disease (L. Simonsen et al., 1997). Knowing when influenza occurs allows leaders to plan and implement control and prevention measures, and to potentially evaluate those measures over time (Muyembe Tamfum et al., 2012)

In addition to detection, some laboratory diagnostics permit further characterization of strains, such as the identification of virus types and/or subtypes (Layne, 2006). The coordinating centers for the World Health Organization (WHO) rely on such work to evaluate strain variability and to inform their recommendations for the annual vaccine strain selection (CDC, 2012; WHO, 2014c). To ensure coverage of vaccine strains, it is essential to have good, reliable global surveillance (Layne, 2006; Schoub, 2010). Not all countries have the capacity to implement and maintain influenza surveillance systems (Schoub, 2010). In developing countries, surveillance systems often depend on additional financial support from donors (Layne, 2006; Lutwama et al., 2012). Evidence provided by burden estimates may draw attention to the public health needs for controlling and preventing influenza and advocate for further country and donor support (Gordis, 2009).

Beyond routine surveillance for seasonal influenza viruses, increased surveillance efforts support detection of novel influenza viruses with pandemic potential (Ayele et al., 2012; Monto, 2004; Radin et al., 2012). During pandemics, burden estimates are generally high, and in many regions of the world too high, to supply the necessary care in both treating ill individuals and protecting healthy individuals within the population (Ayele et al., 2012; WHO, 2009). Early detection of pandemic viruses through global surveillance may lessen the impact if countries are prepared and equipped to recognize and manage disease (Layne, 2006; WHO, 2009). Countries with limited resources and competing priorities are often forced to rebuild capacity (Lutwama et al., 2012). Global estimates of seasonal influenza may provide evidence to support the need to sustain that testing capacity.

In addition to observing seasonal trends of influenza and the high burden of disease during pandemics, epidemiologists may also observe an increased number of influenza-associated hospitalizations and deaths among certain individuals in the population. By identifying the individuals at risk, those who experience the greatest burden of influenza disease, countries can create targeted campaigns (Azziz-Baumgartner et al., 2013; Dena L. Schanzer et al., 2008a). While countries, such as Canada, have observed reductions in influenza-associated mortality and morbidity after the implementation of a universal immunization program, other countries with limited resources may be able to provide similar reductions in disease through targeted campaigns that allow prioritization and effective allocation of resources (Fuller et al., 2013; Kwong et al., 2008; Monto, 2004). Once these campaigns are implemented, recalculated burden estimates may be used to confirm the effectiveness and drive future improvement.

Through the examination of burden estimates on a global scale, epidemiologists can compare and evaluate the effectiveness of interventions against influenza in different settings, among diverse populations, and in relation to other pathogens. Even though vaccination is considered the only effective means of preventing influenza infections, introducing the vaccine may not be cost-effective in certain settings, particularly when disease burdens are greater for other pathogens and resources are limited (CDC, 2010, 2012, 2013; Fiore et al., 2009; WHO, 2005). Over time, this may change, especially if disease burdens for influenza and related infections increase (WHO, 2005). In

populations with a high prevalence of human immunodeficiency virus (HIV), severe outcomes as a result of influenza infections are four to eight times as likely (C. Cohen et al., 2012; Gessner et al., 2013; Gessner et al., 2011). The severity of influenza infections in HIV patients appears to decline when patients receive antiretroviral therapy along with the influenza vaccine (C. Cohen et al., 2012). As individuals recover from influenza infections, they may become susceptible to secondary infections (Shrestha et al., 2013). Shrestha *et al* have shown that influenza infections increase a patient's susceptibility to pneumococcal pneumonia by approximately 100-fold (Shrestha et al., 2013). Vaccines and other interventions against influenza may assist in reducing the morbidity and mortality associated with other pathogens (Shrestha et al., 2013). However, the interaction between influenza and other pathogens is complex. In one hospital setting in the US where influenza vaccine coverage is high (78%), researchers observed an increase in hospitalizations due to other circulating respiratory viruses in adults ≥ 65 years old (Widmer et al., 2012).

Despite interventions such as vaccines, burden estimates may remain high. To uncover the reasons why, further research is needed to monitor trends and severity in disease, and to develop new ways to control and prevent disease. Country leaders and health planners rely on burden estimates to prioritize investments in health and research (Chadha et al., 2013; W. W. Thompson et al., 2009; Yu et al., 2014). Developing vaccines that target conserved regions of the influenza virus may lead to broad protection and a universal vaccine (Schotsaert & Garcia-Sastre, 2014). Diagnostics with high sensitivity and specificity for the influenza could lead to the reduction of nosocomial infections and the unnecessary use of antibiotics (W. P. Glezen et al., 1982; Widmer et al., 2012). Leaders may also use burden estimates to guide policy and medical practice, such as the use of antivirals in hospitalized patients, which have shown to increase the chances of survival, and the development of a standardized influenza case definition to improve identification and treatment (Jain et al., 2009; Kyncl et al., 2005; Mytton, Rutter, & Donaldson, 2012).

With the recent expansion of sentinel surveillance for influenza infections in healthcare facilities of developing countries, more data for influenza-associated hospitalizations is available and not yet summarized. A summary of this data as it

pertains to the adults provides the needed evidence to inform and guide the global public health community in discussions of polices and interventions targeted at influenza-associated hospitalizations.

Chapter III
Methods and Procedures

3.1 Data Sources

We derived our study data from two sources: a systematic review of the published literature of influenza in hospitalized adults and unpublished data from a working group of partners conducting influenza surveillance among hospitalized adults.

Systematic Literature Search

To identify eligible articles, we searched Pubmed, Embase, Web of Science, Global Health, LILACS, IndMed, CINAHL, WHOLIS, and CNKI using the following search terms and respiratory illness keywords: "Influenza" or "viral etiology;" respiratory (tract) infection/disease/illness; pneumonia, bronchiolitis, bronchitis, "influenza-like illness:" and case definitions for ILI (influenza-like illness), SARI (severe acute respiratory illness), ARI (acute respiratory illness), ARLI (acute respiratory like illness), LRTI (lower respiratory tract illness), or CAP (community acquired pneumonia). We conducted our search on all databases simultaneously, over one week. We limited our search to articles published between January 1, 1996 and June 30, 2012. Our search was not restricted by language or location. We relied on multilingual professionals who either worked in the Influenza Division (CDC) or had basic knowledge of influenza and epidemiology to assist in the screening and abstracting of data from non-English papers. Additional papers, outside of the citation search, were identified from the bibliographies of eligible articles.

Supplemental Unpublished Data

In addition to the systemic review of published literature, we invited international collaborators who complete year-round influenza testing of hospitalized adults to participate in the study. Together these collaborators cover most if not all WHO regions and different World Bank income levels. Some collaborators have participated in the

SARI, severe acute respiratory infection, network, and have collected influenza testing for both pediatric and adult populations.

3.2 Data collection

Published Data

After identifying potentially eligible publications in our search, we followed a multi-step process for collecting data. We first reviewed the titles and abstracts from the list of citations captured by our search strategy. We eliminated any review articles or articles unrelated to the influenza virus. We continued to screen the articles deemed eligible by our citation review.

In our screening, we utilized a standard set of inclusion criteria (summarized in box 1). These criteria were defined prior to project implementation and based on previous research (Nair et al., 2011; Lafond et al., 2014; Gessner et al., 2011; Simmerman & Uyeki, 2008). The purpose of the criteria was to identify comparable data sources that provided the percent of adult inpatients that tested positive for influenza viruses (our primary outcome), and compare the effects of factors such as year, age group, location, case definition, or influenza diagnostic tool on the positive influenza-tested percentage (secondary outcomes). Article must provide total number tested for influenza and among those tested the total number of influenza positive for adult inpatients. Articles must have data for inpatients. We defined inpatients as patients admitted into the hospital. Emergency room department admissions were considered outpatients unless later specified that patients required hospitalization. Studies collected data for adults only or reported by age group. Individuals 18 years or older were considered adults if not otherwise noted. To ensure that we included a dataset only once, original research was required. Authors either collected and used data or were the only ones to use data for investigating positive influenza inpatients. Since we are interested in the circulation of influenza among the general population, healthcare-acquired influenza infections were excluded. The circulation of influenza tends to be seasonal in most regions. To control for this seasonality, studies completed at least 12 months of continuous influenza testing.

We required laboratory confirmation of influenza for ensuring accuracy of our primary outcome. Inpatients may present onset and symptoms similar to influenza but do not have an influenza infection according to laboratory test. In light of diagnostic differences in sensitivity and specificity, studies listed the influenza confirmation test. Studies tested a minimum of fifty inpatients for influenza, in attempts to maintain adequate power for estimation and limit type I errors.

Box 1. Inclusion Criteria

1. Adult inpatient data
2. Original research
3. Community-acquired influenza
4. 12 months of continuous influenza testing
5. Laboratory confirmation of influenza
6. Diagnostic test description
7. Total number tested for influenza
8. Total number of influenza positive for adult inpatients
9. Minimum of fifty inpatients for influenza

Once we confirmed that screened article matched the criteria, we abstracted and recorded the outcome measurements and related factors (listed in box 2).

Box 2. Recorded Outcome Measurements

1. Positive percentage of influenza
- What is the total of patients tested for influenza?
- Of this total, how many are positive for influenza, positive for influenza type A and/or influenza type B?

2. Year
- When did the study occur? What are start and end dates?
- Was the study completed during a pandemic or seasonal influenza season?

3. Adult age range
- What is the age range of the adult inpatients tested for influenza?
- If influenza testing results were given by age group, what is the total tested and total positive for the following age groups: 18-45, 45-64, and ≥65?

4. Location
- Where did the studies and testing occur, where were the patients enrolled (city or town, and country)?
- Which WHO region did the study's or working group collaborator's country belong to?
- According to the World Bank income standards, would this country be described as high, middle-high, middle-low, or low income?
- Also, would this country during the testing timeframe be described as industrial or undeveloped?

Box 2. Recorded Outcome Measurements

5. Case definition
- What guidelines are used to direct hospital admission and laboratory testing?
- How do authors/work group collaborators define influenza disease in their studies/populations?

6. Influenza diagnostic tool
- What laboratory test was used to confirm suspected cases?
- What type of specimen was collected and tested?

Two or more reviewers completed each step, ensuring that articles were at least doubly reviewed and screened, and that data was doubly abstracted. Any discrepancies between reviewers were discussed. If discussion did resolve discrepancies, reviewers were asked to re-screen and abstract data. Data collection tools were piloted, tested and results evaluated by reviewers, prior to implementation and for training purposes. We found that piloting the collection tools allowed us to ensure that approach by all reviewers was consistent, utilizing the same definitions, and to confirm that our tools captured our outcomes of interest. We also completed a bias assessment, study and outcome level on the eligible articles (box 3).

Box 3. Bias Assessment

Yes = (score)

1. Selection
   - i. Was a standard criteria, such as a case definition, used in selecting inpatients for influenza testing? (1)
   - ii. Was the method for selecting inpatients for influenza testing unclear or undefined? (0)
2. Comparability
   - i. Within the case definition, does the article describe or list symptoms or signs? (1)
   - ii. Does the article list a syndrome (such as LRTI or community-acquired pneumonia) without describing symptoms (0)?
3. Outcome
   - a. Reporting
   - i. Do the authors clearly provide total number of inpatients tested for influenza and of those tested, the number of inpatients who were positive for influenza? (1)
   - ii. Do authors not clearly provide the total influenza tested and the total positive for influenza? (0)

Unpublished Data

We used a template for collecting standard outcome data from working group participants. Participants provided a basic description of their surveillance system. This basic description includes start year, age group testing, lists of inpatient surveillance sites, case definition used and start time of using definition, sampling strategies used for influenza testing during influenza and non-influenza seasons, type of sample collected and tested, and the diagnostic method used in influenza testing (method, percentage of samples used with each method used, and when method was used). The template also captured influenza testing by year (start and end date for each testing year, from 2005 to 2012), age group (18-49, 50-64, 65-74, and 75+), and serotype (pH1N1, H3N2, B, and seasonal H1N1). Optionally, participants provided site-level results for influenza-testing by age group. No individual patient data was collected.

3.3 Data Management and Analysis

For analysis, we used Stata and SAS version 9.3 software. We divided our datasets into seasonal, pre- and post-pandemic, and pandemic timeframes. We defined pandemic as datasets with data collected during the 2009 year. Seasonal datasets excluded 2009-year data. Our analysis excluded datasets that combined seasonal and pandemic timeframes. We also used two age groups, 18-64 and 65+, for our analysis. We completed descriptive analysis, stratifying by data source (published articles or working group submissions), using SAS. We calculated crude median results for outcomes of interest—number tested, number of influenza positive, and percent positive—using non-parametric tests for difference by Kruskal Wallis, rank sum.

To determine if timeframe influenced our crude proportions, we stratified the datasets by timeframe. We observed differences between age groups, data sources, case definitions, and income levels with the inclusion of pandemic datasets. Due to this observation, we restricted the meta-analysis to seasonal datasets. Using seasonal datasets, we generated adjusted pooled estimates and 95% confidence intervals for the proportion of specimens testing positive for influenza by key age groups, study population types, geographical region, and income and development status. These adjusted pooled estimates and confidence intervals were calculated through the use of the log binomial

model in SAS, accounting for random effects at the dataset level. When the SAS model did not converge or there were insufficient data points, we used the Stata random-effects model, DerSimonian-Laird method, for the adjusted pooled estimates and confidence intervals. If a seasonal dataset provided data by year, we treated each year of data as a single observation in the model and defined datasets as clusters. Due to the known varying sensitivity of influenza diagnostic tests, we also stratified the pooled estimates by polymerase chain reaction (PCR) testing, the gold standard of influenza laboratory confirmation, and compared the stratified estimates to the estimates including all testing methods used.

3.4 Exploratory Analysis

We also conducted exploratory analyses on potential impact of bias, calendar year 2010 data, partial-years data, and multipathogen detection on our crude and pooled estimates. For our calculations of estimates, we used rank sum non-parametric tests and the SAS binomial log regression model.

In our exploratory analysis of bias, we defined total bias as the sum of selection, comparability, and outcome bias. As mentioned earlier, we completed the bias assessment by scoring each published dataset for the three components, using 0 for not meeting the criteria or 1 for meeting the criteria. A total bias of 3 was considered the highest level of quality, while a total bias of 0 was considered the lowest. We explored the impact of article quality on positive proportions.

Since pandemic H1N1 remained in circulation during 2010, we removed 2010-year data and reanalyzed the seasonal datasets. We observed in earlier analysis that the inclusion of pandemic datasets showed variation among key variables. To ensure that our crude and pooled estimates were reliable and we have accounted the full time period in which the pandemic H1N1 influenced our estimates, we calculated and compared the crude and pooled estimates of seasonal datasets without 2010-year data to the estimates including all seasonal datasets.

We defined partial-years data as datasets which completed ongoing influenza testing beyond a 12-month period, such as 15 and 26 months. Datasets with partial years may potentially include multiple peaks of influenza circulation and as a result of this

inclusion, inflate our pooled and crude estimates. We stratified datasets by whether they contained partial years of data and compared the estimates.

We considered datasets which tested for other pathogens in addition to influenza type A and B as datasets completing multipathogen detection. Other viruses frequently co-circulate with influenza. These viruses as well as bacteria can co-exist with influenza in the human hosts and may increase the severity of the infection. To explore whether datasets that tested for other pathogens in addition to influenza were likely to have higher or lower crude proportions and pooled estimates, we stratified the published datasets by multipathogen testing.

3.5 Human Subjects Considerations

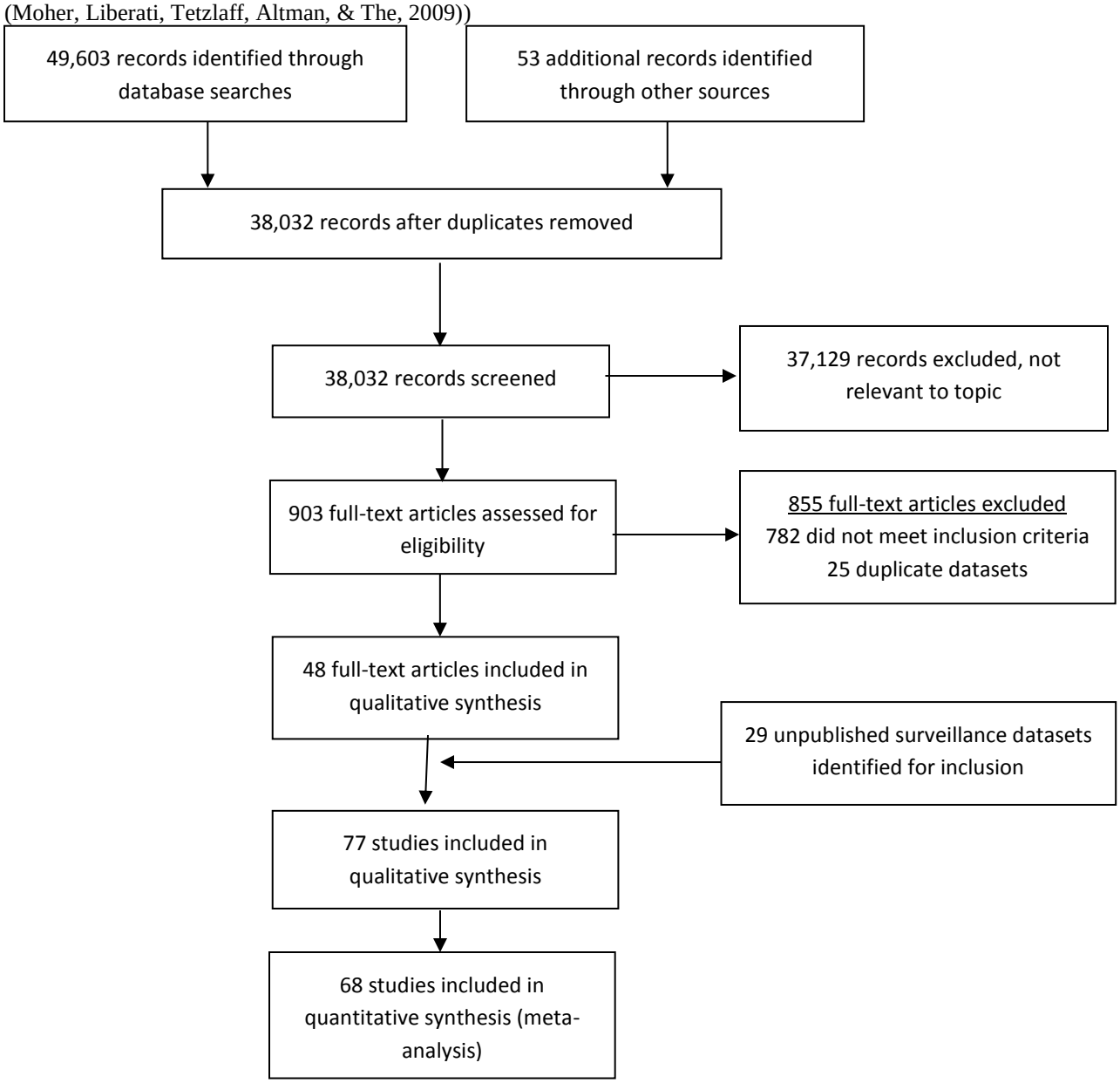
In our study, we used published data and aggregated data from consenting collaborators. No individual patient data was collected. Due to the nature of our sources, no human subject investigational review was required.

Chapter IV Results

4.1 Description of data sources

Figure 1 describes the number of eligible publications for each step in the literature review and the number of eligible surveillance datasets included in analysis. For full details of each search and more information about datasets, refer to appendices 1-3.

Figure 1. Flow diagram of data sources identified for systematic review of influenza testing among hospitalized adults (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA, (Moher, Liberati, Tetzlaff, Altman, & The, 2009))



We described the data by source in table 1. Published and unpublished datasets together covered 31 years, 1981 to 2012. The majority of datasets, whether published or unpublished, was one to two years in duration and had a population size of 100 to 500 individuals. Six published articles and three unpublished datasets only provided combined pre-pandemic/pandemic data (data not provided by year) and were excluded from analyses, which were split into seasonal and pandemic periods. Between the two sources, good global representation was seen for all World Health Organization (WHO) regions. China and Spain provided the most datasets (5 each) followed by Thailand (4), Australia (3), Germany (3), and Italy (3). All income levels and country developmental status, as defined by the World Bank and United Nations Population Division respectively, were covered by the two sources. Data sources did differ as we described in the following paragraphs.

By study design, published datasets were heterogeneous. Age ranges varied and were often not matched with the number of enrollees. Many datasets described the age of their study population as "adult," ≥14 years of age. Published datasets were older than unpublished datasets. Most publications were from the pre-pandemic (pre-2009) timeframe. In confirming influenza, published datasets most commonly used polymerase chain reaction (PCR) with other diagnostic tests. Some of the other tests may include serology, culture, and immunofluorescence. Serology, both single and paired serum, followed PCR for testing. These tests were performed on individuals meeting the preset case definition. The most common influenza case definition was pneumonia; the case definition for severe acute respiratory infection (SARI, (WHO, 2013) was not used in any of the published datasets. Published datasets were predominately from the European region, and more frequently from high income, industrialized countries. One-fourth of the datasets targeted special populations (chronic obstructive pulmonary disease, COPD; immunocompromised; ICU patients; and acute asthma patients). Many datasets also provided results for pathogens other than influenza, most commonly for respiratory syncytial virus (RSV) and parainfluenza. Little information was provided for vaccine status. Majority of published datasets provided comorbidity information, although less than half of the studies provided severity data, percentage of mortality and ICU

admissions among their study populations. From these studies, we calculated a median mortality percentage of 7% and median percentage of ICU admissions of 9%.

Using the influenza surveillance collection form, unpublished datasets captured outcome measures by pre-defined age groups (18-49 years, 50-64 years, 65-74years, and 75+ years). For our analysis, we used two age groups, 18-64 and 65+. The number of unpublished datasets increased with time; years with the largest number of unpublished datasets were those following the pandemic (particularly 2010 and 2011). Unpublished datasets used PCR alone or with other tests as the primary influenza diagnostic test. Pneumonia was not used as the case definition. Instead, unpublished datasets most frequently identified cases using the severe acute respiratory illness (SARI) definition. These datasets provided more data from the Africa, Western Pacific, and Southeast Asia regions. The data were more frequently from lower middle income; all surveillance datasets were from developing countries. Unpublished datasets were from influenza surveillance platforms that did not target special populations, and due to the design of the working group data collection form, data was not collected from working group partners on comorbidities or vaccine status, or on the detection of pathogens other than influenza types A and B.

Table 1. Characteristics of published studies and surveillance data sources about influenza-associated respiratory illness among hospitalized adults, 1981-2012

	48 Published studies n= (%)	29 Unpublished studies n= (%)
Date of studies	1981 to 2010	2003 to 2012
Age group in years*		
≥14	44(92%)	29(100%)
18 – 64	5(10%)	26(90%)
≥65	9(19%)	17(59%)
Study duration in years		
1–2	38(79%)	13(45%)
3–4	6(13%)	10(34%)
5+	4(8%)	6(21%)
Timeframe for outcome data		
Pre-2009**	42(87.5%)	6(14%)
During 2009 ("pandemic")	0%	9(21%)
Post-2009	0%	26(59%)
Total cases tested		
50–99	15(31%)	8(28%)
100–499	31(65%)	10(34%)
500+	2(4%)	11(38%)

	48 Published studies n= (%)	29 Unpublished studies n= (%)
Diagnostic test		
Polymerase Chain Reaction (PCR) only	9(19%)	11(38%)
Immunofluorescence only	1(2%)	0%
Culture only	2(4%)	0%
Serology only	13(27%)	0%
Multiple diagnostic tests, incl. PCR	18(38%)	18(62%)
Multiple diagnostic tests, excl. PCR	5(10%)	0%
Case definition‡		
Acute Respiratory Infection	4(8%)	1(3%)
Acute Lower Respiratory Infection	1(2%)	3(10%)
Pneumonia	29(60%)	0%
Severe Acute Respiratory Illness	0%	23(79%)
Other§	14(29%)	2(7%)
Study population		
General adult population	36(75%)	29(100%)
COPD	7(15%)	0%
Immunocompromised	2(4%)	0%
Other‖	3(6%)	0%
WHO region		
African	1(2%)	8(28%)
Americas	5(10%)	5(17%)
Eastern Mediterranean	2(4%)	1(3%)
European	25(52%)	2(7%)
Southeast Asian	2(4%)	6(21%)
Western Pacific	13(27%)	7(24%)
World Bank income level¶		
Low Income	1(2%)	9(31%)
Lower Middle Income	3(6%)	15(52%)
Upper Middle Income	6(13%)	5(17%)
High Income	38(79%)	0%
Development status†		
Developing	13(27%)	29(100%)
Industrialized	35(73%)	0%
Comorbidity Data Provided	40(83.3%)	0%
Influenza Vaccine Status Data Provided	12(25%)	0%
Multipathogen Detection Data Provided		
Bacteria₸	38(79%)	0%
Respiratory syncytial virus	40(83%)	0%
Parainfluenza	40(83%)	0%
Adenovirus	35(73%)	0%
Rhinovirus	24(50%)	0%
Human metapneumovirus	20(42%)	0%
Other viruses¥	31(65%)	0%

*Age groups include datasets that use subset within the given range, e.g., "≥14 Years" includes datasets of adults 30 years and older, but not those restricted to 40 and older. However, each age-based estimate is only included in one grouping. See supplement for a full description of age ranges.
**Pandemic defined as calendar year 2009. Six published articles and three working group datasets only provided combined pre-pandemic/pandemic estimates.
‡Case definitions as defined per individual study criteria
§ Includes: acute febrile illness, respiratory infection, acute exacerbation of chronic illness
‖ Includes: ICU patients only, acute asthma patients
¶Obtained from http://siteresources.worldbank.org/DATASTATISTICS/Resources/OGHIST.xls
†Source: United Nations Population Division (UNPD), 2012 World Population Prospects Report
₸ Testing for Bacteria Includes: *Streptococcus pneumoniae, Haemophilus Influenzae, Legionella pneumophila, Coxiella burnetti, Mycoplasam pneumoniae, Chlamydophila pneumonia, C. psittaci, Pseudomonas* spp, *Klebsiella*, other *Enterobacteriaceae* spp, *Staphylococcus aureus, Pasteurella spp,* β-haemolytic *Streptococcus, and* Mycobacterium, *Moraxella catarrhalis, Bacillus subtilis, Leptospira*
¥Other viruses include: enterovirus, coronavirus, herpes simplex

4.2 Median Crude Influenza-positive Proportions

4.2a. Crude proportions for all (eligible) datasets

In table 2, we provided crude estimates of respiratory samples from hospitalized adults testing positive for influenza by a number of key variables, including age range, study population type, income level, case definition, diagnostic test, WHO region, country development, documented comorbidities, and influenza vaccine status among both published and unpublished datasets. All eligible datasets conducted testing for both influenza type A and B, and provided data for populations at 14 years of age or older. A limited number of datasets used immunofluorescence and culture as their only diagnostic tool. Eastern Mediterranean was the least represented WHO region. The most common age range for the influenza-tested individuals was between 18 and 64 years of age. The median number of tested individuals was larger for unpublished datasets. The largest median number tested for influenza was diagnosed using the acute respiratory infection case definition. The immunocompromised population and culture only diagnostic also had a large median influenza-tested population, although they both were among the lowest median percent influenza-positive proportion. We noted a low median percent influenza-positive proportion for industrialized countries and when using pneumonia as the case definition. Although not significant by Kruskal-Wallis, the European WHO region had the lowest positive proportion when compared to other regions. We observed the largest median influenza-positive proportion for the pandemic (2009) timeframe followed by datasets which used multiple diagnostics excluding PCR. ICU patients and acute asthma patients together, labeled as "other," had a large median influenza-positive proportion. According to Kruskal-Wallis or Wilcoxon rank sum, there were significant differences in the median percent influenza-positive by a number of key variables: study types (published vs non-published), timeframes (pre- and post- vs during pandemic), and UN country developmental statuses.

Table 2. Crude proportion of respiratory samples from hospitalized adults testing positive for influenza by age group, study design, and population including all datasets*§

	No. of studies (n=)	Median Number (IQR)	Median Percent Positive (IQR)		p-value**
			Tested	Positive	
Age group in years					
≥14	64	258(147, 753)	21(11, 72)	10% (0.06, 0.18)	0.1254
18 to 64	26	605(285, 1235)	72(33, 356)	14% (0.09, 0.19)	
≥45	27	300(107, 718)	27(9, 92)	10% (0.08, 0.16)	
≥65	23	159(76, 482)	20(7, 55)	11% (0.06, 0.15)	
Type of study					
Unpublished surveillance	26	760(317, 1538)	80(37, 388)	13% (0.08, 0.24)	*0.0094*
Published	39	190(107, 283)	14(7, 21)	8% (0.04, 0.17)	
Timeframe for outcome data					
Pre-2009†	47	190(107, 290)	14(7, 22)	8% (0.04, 0.16)	*0.0004*
During 2009 ("pandemic")	9	501(123, 835)	162(52, 187)	23% (0.14, 0.34)	
Post-2009	26	618(218, 1065)	55(27, 151)	12% (0.08, 0.20)	
Diagnostic test					
PCR only	15	510(205,849)	37(21, 81)	14% (0.06, 0.22)	0.2597
Immunofluorescence only	1	130	9	7%	
Culture only	1	785	11	1%	
Serology Only	10	240(135, 308)	14(4, 22)	6% (0.04, 0.16)	
Multiple diagnostic tests, incl. PCR	33	266(179, 720)	21(9, 110)	9% (0.05, 0.17)	
Multiple diagnostic tests, excl. PCR	5	84(79, 157)	15(6, 20)	20% (0.07, 0.22)	
Case definition					
Acute Respiratory Infection	4	534(262, 1481)	16(10, 205)	6% (0.02, 0.13)	0.0724
Acute Lower Respiratory Infection	3	206(107, 12779)	37(14, 1324)	13% (0.10, 0.18)	
Pneumonia	24	189(124, 250)	14(7, 20)	7% (0.04, 0.10)	
Severe Acute Respiratory Illness	21	720(317, 1457)	80(52, 211)	13% (0.08, 0.26)	
Other	13	198(90, 510)	20(7, 37)	16% (0.06, 0.22)	
Study population					
General adult population	54	296(193, 800)	29(13, 80)	10% (0.06, 0.18)	0.1680
COPD	6	98(85, 148)	12(3, 22)	12%(0.02, 0.22)	
Immunocompromised	2	457(128, 785)	7(2, 11)	1% (0.01, 0.02)	
Other	3	107(79, 187)	19(7, 20)	18% (0.04, 0.25)	
WHO region					
African	8	338(217, 632)	23(14, 64)	8% (0.05, 0.14)	0.4600
Eastern Mediterranean	2	422(124, 720)	112(13, 211)	20% (0.10, 0.29)	
European	22	239(135, 324)	14(7, 34)	8% (0.02, 0.16)	
Americas	8	262(162, 1261)	18(9, 154)	10%(0.05, 0.17)	
Southeast Asian	7	748(199, 2438)	57(7, 558)	10% (0.06, 0.24)	
Western Pacific	18	208(92, 804)	28(19, 72)	14% (0.08, 0.18)	

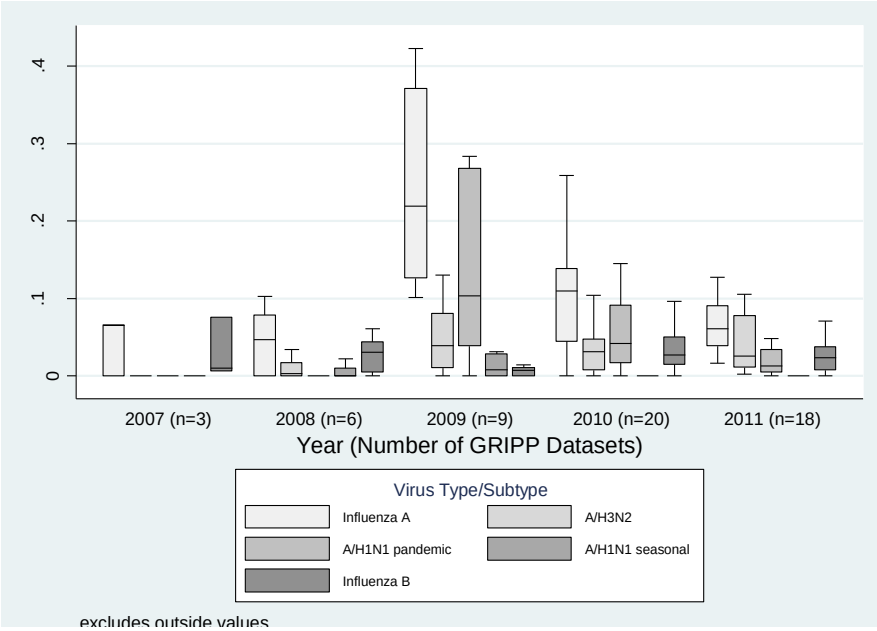
	No. of studies (n=)	Median Number (IQR)	Median Percent Positive (IQR)		p-value**
			Tested	Positive	
World Bank income level					
Low	10	464 (228, 800)	54(29, 80)	12% (0.06, 0.17)	0.0850
Lower Middle	15	783(268, 1498)	110(14, 468)	14% (0.06, 0.26)	
Upper Middle	8	211(130, 1462)	29(12, 254)	13% (0.08, 0.19)	
High	32	187(107, 283)	14(7, 22)	8% (0.03, 0.14)	
Development Status					
Developing	35	626(205, 1394)	55(15, 211)	13% (0.07, 0.20)	*0.0028*
Industrialized	30	198(107, 296)	14(6, 21)	7% (0.02, 0.13)	
Percent Comorbidity‡					
<65%	8	160(121, 258)	11(6, 22)	8% (0.04, 0.10)	0.8279
≥65% and <100%	6	250(130, 296)	9(6, 16)	7% (0.03, 0.08)	
100%	10	107(85, 148)	15(3, 20)	12% (0.02, 0.22)	
no data	43	359(206, 1065)	37(15, 120)	12% (0.06, 0.19)	
Vaccine Coverage‡					
<40%	5	198(137, 211)	16(4, 26)	8% (0.02, 0.19)	0.7540
≥40%	5	217(148, 304)	7(5, 29)	8% (0.04, 0.10)	
no data	57	283(130, 800)	21(13, 80)	10% (0.06, 0.18)	

*Six eligible articles provided data for influenza A only, and were excluded from the overall positive analyses
§These crude estimates include all datasets: pre-pandemic, pandemic, and post-pandemic.
**Kruskal-Wallis/Wilcoxon rank sum test.
†Pandemic defined as calendar year 2009. Nine studies only provided combined pre-pandemic/pandemic estimates. Since data was provided by year in the unpublished datasets, three unpublished datasets were included in two timeframes; six unpublished datasets were in all three timeframes.
‡Data only available in published studies. Fifteen studies provided approximate totals for percent comorbidity and one study for vaccine coverage. These were excluded from analysis. Kruskal Wallis or Wilcoxon rank sums of defined groups; excluded no data.

4.2b.Crude positive proportions by year and virus type or subtype

We used boxplots to present the total proportion of positive influenza by year and by virus type or subtype in figure 2. Since unpublished datasets were the only source to provide data by year and by virus type or subtype, we constructed the boxplots using the unpublished datasets. Although unpublished datasets covered 2003 to 2012, we limited our analysis to years with more than one dataset. We had one dataset for each of the following years: 2003, 2004, 2005, 2006, and 2012. Virus type A was most commonly detected during 2007 to 2011. The largest subtype-specific median influenza-positive proportion was seen in 2009 for influenza A (H1N1) pandemic virus. Pandemic H1N1 decreased in 2010, but was still high. In 2011, pandemic H1N1further decreased. Cases of seasonal influenza A (H1N1) were the least commonly detected subtype, and were only detected in 2009. Influenza A (H3N2) virus was detected from 2008 through 2011, when it had its highest proportion positive among these datasets. Influenza type B cases were confirmed and reported throughout the time period (2007 to 2011) with u-shaped positive proportion distribution, decreasing in 2009 and increasing in 2010.

Figure 2. Boxplot of the proportion of adult respiratory samples testing positive for influenza virus by year and virus



4.2c. Crude positive proportions by population characteristics

Some publications provided more details about their study populations, such as the percentage of study participants with comorbidities and those who have received the influenza vaccine within the last twelve months. In table 2 and 3, we observed a slight increase in median percent influenza-positive proportions as the percentage of vaccine coverage and comorbidities among the study population increases. This increase, however, as calculated by Kruskal-Wallis or Wilcoxon rank sums, is not statistically significant (p-values >0.05). It is important to note that majority of studies (49 to 65 of the 77 studies) lacked comorbidity and vaccine coverage information. Of the comorbidities reported, lung disease was the most common.

4.2d. Pandemic and seasonal crude proportions

To determine whether the data from the pandemic period was influencing the trends in the median positive proportion by other key variables, we removed data from this timeframe from the crude analyses, and observed a decrease in statistical significance in median positive proportions for timeframe variable. In table 3, we showed the crude estimates with seasonal (pre and post pandemic) data only. After removing the pandemic timeframe from analysis, statistical significance diminished for all groupings, except for

UN country development status and timeframe. The highest median influenza-positive proportion slightly decreased from 23% to 20%. Studies which used multiple diagnostics excluding PCR had the highest median positive proportion. This decrease in median positive proportion was observed for many variables, such as age group 18-64 (14% all datasets to 12% seasonal datasets only) and developing countries (13% all to 10% seasonal). By the number of datasets, we noted that most seasonal datasets used either SARI or pneumonia as their case definition, tested individuals using multiple tests including PCR, and came from the European WHO region, high or lower middle income levels, and developing countries. Datasets, which used acute lower respiratory infection as the case definition, had the largest median number of individuals tested for influenza (1662, median range = 84 to 1662) and the largest median number of individuals with positive influenza laboratory results (164, median range = 7 to 164). Datasets which used culture or immunofluorescence as their primary diagnostic test had the lowest median number of laboratory-confirmed positive influenza cases.

We also stratified crude proportions by pandemic datasets alone (appendix 4). Pandemic datasets were smaller and lacked power. Generally, when pandemic data was available for variables, the pandemic crude proportions were larger than seasonal crude proportions (12-42%). None of the published datasets in our systematic review focused on the pandemic year alone. We observed a slight statistical difference between case definitions, acute lower respiratory infection versus severe acute respiratory infection, in the pandemic datasets (p-value by Kruskal-Wallis = 0.0404). No other subgroupings were statistically differed by Kruskal-Wallis or Wilcoxon rank sum test.

Table 3. Seasonal crude proportions of respiratory samples from hospitalized adults testing positive for influenza by age group, study design, and population*§

	No. of studies (n=)	Median Number (IQR)	Median Percent Positive (IQR)		p-value**
			Tested	Positive	
Age group in years					
≥14	61	209(124, 473)	19(9, 46)	10% (0.05, 0.15)	0.3099
18 to 64	25	199(112, 528)	22(12, 75)	12% (0.06, 0.16)	
≥45	26	176(86, 558)	18(7, 74)	10% (0.07, 0.14)	
≥65	20	149(88, 441)	16(7, 50)	10% (0.06, 0.15)	
Type of study					
Unpublished surveillance	25	232(136, 805)	26(13, 109)	11% (0.06, 0.15)	0.2124
Published	39	190(107, 283)	14(7, 21)	8% (0.04, 0.17)	

	No. of studies (n=)	Median Number (IQR)	Median Percent Positive (IQR)		p-value**
			Tested	Positive	
Diagnostic test					
PCR only		164(117, 401)	20(13, 36)	13% (0.07, 0.17)	0.1486
Immunofluorescence only	15	130	9	7%	
Culture only	1	785	11	1%	
Serology Only	10	240(135, 308)	14(4, 22)	6% (0.02, 0.16)	
Multiple diagnostic tests, incl. PCR	32	229(136, 551)	19(8, 70)	8% (0.04, 0.13)	
Multiple diagnostic tests, excl. PCR	5	84(79, 157)	15(6, 20)	20% (0.07, 0.22)	
Case definition					
Acute Respiratory Infection	4	566(283, 785)	21(11, 99)	9% (0.03, 0.13)	0.3623
Acute Lower Respiratory Infection	3	1662(826, 2019)	164(40, 237)	13% (0.09, 0.14)	
Pneumonia	24	189(124, 250)	14(7, 20)	7% (0.04, 0.10)	
Severe Acute Respiratory Illness	20	192(117, 401)	17(9, 41)	10% (0.06, 0.15)	
Other	14	198(90, 510)	20(7, 36)	16% (0.04, 0.22)	
Study population					
General adult population	53	228(135, 510)	19(9, 52)	10% (0.06, 0.15)	0.1505
COPD	6	98(85, 148)	12(3, 22)	12%(0.02, 0.22)	
Immunocompromised	2	457(128, 785)	7(2, 11)	1% (0.01, 0.02)	
Other	3	107(79, 187)	19(7, 20)	18% (0.04, 0.25)	
WHO region					
African	8	177(111, 233)	14(8, 27)	8% (0.06, 0.14)	0.9136
Eastern Mediterranean	1	124	13	10%	
European	22	198(123, 250)	14(8, 25)	8% (0.03, 0.15)	
Americas	8	233(133, 437)	18(9, 46)	10%(0.05, 0.14)	
Southeast Asian	7	1130(143, 1680)	85(16, 236)	12% (0.06, 0.17)	
Western Pacific	18	203(109, 401)	22(6, 30)	10% (0.05, 0.18)	
World Bank income level					
Low	10	184 (92, 358)	16(13, 28)	10% (0.06, 0.15)	0.4555
Lower Middle	14	250(140, 955)	26(8, 115)	10% (0.04, 0.16)	
Upper Middle	8	566(130, 1462)	68(15, 120)	12% (0.08, 0.17)	
High	32	187(107, 283)	14(7, 22)	8% (0.03, 0.14)	
Development Status					
Developing	34	208(123, 800)	24(13, 84)	10% (0.06, 0.16)	*0.0492*
Industrialized	30	198(107, 296)	14(6, 21)	7% (0.02, 0.13)	
Percent Comorbidity‡					
<65%	8	160(122, 258)	11(6, 22)	8% (0.04, 0.10)	0.8279
≥65% and <100%	6	250(130, 296)	9(6, 16)	7% (0.03, 0.08)	
100%	10	107(85, 148)	15(3, 20)	12% (0.02, 0.22)	
no data	42	231(136, 582)	21(13, 81)	10% (0.06, 0.16)	
Vaccine Coverage‡					
<40%	5	198(137, 211)	16(4, 26)	8% (0.02, 0.19)	0.7540
≥40%	5	217(148, 304)	7(5, 29)	8% (0.04, 0.10)	
no data	56	208(117, 536)	19(9, 41)	10% (0.06, 0.15)	

*Six eligible articles provided data for influenza A only, and were excluded from the overall positive analyses

§These crude estimates include all datasets: pre-pandemic, pandemic, and post-pandemic.
**Kruskal-Wallis/Wilcoxon rank sum test.
†Pandemic defined as calendar year 2009. Nine studies only provided combined pre-pandemic/pandemic estimates. Since data was provided by year in the unpublished datasets, three unpublished datasets were included in two timeframes; six unpublished datasets were in all three timeframes.
‡Data only available in published studies. Fifteen studies provided approximate totals for percent comorbidity and one study for vaccine coverage. These were excluded from analysis. Kruskal Wallis or Wilcoxon rank sums of defined groups; excluded no data.

4.3 Pooled estimates of adult influenza respiratory hospitalizations

Using the binomial regression model in SAS, we calculated pooled estimates for the positive proportion of adult influenza hospitalizations by age range, study population type, country developmental status, WHO region, and country income level (table 4). We included sample size and 95% CI. Due to statistical, significant differences observed in key variables when including pandemic datasets, we used only seasonal datasets in our pooled estimate calculations. We calculated an overall pooled estimate of 11% (95% CI, 0.09-0.12). Pooled estimates ranged from 7% to 16%. Whether restricting analysis to PCR only or including all tests, we calculated similar median positive pooled estimates for both overall and stratified estimates. We observed very little change in median influenza-positive crude proportions and median positive pooled estimates for age groups. We noted consistent results, across stratified estimates, for country developmental status and country income level. Lower income countries, where PCR was used exclusively, had a higher median positive pooled estimate than higher income countries. Developing countries had a higher (11-12%) median positive pooled estimate than industrialized countries (8%).

Table 4: Pooled estimates of global adult influenza-associated hospitalizations, by age group, study population, income level and WHO region

	PCR Tested N*	PCR tested Pooled % Positive (95% CI)	N†	Pooled % Positive (95% CI)†
Age group in years				
≥14	62	11% (0.09, 0.13)	88	11% (0.09, 0.12)
18 to 64	44	12% (0.09, 0.15)	50	12%(0.10, 0.15)
≥45	33	10% (0.09, 0.11)	41	10% (0.09, 0.11)
≥65	23	10% (0.10, 0.10)	31	10% (0.10, 0.10)
Study population				
General adult population	59	11% (0.09, 0.13)	80	11% (0.09, 0.13)
Special population**	5	9% (0.03, 0.30)	9	7% (0.03, 0.16)
WHO region				
African	14	9% (0.07, 0.12)	15	9% (0.07, 0.12)
Americas	3	9% (0.03, 0.23)	12	11% (0.08, 0.15)
Eastern Mediterranean			one dataset‡	
European	12	16% (0.08, 0.34)	24	10% (0.06, 0.18)

	PCR Tested N*	PCR tested Pooled % Positive (95% CI)	N†	Pooled % Positive (95% CI)†
WHO region				
Southeast Asian	14	13% (0.08, 0.19)	14	12% (0.08, 0.19)
Western Pacific	21	11% (0.08, 0.14)	25	11% (0.08, 0.14)
Income level				
Low Income	17	13% (0.10, 0.17)	18	13% (0.10, 0.16)
Lower Middle Income	25	12% (0.08, 0.18)	31	12% (0.09, 0.17)
Upper Middle Income	7	10% (0.07, 0.16)	10	10% (0.07, 0.14)
High Income	15	9% (0.06, 0.12)	32	8% (0.06, 0.11)
Development status†				
Developing	51	11% (0.09, 0.14)	61	12% (0.10, 0.14)
Industrialized	13	8% (0.06, 0.12)	30	8% (0.05, 0.10)

*Number of data points included in model, including multiple individual years from a single dataset, when available
**Includes ICU patients, acute asthma patients, COPD patients, and immunocompromised patients
†All diagnostic tests included
‡no PCR data
§Includes: ICU patients only, acute asthma patients, immunocompromised patients, and COPD patients

4.4. Assessment of the impact of dataset quality on influenza-positive proportions

Exploring the impact of article quality on our outcome of interest, we found no significant difference in the median influenza-positive proportions among published datasets by total bias score (p-value = 0.9255; appendix 5). In our assessment, we evaluated selection, comparability, and outcome bias, giving each dataset a bias score of 0 (undefined) or 1 (clearly defined). Total bias was the sum of this assessment, with larger totals correlating with the higher quality. This assessment was limited to published datasets. Thirty-eight percent of published datasets were of high quality with total bias score of 3. Slightly more datasets were of medium quality, total bias scores of 2 (43%). A small subset of datasets had a total bias score of ≤1 (19%). When we stratified the published datasets by PCR testing, we observed a statistical difference in median proportion positive by selection bias score (p-value = 0.0394); datasets with high quality scores, bias score of 1, had a larger median positive proportion (11% compared to 5% for datasets with a selection bias score of 0). The statistical difference seen in selection bias after stratifying datasets by PCR testing did not influence the overall bias assessment (p-value = 0.1866). We also noted a larger median positive proportion for datasets where PCR was the primary diagnostic test, and published PCR datasets tended to be of high quality with a total bias score of 3 (of 3). After we stratified by timeframe, we noted that the pandemic datasets had larger median positive proportions as the total bias score increased (14% when total bias score equaled 3 and 5% when total bias score equaled 2). Seasonal datasets exhibited little to no change in median positive proportion with varying

bias assessment scores (10% positive proportion for datasets with total bias score of 0 or 1, 7% positive proportion for datasets with total bias score of 2, and 8% positive proportion for datasets with total bias of 3).

4.5 Exploratory Analyses

4.5a. Impact of pandemic H1N1in 2010 calendar year

To evaluate the possible influence of other factors on the calculated crude proportions and pooled estimates, we conducted several post-hoc exploratory analyses. The first factor we evaluated was inclusion of calendar year 2010 data in seasonal influenza (non-pandemic) estimates. In our primary analyses, we defined pandemic datasets as datasets including the 2009 year. However, as seen in figure 2, pandemic H1N1 continued to circulate in 2010. As we previously described in table 3, we observed a decrease in statistical differences among key variables when we removed 2009-year data. To explore whether 2010-year data influenced crude proportions and/or pooled estimates for seasonal influenza, we reanalyzed the seasonal data, excluding data points from 2010 and compared these findings to the main results (appendix 6). When reviewing the datasets without 2010-year data, we observed slight decreases in crude proportions (1-20%; examples include 6% without 2010 vs 9% in seasonal for acute respiratory infection case definition). The ≥65 age group crude proportions increased after removal of 2010 data (10% to 11%). No statistical significance was noted among the crude proportions by Kruskal-Wallis or Wilcoxon rank sums in the datasets without 2010-year data. Pooled estimates were similar prior to and after stratification, typically 1% to 3% lower after 2010-year data was removed. Highest pooled estimate, before and after stratification, was for datasets from the European WHO region which used PCR as the primary diagnostic test (16%).

4.5b. Potential impact of testing timeframe and detection of other pathogens

4.5bi. Partial year influenza testing stratification

In this study, some datasets collected data for one or more full 12-month periods, while others had a time frame of data collection exceeding a multiple of 12 months of

ongoing influenza testing (such as 18 or 30 months). We referred to these datasets as datasets with partial years of influenza data (appendix 7). To ensure that the datasets with partial years did not inflate our pooled and crude estimates due to their potential inclusion of multiple peaks of influenza circulation, we stratified the datasets by whether they contained partial years of data and compared the estimates. After stratifying the datasets, we noticed that there were less datasets with partial-year data than with data completed during 12-month periods (36 partial-year datasets had data for the ≥14 year-old age group, while 73 full-year datasets included data for the same age group variable, for an example). A few variables were specific to datasets with or without partial years. Datasets that used immunofluorescence as the only diagnostic test or were from the Eastern Mediterranean WHO region completed influenza testing ongoing beyond a multiple of 12 months; using culture only or multiple diagnostic testing excluding PCR were only seen in datasets without partial-year data.

Overall, datasets with partial years had similar positive crude proportions, 0-19%, compared to datasets without partial years, 0-20%. The multiple tests excluding PCR variables remained the largest crude proportions in the datasets without partial years (20%). The PCR only datasets with partial-year data had a crude proportion of 19%. This crude proportion decreased by 8% when datasets with partial-year data were excluded and by 6% when analyzing all eligible seasonal datasets. We noted similar levels of decrease in crude proportions after removing partial-year datasets for COPD study population (16% partial-year to 8% full-year), Western Pacific WHO region (17% partial-year to 9% full-year), and industrialized countries (10% partial-year to 5% full-year). Increases in crude proportions were observed in datasets without partial-year data. Datasets from the Americas WHO region increased 5% after the removal of datasets with partial-year data.

As calculated by Kruskal-Wallis or Wilcoxon rank sums, we observed statistical differences for case definition in partial-year datasets (p-value = 0.032). We noted more statistical differences for crude proportions in datasets without partial years (pre- and post-pandemic timeframe, p-value = 0.038; and development status, p-value = 0.0464).

When we evaluated the pooled estimates by partial year stratification, datasets with partial years versus datasets with full years, we observed little difference in

estimates between partial and full year datasets including all diagnostic tests (9-20% and 4-21% respectively). Pooled estimates for special populations decreased when we removed partial-year datasets (20% partial-year to 4% full-year datasets). We also noticed a decrease in pooled estimates for datasets from the Southeast Asian WHO region after the removal of partial-year datasets (17% partial-year to 11% full-year). European WHO region datasets increased from 11% with partial-year datasets to 21% without partial-year datasets.

4.5bii. Multipathogen Detection

Other viruses frequently co-circulate with influenza. These viruses as well as bacteria can co-exist with influenza in the human hosts and may increase the severity of the infection. To explore whether datasets that tested for other pathogens in addition to influenza were likely to have higher or lower crude proportions and pooled estimates, we stratified the published datasets by multipathogen testing (appendix 8). Only one published, seasonal dataset did not test for other pathogens in addition to influenza type A and B. Comparing the crude and pooled estimates from the multipathogen testing datasets, published only, to those in the seasonal datasets, published and unpublished, we noted little change in the estimates (0-6% difference seen among the key variables). The overall pooled estimate for the multipathogen testing datasets was 8% (compared to the seasonal, 11%). Similar to the seasonal datasets, developing countries had higher pooled estimates than industrialized countries (12% vs 7%) in the multipathogen testing datasets. We were unable to calculate pooled estimates for three of the six WHO regions (African, Eastern Mediterranean, and Southeast Asia), and for low and lower middle income levels using the multipathogen testing datasets. With the seasonal datasets, we calculated pooled estimates for all variables of interest; we included data from lower income countries and all WHO regions in our analysis by supplementing the literature review with surveillance data. No statistical significance was observed in the crude proportions for the multipathogen testing datasets.

To evaluate whether testing for a specific pathogen in addition to influenza influenced the influenza-positive crude proportions and/or total tested for influenza, we stratified the crude proportions in the multipathogen testing datasets by other pathogen

testing. We found that influenza-positive crude proportions increased when excluding datasets that tested for RSV, adenovirus, or bacteria (8% prior to stratification; 11% without RSV, 22% without adenovirus, and 14% without bacteria). The crude proportions further increased when we restricted the analysis to PCR data (17% without bacteria, for example). We observed larger median totals tested for influenza when we excluded datasets that tested for RSV; parainfluenza; bacteria; or enterovirus, coronavirus, and herpes simplex. Totals increased when we included datasets that tested for adenovirus or rhinovirus.

Chapter V Discussion

5.1 Summary of findings

By combining findings from the published literature with additional unpublished surveillance data, we obtained influenza testing results from 50 countries with varying income levels, country development status, vaccine policies, and health-seeking behaviors over a 31-year period of time. We estimated that 11% (95% CI, 0.09 – 0.12) of global adult respiratory hospitalizations were associated with seasonal (non-pandemic) influenza. This pooled estimate increased as country income level decreased and as country development status decreased (8% (0.06, 0.11) for high income, 10% (0.07, 0.14) for upper middle income, 12% (0.09, 0.17) for lower middle income, and 13% (0.10, 0.14) for low income; 8% (0.05, 0.10) for industrialized countries and 12% (0.10, 0.14) for developing countries). The crude (median) proportions were influenced by the pandemic time period, with the largest proportion positive (23% IQR 0.14-0.34) occurred during 2009. The crude proportion positive for influenza during non-pandemic periods was not statistically different by age group, data source, case definition, or country income level.

5.2 Evaluation of potential impact on estimates by key variables or with inclusion of pandemic virus

Impact of country income level and development status

Country income and development status had an inverse relationship with the influenza-positive pooled estimate and seasonal crude proportions, with increasing prevalence of influenza as country income decreased. Comparing the datasets by country development status, we notice that majority of datasets provided by developing countries were unpublished, used PCR as their main diagnostic test, and were collected post 2009 pandemic. Timeframe at which specimens were collected and analyzed may influence the positive-influenza proportion. At times of heightened awareness of influenza, enrollment increases (Ayele et al., 2012). Perhaps, more individuals with influenza seek care and

tested positive for influenza after than before 2009. Prior to 2009, influenza data from developing, low-income countries was limited, as seen with our meta-analysis and others (Briand, Mounts, & Chamberland, 2011; Gessner et al., 2011; Peasah et al., 2013; Savy et al., 2013; Simmerman & Uyeki, 2008). With the later time period of testing, developing countries were able to use more sensitive methods such as PCR (Das, Spackman, Pantin-Jackwood, & Suarez, 2009; Kumar & Henrickson, 2012; Pasick, 2008; WHO, 2011a). Industrialized countries included our meta-analysis used other tests (immunofluorescence, cell culture, and immunoassays), which may have lower sensitivity or require advanced technical skill, in addition to PCR (Harper et al., 2009; Kumar & Henrickson, 2012). Depending on the testing algorithm and interpretation of results, some influenza cases may have been missed (Harper et al., 2009; Kumar & Henrickson, 2012).

While industrialized countries have well-established influenza vaccination programs, high vaccine coverage (≥60% among adults ≥65 years old), and in many cases stockpiles of vaccines available, developing countries, low and middle income countries struggle to have influenza vaccine recommendations or policies established (Mereckiene et al., 2010; MIV, 2005; Oshitani, Kamigaki, & Suzuki, 2008; Samaan et al., 2013). During our study timeframe, the influenza vaccine available may have provided sufficient protection against circulating strains and as result, countries distributing the vaccine to their population were able to prevent influenza disease, decreasing the number of individuals who tested positive for influenza. Although influenza vaccine effectiveness was reported low during the 2003-2004 season in the United States (Herrera et al., 2007), the increased vaccine coverage during 2010-2011 and 2012-2013 seasons averted more influenza illness and hospitalizations (Bresee et al., 2013; Kostova et al., 2013).

Differences in host immunity and virulence of influenza may contribute to the variation in influenza positive proportions among developing, lower income countries and industrialized, high income countries (Freitas et al., 2013; Yang, Chiu, et al., 2011; Yu et al., 2014). Influenza disease may lead to more severe outcomes in developing countries due to higher prevalence of HIV and malnutrition (Freitas et al., 2013; Tempia et al., 2014). Adults infected with HIV are at greater risk of influenza-associated hospitalizations (C. Cohen et al., 2012; Gessner et al., 2013). In addition to increased risk

of severe influenza disease, immunocompromised adults shed seasonal influenza virus detectable by PCR for longer periods of time than immunocompetent adults (Klimov et al., 1995; van der Vries et al., 2013; Weinstock, Gubareva, & Zuccotti, 2003). Prolonged shedding of pandemic H1N1 virus was detected in both immunocompromised and immunocompetent adults (Fleury et al., 2009). The variation of co-circulating viruses and bacteria between developing and industrialized countries may also contribute to the difference in disease severity (Madhi & Klugman, 2004; Morens, Taubenberger, & Fauci, 2008). Environmental factors, such as crowded living conditions with close proximity to animals, temperature, and humidity, may increase likelihood of influenza transmission and/or promote viral survival in developing, lower income countries (Freitas et al., 2013; Yang, Chiu, et al., 2011). Sutanto *et al* observed a decrease in influenza severe outcomes when accessibility to health care increased (Sutanto et al., 2002). Developing, low income countries often have insufficient number of nurses and doctors on staff, hospital beds available, and medical supplies (Oshitani et al., 2008). A low income country with large populations, such as Bangladesh, have modest health care infrastructure (Homaira et al., 2012). With this lack of access to adequate medical care and modest health infrastructures, developing countries experience higher mortality rates due to influenza than industrialized countries, according Oshitani and colleagues (Oshitani et al., 2008).

Impact of pandemic H1N1

As we noticed in our analysis, the pandemic H1N1 season was very different from other influenza seasons. The largest positive proportions were seen during the pandemic. Globally, H1N1 contributed to 201,000 respiratory deaths and 83,300 cardiovascular deaths (F. Dawood et al., 2012). When examining the positive proportions by age group, we observed slightly higher positive proportions in younger adults, 18-64 years old, than older adults, 65 years or older (not statistically significant). This finding is consistent with surveillance studies of influenza-associated hospitalizations conducted in the United States and India (Chadha et al., 2013; C. M. Cox et al., 2012; N. J. Cox & Subbarao, 2000). During the pandemic in the United States, influenza-associated hospitalizations among younger adults increased 6-folds, in comparison to the average number of hospitalizations in this age group during the prior four influenza seasons (C. M. Cox et

al., 2012). In India, the highest number of hospitalizations due to pandemic H1N1 was among individuals 5-29 years old (Chadha et al., 2013). Although hospitalizations among younger adults increased during the pandemic, hospitalizations among adults ≥75 years old decreased (C. M. Cox et al., 2012). A large portion of older adults had pre-existing, cross-reactive antibodies to pandemic H1N1, according to a serological survey of adult serum prior to 2009; these antibodies provided immune protection (Hancock et al., 2009).

Impact of age

After the removal of pandemic H1N1 data (2009 year data), we observed no difference in positive proportions by age group (12% (IQR, 0.06-0.16) for 18-64 year olds and 10% (IQR, 0.06, 0.15) for 65+). Behbehani *et al* described this lack of difference in their published dataset, when they conducted a year-long study to evaluate the causes of community-acquired pneumonia in hospitalized adults in Kuwait (Behbehani et al., 2005). Earlier studies show that complications, hospitalizations, and deaths due to season influenza were greatest among adults ≥65 years of age (CDC, 2010). Due to the higher risk for severe outcomes, existing influenza vaccination policies for adults typically target this age group (CDC, 2013; Mereckiene et al., 2010; MIV, 2005; WHO, 2012a, 2012b). According to recent studies, a large portion of adults ≥65 years old are receiving the vaccine (Mereckiene et al., 2010). This increase in vaccine uptake among this age group may have prevented disease, if the received vaccine induced an adequate immune response in vaccinees against circulating influenza strain(s) (CDC, 2010). Vaccine effectiveness, however, is known to be lower in older adults than younger adults due dysregulation of the immune system, termed immunosenescence (Reber et al., 2012). Older adults may have acquired immunity to circulating strains through prior exposure, as seen in the pandemic timeframe (Hancock et al., 2009; Hardelid et al., 2010; Miller et al., 2010; Talbot & Falsey, 2010). On the other hand, the datasets included in our study may have missed influenza cases in older adults due to atypical presentation, not fitting the case definitions, or the inability to collect specimens (Talbot & Falsey, 2010; Babcock, Merz, Dubberke, & Fraser, 2008). Influenza often presents without fever in older adults and patients with COPD (Talbot & Falsey, 2010). When comparing laboratory-confirmed influenza cases, younger adults matched the influenza-like-illness

case definitions more frequently than older adults (Babcock et al., 2008; Radin et al., 2012). Older adults tend to have less secretions and increased nasal dryness; both of which increase the difficulty of collecting specimens and may result in more discomfort during the collection process (Talbot & Falsey, 2010). As found from community surveys, health-seeking behaviors depend on socioeconomic status, disease severity, and age. Children were more likely to be treated than adults in New Mexico, United States (D. L. Thompson et al., 2013). During the 2005-2010 influenza seasons in Hong Kong, Wang *et al* observed an increase in excess influenza-related hospitalizations among children and young adults and a decrease among adults ≥65 years old (Wang et al., 2012). Heighten public awareness of respiratory viruses due to SARS may explain the change in health-seeking behavior among parents and young adults (Wang et al., 2012). Older adults and adults with underlying conditions usually seek care for influenza-like-symptoms only after the illness worsens (Biggerstaff et al., 2014). Since influenza illness can lead to secondary infections and/or complications of underlying conditions, older adults and adults with underlying conditions may go undiagnosed and not tested for influenza (Biggerstaff et al., 2014). If even tested for influenza, these patients may not be shedding virus at the time of receiving care (Biggerstaff et al., 2014). The differences in age distribution among the study populations may also explain the lack of difference between the age groups. In developing countries, especially in countries with high prevalence of HIV and malnutrition, life expectancy is lower than industrialized countries (Gordon et al., 2010; Radin et al., 2012; Takahashi et al., 2013). As a result, the population proportion of elderly in Vietnam, for example, is lower than the proportion of the population living in the United States (Takahashi et al., 2013). Because our age cut-offs primarily reflect the unpublished surveillance data, which was collected from developing countries only, the older age group may not be well-represented.

Impact of diagnostic tests used

In our analysis, diagnostic test used did not influence the pooled estimates and positive proportions. Influenza diagnostic tests have varying sensitivity and specificity (Leekha et al., 2013; Sawatwong et al., 2012; Talbot & Falsey, 2010). When respiratory specimens are collected soon after onset and stored properly, PCR is considered the most

sensitive test, even for adults ≥ 65 years old (Ellis & Curran, 2011; Hopkins, Moorcroft, Correia, & Hart, 2011; Leekha et al., 2013; Sawatwong et al., 2012; Talbot & Falsey, 2010). PCR datasets from a similar meta-analysis of children hospitalized due to respiratory infections had higher influenza-positive crude and pooled estimates than non-PCR datasets (Lafond et al., 2014). In our study, majority of the datasets (100% unpublished datasets and 50% published datasets) used PCR alone or with other tests. Our analysis may have been limited by the number of datasets not using PCR (56 PCR vs 21 non-PCR). Of those not using PCR, 86% used paired or single serum serology. While paired serum serology measures fold-rise in antibody titers from initial exposure (vaccine or infection) to recovery, single serum serology measures one point in time with pre-established limits (Broor, Chahar, & Kaushik, 2009; Kumar & Henrickson, 2012). These pre-established limits do not account for pre-existing antibodies due to prior exposure or recent vaccination, which may result in false positives (Broor et al., 2009; Kumar & Henrickson, 2012). Prior exposure to certain influenza virus types and/or subtypes is common in adults, especially older adults (Talbot & Falsey, 2010). We found a 20% influenza positive proportion among datasets that used multiple tests excluding PCR in our crude analysis; some of these datasets included single serum serology. False positives may also result from PCR. Due to its high sensitivity, PCR detects virus in environmental contaminants and after the virus no longer replicates (Hopkins et al., 2011; Sawatwong et al., 2012). The use of multiple tests may provide a more accurate picture of true infections (Sawatwong et al., 2012; Talbot & Falsey, 2010).

Impact of case definition

Case definitions change over time to improve sensitivity and specificity of influenza detection. The exclusion of difficulty breathing or shortness of breath, replacing the terms with cough, improved the sensitivity and specificity of the SARI case definition among hospitalized patients (Gupta et al., 2013; Hirve et al., 2012; Nachtnebel et al., 2012). Authors who evaluated the pneumonia case definition in three states reminded the readers that influenza hospitalizations are associated with other diseases (circulatory, neurological, etc.) in addition to pneumonia, and restricting to the use of the pneumonia case definition alone may underestimate the burden of influenza hospitalizations (Ortiz et

al., 2014). Although case definitions are often subjective and may have differing levels of sensitivity and specificity (Nichol & Mendelman, 2004), we did not observe statistically significant differences, through non-parametric testing, between case definitions in our eligible datasets.

Impact of WHO region

In addition to World Bank and UN development status, WHO region is another method of defining a global region (WHO, 2014a). WHO created six regions to ease disease reporting and disease data analysis (WHO). Differences in influenza seasonality and disease severity have been observed among the WHO regions. The pandemic H1N1 remained in circulation longer in the Southeastern Asia and African WHO regions than in the other four regions, for example (WHO, 2010). Despite differences, we observed no statistically significant differences in positive crude proportions for our datasets between the WHO regions, implying that WHO regions in our study does not impact positive proportions. To improve the estimate for the Eastern Mediterranean WHO region, only one dataset was available from this region, more research is needed.

5.3 Limitations and exploratory analysis

Our study is subject to several limitations. Our data were heterogeneous due to variability in data sources' time frames, testing criteria or case definitions, and testing procedures. Diagnostic tests also vary in sensitivity and specificity (Leekha et al., 2013; Sawatwong et al., 2012; Talbot & Falsey, 2010). As the timing between disease onset and specimen collection increases, the ability to detect influenza viruses decreases, especially in adults who shed less virus than children (W. P. Glezen, Greenberg, Atmar, Piedra, & Couch, 2000; Leekha et al., 2013; Sawatwong et al., 2012; Talbot & Falsey, 2010). Further, hospital admission relied on care-seeking behavior and hospital or healthcare facility admission policies (Gordis, 2009; Parashar et al., 2003), which may have increased or decreased enrollment and did not necessarily influence the percent positive for influenza. The severity of influenza may vary by population (Gordis, 2009). We may not have accounted for all severe influenza cases, especially in resource-limited areas and when patients had non-respiratory presentations of influenza (Freitas et al., 2013;

Oshitani et al., 2008; Radin et al., 2012). We assumed that influenza caused the hospitalization and do not account for co-infections and underlying conditions in our entire study population. Other viruses, such as respiratory syncytial virus and parainfluenza virus, often co-circulate with influenza (Zhou et al., 2012). While all but two published datasets tested for other pathogens, we are unaware of whether surveillance sites considered other pathogens as the cause of illness. When other pathogens in addition to influenza were detected in patients among published datasets, the main pathogen contributing to the hospitalization was unknown. Co-infections and certain underlying conditions have shown to increase the severity of influenza infections (Dena L. Schanzer et al., 2008a). Severity of influenza disease is unknown due to the lack of patient outcome data in the majority of study datasets. We may have a reduced likelihood of publication bias for influenza results in our findings due to the inclusion of published datasets which tested for other pathogens in addition to influenza or found no confirmed cases of influenza. Also, according to the Campbell Collaboration Reviews, we may have removed or at least decreased the effect of publication bias by including unpublished datasets (C2, 2014). From our quality assessment, 81% of published datasets were of median to high quality. To minimize our study limitations, we used a randomized effect model and stratified our data by potential factors—the detection of pandemic H1N1 during the 2010 calendar year, data collected during multiple influenza seasons, and the detection of other pathogens that co-circulate with influenza.

We found no indication that 2010 calendar year data, partial year data, and multi-pathogen testing data impacted the overall seasonal pooled estimates (0-19%). Beginning in April 2009, public health officials across the globe began to identify pandemic H1N1 cases (WHO, 2010). The report further described the decreased number of cases due to pandemic H1N1 in most countries and the increased rates of cases due to influenza type B (WHO, 2010). Our boxplot demonstrated this trend. As we described earlier, the inclusion of pandemic data (from calendar year 2009) impacted our crude and pooled estimates. While the pandemic virus, continued to circulate after 2009, it did not have the same impact in 2010, as seen in our crude and pooled estimates when stratifying seasonal results to include or exclude 2010 calendar year data.

Datasets with partial year data (e.g., >12 months but <24 months) could have potentially over- or under-estimated the proportion of hospitalizations due to influenza if they over-represented or under-represented months with peak influenza circulation. Although some datasets in our study included partial year data, we did not see this impact our global pooled estimates. We also included countries with subtropical and tropical climates where influenza occurs year-round (Simmerman & Uyeki, 2008; Cécile Viboud et al., 2006). The Southeast Asian WHO region includes some subtropical countries (Simmerman & Uyeki, 2008). Even though we found slightly higher crude and pooled estimates for this region when including datasets with partial years, we are limited in drawing conclusions due to the small number of datasets with partial year data from this region and not knowing whether influenza-positive cases increased after the completion of the study.

5.5 Closing remarks

In this first attempt to summarize the global burden of severe influenza infection among both younger and older adults, we found 11% of cases from adult respiratory hospitalizations worldwide were laboratory-confirmed for influenza. This estimate indicates that all adults, independent of age and country origin, are affected by influenza. For countries without reliable influenza data, we provide an estimate that they may use in planning and allocating resources for the control and prevention of influenza in their adult populations. From a global health perspective, it is important to understand how to use this estimate for health planning and strategy; this will require further discussion. In calculating this estimate, we focused on the most recognizable presentation of influenza in hospitalized patients, respiratory infections (CDC, 2010; Hirve et al., 2012). Although influenza has been identified in patients who are admitted for other reasons (circulatory and even all-causes according to the hospital admission forms), these patients are not typically tested for influenza due to high costs and labor demands (W. W. Thompson et al., 2009). Vaccine status of hospitalized patients and the use of other interventions are not often recorded. As more data becomes available, researchers will be able to evaluate the effectiveness of influenza vaccines and other interventions on preventing and reducing influenza hospitalizations. Since influenza is a mutable virus, the global

estimate is likely to vary from year to year, depending on the virus type in circulation and the occurrence of a pandemic (CDC, 2013). The interaction between influenza and other pathogens is complex and may contribute to severe outcomes (Rothberg, Haessler, & Brown, 2008). Evaluating this interaction may provide some insight for preventing such outcomes. Currently, annual influenza vaccination is the main method of prevention (CDC, 2013; Couch, 2000). The use of a universal vaccine, especially if it provides long-lasting broad coverage and is effective in adults with aging immune systems, will likely lead to reductions in influenza hospitalizations (McElhaney, 2005; Schotsaert & Garcia-Sastre, 2014). In effort to identify the circulating influenza virus and potentially improve the selection of vaccine strains, it is important to continue supporting the increased capacity of influenza testing and vaccine production in developing countries (Friede et al., 2011; Mmbaga et al., 2012; Partridge & Kieny, 2013). Many developing countries cannot afford to vaccinate (Oshitani et al., 2008); efforts to decrease vaccine costs and to determine more feasible vaccination approaches for developing countries are needed. Whether living in a developing or industrialized country, adults of all ages are affected by influenza. Severity of disease varies and the burden of this severity as seen with hospitalizations will change with time. With strengthen surveillance systems and the continuation of collecting and publishing data, burden estimates will become more robust.

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Appendices

Appendix 1. Literature Search Methodology by Database
(Web appendix from Lafond et al., 2014)

Pubmed: 3596 results
1. influenza, human[sh] OR influenza A virus[majr] OR influenza B virus[majr] OR influenza C virus[majr] OR influenza[all] OR viral etiology[all]
2. respiratory tract infections[sh] OR respiratory tract diseases[sh]
3. pneumonia[majr] OR pneumonia, viral[sh]
4. bronchiolitis[sh] OR bronchiolitis, viral[sh] OR bronchopneumonia[sh]
5. influenza-like illness[all]
6. acute respiratory[all] OR acute lower respiratory[all] OR lower respiratory[all]
7. ILI[all] OR SARI[all] OR ALRI[all] OR LRTI[all] OR CAP[all]
8. 1 AND (2 OR 3 OR 4 OR 5 OR 6 OR 7)
9. Limit 8 to ("1996/01/01"[PDAT] : "3000/12/31"[PDAT]) AND "humans"[MeSH Terms])

Embase (Ovid): 34349 results
1. exp influenza/ OR exp influenza virus/ OR exp influenza A/ OR exp influenza B/ OR exp influenza C/ OR exp influenza virus A / OR exp influenza virus B / OR exp influenza virus C / OR exp seasonal influenza/ OR influenza.mp OR viral etiology.mp
2. exp respiratory tract infection/ OR exp acute respiratory tract disease/
3. exp pneumonia/ OR exp virus pneumonia/
4. exp bronchiolitis/ OR exp viral bronchiolitis/ OR exp bronchitis/
5. exp flu like syndrome/ OR influenza-like illness.mp
6. ILI.mp OR SARI.mp OR ARI.mp OR ALRI.mp OR LRTI.mp OR CAP.mp
7. 1 AND (2 OR 3 OR 4 OR 5 OR 6)
8. Limit 7 to (human and yr=”1996-Current”)

Global Health (Ovid): 4068 results
1. exp influenza/ OR exp influenza viruses/ OR exp Influenzavirus A/ OR exp Influenzavirus B/ OR exp Influenzavirus C/ OR influenza.mp OR viral etiology.mp
2. exp respiratory diseases/ or exp lower respiratory tract infections
3. exp pneumonia/
4. exp bronchiolitis/ OR exp bronchitis/
5. influenza-like illness.mp OR ILI.mp OR SARI.mp OR ARI.mp OR ALRI.mp OR LRTI.mp OR CAP.mp
6. 1 AND (2 OR 3 OR 4 OR 5)
7. Limit to yr=”1996-Current”

CINAHL via EBSCOhost: 630 results

(TX influenza OR TX influenza virus OR TX viral etiology)
AND
(TX respiratory infections OR TX pneumonia OR TX influenza-like illness OR TX acute respiratory OR TX lower respiratory OR TX "ILI" OR TX "SARI" OR TX "ALRI" OR TX "ARI" OR TX "LRTI" OR TX "CAP")
Limiters: 1996-2012; human
WHOLIS: 10
(influenza OR influenza virus OR viral etiology)

CINAHL via EBSCOhost (continued)

AND

(respiratory infection OR respiratory disease OR respiratory illness OR acute respiratory OR lower respiratory OR pneumonia OR bronchiolitis OR bronchitis OR SARI OR ILI OR ARI OR ALRI OR LRTI OR CAP)

Publication year: 1996-2012

Web of Science via Web of Knowledge: (SCI-EXPANDED): 6018

(TS= (Influenza) OR TS=(viral etiology))

AND

(TS=(Acute Respiratory Infections) OR TS=(respiratory diseases) OR TS=(respiratory illnesses) OR TS=(Pneumonia) OR TS=(influenza-like illness) OR TS=(lower respiratory tract infections) OR TS=(bronchiolitis) OR TS=(bronchitis))

Time span= 1996-2012

LILACS and IndMed: 275, 4

(Influenza)

AND

(respiratory disease OR respiratory infection OR OR pneumonia)

CNKI: 883 results

甲流 or **流感** or **病毒病原学** (influenza group keywords) And **呼吸系**统感染 (respiratory infection)

甲流 or **流感** or **病毒病原学**(influenza group keywords)And **呼吸系**统疾病 (another name of respiratory infection)

甲流 or **流感** or **病毒病原学** (influenza group keywords) And **肺炎** or**下支气管炎** (pneumonia or bronchiolitis)

甲流 or **流感** or **病毒病原学** (influenza group keywords) And **肺炎** or **上支气管炎** (pneumonia or bronchitis)

甲流 or **流感** or **病毒病原学** (influenza group keywords) And **流感病**样病例 (ILI Chinesename) or ILI

甲流 or **流感** or **病毒病原学** (influenza group keywords) And **急性呼吸道感染**(sari chinese name) or SARI

甲流 or **流感** or **病毒病原学** (influenza group keywords) And ARI

甲流 or **流感** or **病毒病原学** (influenza group keywords) And **急性下呼吸道感染** (LRTI Chinese name) or LRTI

甲流 or **流感** or **病毒病原学** (influenza group keywords) And **急性上呼吸道感染** (LRTI Chinese name) or LRTI

甲流 or **流感** or **病毒病原学** (influenza group keywords) And **非典型肺炎** (SARS Chinese name) or SARS

甲流 or **流感** or **病毒病原学** (influenza group keywords) And **社区活**动感染 (CAP Chinese name) or CAP

Appendix 2. Summary of Published Datasets Used in Analyses

Location	Years	Study Population	Case Definition	Age Range	Diagnostic Test	% Influenza Positive ≥14	% Influenza Positive 15-64	% Influenza Positive ≥45	% Influenza Positive ≥65	Total % Influenza Positive
Multiple Sites, Kuwait[1]	2000-2001	general	Pneumonia	>=18	Enzyme-linked Immunosorbent Assay (Paired or Single serum)	10.5	-	7.4	-	10.5
Shatin, Hong Kong[2]	2004-2005	COPD	Acute Exacerbations of COPD with Pneumonia	Adults	Polymerase Chain Reaction, Viral Culture (Respiratory Specimen), and Complement Fixation (Paired Sera)	7.6	-	-	-	7.6
Noumea, New Caledonia[3]	2006-2007	general	Pneumonia	>=18	Polymerase Chain Reaction, Immunofluorescence Assay (Respiratory Specimen), and Serology (Paired Sera)	19.0	-	-	-	19.0
Coast Province, Kenya[4]	1994-1996	general	Pneumonia	>=18	Complement Fixation (Paired Sera)	6.1	-	-	-	6.1
Chiang Mai, Thailand[5]	2006-2008	general	Pneumonia	>=18	Polymerase Chain Reaction	5.9	-	-	-	5.9
Multiple Sites, Thailand[6]	2001-2002	general	Acute Febrile Illness	>=18	Enzyme-linked Immunosorbent Assay (Paired Sera)	-*	-	-	-	-
Santiago, Chile[7]	2003-2004	general	Pneumonia	>=18	Immunofluorescence Assay	6.9	-	-	-	6.9
Buenos Aires, Argentina[8]	1998-2001	general	Pneumonia	>=18	Immunofluorescence Assay, Viral Culture (Multiple Respiratory Specimens), and Complement Fixation (Sera)	2.0	-	-	-	2.0
Shenzhen, China[9]	2003-2005	general	Pneumonia	>=18	Polymerase Chain Reaction	22.8	-	-	-	22.8

Location	Years	Study Population	Case Definition	Age Range	Diagnostic Test	% Influenza Positive ≥14	% Influenza Positive 15-64	% Influenza Positive ≥45	% Influenza Positive ≥65	Total % Influenza Positive
Dalian, China[10]	1997-2000	general	Pneumonia	>=18	Enzyme-linked Immunosorbent Assay (Blood)	-*	18.0*	15.0*	14.5*	-*
Shenzhen, China[11]	2007-2008	general	Respiratory Infection	>=18	Polymerase Chain Reaction	17.3	18.2	19.0	15.8	17.3
Barcelona, Spain[12]	1991-1995	Immunocompromised	Acute Respiratory Infection	Adults	Viral Culture	1.4	-	-	-	1.4
Cologne, Germany[13]	2003-2004	Immunocompromised	Pneumonia	>=18	Polymerase Chain Reaction, Viral Culture, and Antigen Detection (Respiratory Specimen)	1.6	-	-	-	1.6
Multiple Sites, Spain[14]	1992-1994	COPD	Pneumonia	Adults	Complement Fixation (Paired Sera)	-	-	-	-	-
Bochum, Germany[15]	1998-1999	COPD	Acute Exacerbations of COPD	>=18	Polymerase Chain Reaction	22.4	-	-	-	22.4
Beer-Sheva, Israel[16]	1997-1999	COPD	Acute Exacerbations of COPD	>=65	Enzyme Immunoassay (paired sera)	-	-	-	-	15.8
Utrecht, Netherlands[17]	2002-2004	general	Lower Respiratory Infection	>=18	Polymerase Chain Reaction, Viral Culture, and Immunofluorescence Assay (Multiple Respiratory Specimens)	13.1	-	-	-	13.1
Beer-Sheva, Israel[18]	1991-1992	general	Pneumonia	>=18	Complement Fixation (Paired Sera)	5.8	-	-	-	5.8
Leiden, Netherlands[19]	1991-1993	general	Pneumonia	>=18	Complement Fixation (Paired Sera)	5.9	-	-	-	5.9
Barcelona, Spain[20]	1995-2001	general	Pneumonia	>=18	Enzyme Immunoassay (Paired Sera)	-*	-	-	-	-

Location	Years	Study Population	Case Definition	Age Range	Diagnostic Test	% Influenza Positive ≥14	% Influenza Positive 15-64	% Influenza Positive ≥45	% Influenza Positive ≥65	Total % Influenza Positive
Nottingham, United Kingdom[21]	1998-1999	general	Pneumonia	>=18	Complement Fixation (Paired Sera)	20.8	-	-	19.6	20.8
Province of Kuopia, Finland[22]	1981-1982	general	Pneumonia	Adults	Complement Fixation (Paired Sera)	2.2	6.7	0.9	-	2.2
Turku, Finland[23]	1999-2004	general	Pneumonia	>=18	Polymerase Chain Reaction, Fluoroimmunoassay (Multiple Respiratory Specimens), and Serology (Paired Sera)	7.8	-	-	-	7.8
Alkmaar, Netherlands[24]	1998-2000	general	Pneumonia	>=18	Polymerase Chain Reaction (Respiratory Specimen) and Enzyme-linked Immunosorbent Assay (Paired Sera)	4.5	-	-	-	4.5
Leiden, Netherlands[25]	2000-2002	general	Pneumonia	>=18	Polymerase Chain Reaction (Multiple Respiratory Specimens) and Complement Fixation (Paired Sera)	9.8	-	-	-	9.8
Barcelona, Spain[26]	2003-2004	general	Pneumonia	>=18	Polymerase Chain Reaction, Immunofluorescence Assay, Viral Culture (Respiratory Specimen), and Complement Fixation (Paired Sera)	8.1	-	-	-	8.1

Location	Years	Study Population	Case Definition	Age Range	Diagnostic Test	% Influenza Positive ≥14	% Influenza Positive 15-64	% Influenza Positive ≥45	% Influenza Positive ≥65	Total % Influenza Positive
Stockholm, Sweden[27]	2004-2005	general	Pneumonia	>=18	Polymerase Chain Reaction, Viral Culture (Respiratory Specimen), and Enzyme-linked Immunosorbent Assay (Paired Sera)	7.6	-	-	-	7.6
Schiedam, Netherlands[28]	1998-1999	general	Pneumonia	>=18	Complement Fixation and Immunofluorescence (Single or Paired Sera)	21.7	-	-	-	21.7
Rome, Italy[29]	2004-2005	general	Pulmonary Diseases	Adults	Polymerase Chain Reaction	1.0	-	-	-	1.0
Turin, Italy[30]	2008-2008	general	Respiratory Infection	>=18	Polymerase Chain Reaction and Viral Culture	0.6	-	-	-	0.6
Caen, France[31]	2003-2004	other	Intubation in ICU patients	Adults	Polymerase Chain Reaction, Immunofluorescence Assay, and Viral Culture	3.7	-	-	-	3.7
St Louis, Missouri, United States[32]	2005-2006	general	Acute Respiratory Infection	Adults	Polymerase Chain Reaction, Immunofluorescence Assay, and Viral Culture	2.8	-	-	-	2.8
Houston, Texas, United States[33]	1993-1995	general	Acute Respiratory Infection	>=18	Polymerase Chain Reaction, Viral Culture (Multiple Respiratory Specimens), and Hemagglutination Inhibition Assay (Paired Sera)	8.7	9.5	8.5	6.5	8.7

Location	Years	Study Population	Case Definition	Age Range	Diagnostic Test	% Influenza Positive ≥14	% Influenza Positive 15-64	% Influenza Positive ≥45	% Influenza Positive ≥65	Total % Influenza Positive
Edmonton, Canada[34]	2004-2006	general	Pneumonia	Adults	Polymerase Chain Reaction and Immunofluorescence Assay	3.6	-	-	-	3.6
Singapore, Singapore[35]	1995-1997	COPD	Acute Exacerbations of COPD	Adults	Complement Fixation (Paired Sera)	24.4	-	-	-	24.4
Melbourne, Australia[36]	2003-2005	COPD	Acute Exacerbations of COPD	>=65	Polymerase Chain Reaction (Multiple Respiratory Specimens) and Complement Fixation (Paired Sera)	-	-	2.0	-	2.0
Multiple Sites, Japan[37]	1994-1997	general	Pneumonia	>=18	Complement Fixation (Paired or Single Serum)	1.4	-	-	-	1.4
Christchurch, New Zealand[38]	1999-2000	general	Pneumonia	>=18	Polymerase Chain Reaction, Viral Culture (Respiratory Specimen), Immunofluorescence Assay, and Complement Fixation (Paired Sera)	9.5	-	-	-	9.5
Multiple Sites, Japan[39]	1998-2000	general	Pneumonia	>=65	Viral Culture (Respiratory Specimen) and Complement Fixation (Paired Sera)	-	-	-	7.1	7.1
Newcastle, Australia[40]	2000-2003	other	Acute Exacerbations of COPD	>=65	Polymerase Chain Reaction, Immunofluorescence Assay (Paired Sera), and Viral Culture (Multiple Respiratory Specimens)	-	-	17.8	-	17.8

Location	Years	Study Population	Case Definition	Age Range	Diagnostic Test	% Influenza Positive ≥14	% Influenza Positive 15-64	% Influenza Positive ≥45	% Influenza Positive ≥65	Total % Influenza Positive
Melbourne, Australia[41]	1993-1994	other	Acute Exacerbation of Asthma	>=18	Viral Culture (Respiratory Specimen) and Complement Fixation (Paired Sera)	25.3	-	-	-	25.3
Ljubljana, Slovenia[42]	1996-1997	general	Pneumonia	>=18	Viral Culture (Respiratory Specimen) and Complement Fixation (Paired Sera)	1.9	-	-	-	1.9

* Estimates for Influenza A only

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Appendix 3. Summary of unpublished (surveillance) datasets

Country	Years	Number of inpatient sites	Total number tested
Angola	2009 - 2011	2	111
Bangladesh	2007- 2011	12	3338
Cambodia	2009 - 2011	3	849
China(IEIP)	2010 - 2012	1	2178
China (Sentinel)	2011 - 2012	10	1462
Costa Rica	2006 - 2009	10	115
Cote d'Ivoire	2009 - 2011	3	53
DRC	2009 - 2011	3	359
El Salvador	2007 - 2011		1754
Ghana	2009 - 2011	4	695
Guatemala	2008 - 2011	3	1457
India (Ballabgarh)	2009 - 2011	33	651
India (Vadu)	2009 - 2011	38	1538
Indonesia	2011	11	179
Kenya	2006 - 2011	9	569
Kyrgyz	2009 - 2011	4	266
Lao	2008 - 2011	5	206
Mexico	2003 - 2010	1	205
Moldova	2009 - 2011	9	1394
Mongolia	2006 - 2011	35	3256
Morocco	2007 - 2011	16	720
Nigeria	2008 - 2011	4	317
Paraguay	2010 - 2011	4	1065
Philippines	2009 - 2011	6	626
South Africa	2009 - 2011	5	6370
Tanzania	2008 - 2011	5	205
Thailand (RPS)	2005 - 2011	20	12779
Thailand (MOPH)	2010 - 2011	3	218
Vietnam	2011 - 2012	8	800

Appendix 4. Pandemic crude proportion of respiratory samples from hospitalized adults testing positive for influenza by age group, study design, and population including all datasets*†

	No. of studies (n=)	Median Number (IQR)	Median Percent Positive (IQR)		p-value**
			Tested	Positive	
Age group in years					
≥14	9	501(123, 835)	162(52, 187)	23% (0.13, 0.34)	0.8651
18 to 64	8	567(229, 856)	113(11, 227)	22% (0.15, 0.30)	
≥45	6	246(159, 332)	43(40, 56)	19% (0.14, 0.25)	
≥65	4	147(110, 444)	23(20, 379)	18% (0.16, 0.60)	
Diagnostic test					
PCR only	3	95(70, 830)	13(9, 162)	14% (0.13, 0.20)	0.1213
Immunofluorescence only	0	0	0	0%	
Culture only	0	0	0	0%	
Serology Only	0	0	0	0%	
Multiple diagnostic tests, incl. PCR	6	668(447, 1752)	180(103, 316)	29% (0.23, 0.38)	
Multiple diagnostic tests, excl. PCR	0	0	0	0%	
Case definition					
Acute Respiratory Infection	0	0	0	0%	0.0404
Acute Lower Respiratory Infection	2	911(70, 1752)	98(9, 187)	12% (0.11, 0.13)	
Pneumonia	0	0	0	0%	
Severe Acute Respiratory Illness	21	720(317, 1457)	162(52, 316)	24% (0.20, 0.38)	
Other	0	0	0	0%	
WHO region					
African	1	95	13	14%	0.3330
Eastern Mediterranean	1	501	172	34%	
European	1	123	52	42%	
Americas	2	641(447, 835)	210(103, 316)	30%(0.23, 0.38)	
Southeast Asian	2	1291(830, 1752)	175(162, 187)	15%(0.11, 0.20)	
Western Pacific	2	969(70, 1869)	232(9, 454)	19% (0.13, 0.24)	
World Bank Income Level					
Low	4	109(83, 477)	33(11, 107)	17%(0.13, 0.31)	0.6242
Lower Middle	5	835(501, 1752)	187(172, 316)	24%(0.23, 0.34)	
Upper Middle	0	0	0	0%	
High	0	0	0	0%	

*Six eligible articles provided data for influenza A only, and were excluded from the overall positive analyses

**Kruskal-Wallis/Wilcoxon rank sum test.

†Pandemic defined as calendar year 2009. Nine studies only provided combined pre-pandemic/pandemic estimates. Since data was provided by year in the unpublished datasets, three unpublished datasets were included in two timeframes; six unpublished datasets were in all three timeframes.

Appendix 5. Assessment of the Impact of Dataset Quality on Positive Proportions

5a. Median Influenza-Positive Proportion for Respiratory Samples from Hospitalized Adults in Published Datasets only shown below by Bias Score

bias	low score		medium score		high score		KW p-value
	No. of datasets (n=)	Median Percent Positive (IQR)	No. of datasets (n=)	Median Percent Positive (IQR)	No. of datasets (n=)	Median Percent Positive (IQR)	
selection	10	6% (0.03, 0.10)			31	8% (0.04, 0.17)	0.8081
comparability	9	6% (0.02, 0.14)			32	8% (0.05, 0.18)	0.7528
outcome	14	9% (0.06, 0.13)			27	8% (0.04, 0.18)	0.9124
total	8	8% (0.02, 0.13)	17	7% (0.05, 0.16)	16	8% (0.04, 0.19)	0.9255

Total bias = selection bias + comparability bias + outcome bias

Low score is a score of 1 or 0 for total and a score of 0 for individual bias.

Medium score is a score of 2 for total; no medium score used for individual bias.

High score is a score of 3 for total and score of 1 for individual bias.

5b. Median Influenza-Positive Proportion Stratified by PCR testing

5bi. PCR tested

Bias	low score		medium score		high score		KW p-value
	No. of datasets (n=)	Median Percent Positive (IQR)	No. of datasets (n=)	Median Percent Positive (IQR)	No. of datasets (n=)	Median Percent Positive (IQR)	
selection	6	5% (0.03, 0.10)			12	13% (0.08, 0.18)	0.0394
comparability	5	9% (0.04, 0.10)			13	10% (0.07, 0.18)	0.4597
outcome	3	10% (0.10, 0.13)			15	8% (0.05, 0.18)	0.3743
Total	4	10% (0.03, 0.13)	6	5% (0.04, 0.09)	8	14% (0.08, 0.21)	0.1866

5bii. No PCR

Bias	low score		medium score		high score		KW p-value
	No. of datasets (n=)	Median Percent Positive (IQR)	No. of datasets (n=)	Median Percent Positive (IQR)	No. of datasets (n=)	Median Percent Positive (IQR)	
selection	3	20% (0.02, 0.24)			18	6% (0.02, 0.10)	0.3657
comparability	3	2%(0.01, 0.25)			18	7% (0.02, 0.16)	0.763
outcome	11	7% (0.01, 0.16)			10	5% (0.02, 0.20)	0.7782
Total	3	2% (0.01, 0.25)	11	8% (0.06, 0.20)	7	4% (0.02, 0.07)	0.5196

5c. Median Influenza-Positive Proportion Stratified by Timeframe

5ci.Seasonal

bias	low score		medium score		high score		KW p-value
	No. of datasets (n=)	Median Percent Positive (IQR)	No. of datasets (n=)	Median Percent Positive (IQR)	No. of datasets (n=)	Median Percent Positive (IQR)	
selection	10	8% (0.03, 0.11)			32	8% (0.04, 0.17)	0.8081
comparability	9	9% (0.03, 0.11)			33	8% (0.05, 0.17)	0.7528
outcome	15	9% (0.06, 0.13)			27	8% (0.04, 0.18)	0.9124
total	8	10% (0.02, 0.13)	17	7% (0.05, 0.16)	16	8% (0.05, 0.18)	0.9255

Appendix 6. Evaluating Impact of pandemic H1N1 in 2010 calendar year

6a. Crude positive proportions for seasonal influenza by 2010 data

	Datasets without 2010 Data		
	No. of studies (n=)	Median Percent Positive (IQR)	p-value
Age group in years			
≥14	65	8% (0.04, 0.14)	0.902
18 to 64	30	11% (0.06, 0.15)	
≥45	25	8% (0.02, 0.13)	
≥65	19	11% (0.06, 0.15)	
Type of study			
Unpublished surveillance	30	10% (0.04, 0.14)	0.8512
Published	39	8% (0.04, 0.17)	
Diagnostic test			
Polymerase Chain Reaction (PCR) only	13	11% (0.10, 0.17)	0.094
Immunofluorescence only	1	7%	
Culture only	1	1%	
Serology Only	10	6% (0.02, 0.16)	
Multiple diagnostic tests, incl. PCR	39	8% (0.03, 0.11)	
Multiple diagnostic tests, excl. PCR	5	20% (0.07, 0.22)	
Case definition			
Acute Respiratory Infection	4	6% (0.02, 0.11)	0.4646
Acute Lower Respiratory Infection	6	12% (0.07, 0.14)	
Pneumonia	24	7% (0.04, 0.10)	
Severe Acute Respiratory Illness	24	9% (0.03, 0.12)	
Other	11	16% (0.04, 0.22)	
Study population			
General adult population	58	8% (0.05, 0.13)	0.1549
COPD	6	12% (0.02, 0.22)	
Immunocompromised	2	1% (0.01, 0.02)	
Other	3	18% (0.04, 0.25)	
WHO region			
African	8	8% (0.06, 0.12)	0.9827
Eastern Mediterranean	1	10%	
European	22	8% (0.02, 0.16)	
Americas	9	7% (0.04, 0.10)	
Southeast Asian	9	10% (0.06, 0.14)	
Western Pacific	20	9% (0.03, 0.18)	
World Bank income level			
Low	10	10% (0.06, 0.14)	0.436
Lower Middle	19	6% (0.03, 0.14)	
Upper Middle	8	12% (0.08, 0.19)	
High	32	8% (0.03, 0.14)	
Development Status			
Developing	39	10% (0.06, 0.14)	0.2261
Industrialized	30	7% (0.02, 0.13)	

*Thirteen eligible articles provided data for influenza A only, and were excluded from the overall positive analyses

**Kruskal-Wallis/Wilcoxon rank sum test.

†Pandemic defined as calendar year 2009. Nine studies only provided combined pre-pandemic/pandemic estimates.

6b. Pooled estimates for seasonal influenza without 2010

	Datasets without 2010 Data			
	PCR Tested N*	PCR tested Pooled % Positive (95% CI)	N†	Pooled % Positive (95% CI)†
Age group in years				
≥14	42	10% (0.08, 0.13)	66	9% (0.08, 0.11)
18 to 64	26	11% (0.07, 0.17)	30	11% (0.07, 0.17)
≥45	19	9% (0.09, 0.10)	25	9% (0.09, 0.09)
≥65	13	did not converge	19	did not converge
Study population				
General adult popn	39	10% (0.08, 0.13)	58	10% (0.08, 0.12)
Special population**	5	9% (0.03, 0.30)	9	12% (0.07, 0.22)
WHO region				
African	7	9% (0.07, 0.12)	8	9% (0.07, 0.11)
Americas	2	6% (0.0001, 47)	9	8% (0.05, 0.12)
Eastern Mediterranean	0	0%	1	
European	10	16% (0.07, 0.38)	22	10% (0.05, 0.18)
Southeast Asian	9	did not converge	9	did not converge
Western Pacific	16	10% (0.08, 0.13)	20	10% (0.08, 0.13)
Income level				
Low Income	9	8% (0.04, 0.14)	10	8% (0.05, 0.13)
Lower Middle Income	15	11% (0.04, 0.32)	19	11% (0.05, 0.25)
Upper Middle Income	5	10% (0.07, 0.15)	8	10% (0.08, 0.14)
High Income	15	9% (0.06, 0.12)	32	8% (0.06, 0.11)
Development status†				
Developing	31	10% (0.07, 0.15)	39	10% (0.08, 0.13)
Industrialized	13	8% (0.06, 0.12)	30	7% (0.5, 0.10)

*Number of data points included in model, including multiple individual years from a single dataset, when available
**Includes ICU patients, acute asthma patients, COPD patients, and immunocompromised patients
†All diagnostic tests included
‡no PCR data
§Includes: ICU patients only, acute asthma patients, immunocompromised patients, and COPD patients

Appendix 7. Evaluating Impact of Partial-year Influenza Testing

7a. Seasonal crude positive proportions for datasets stratified by partial-years

	Datasets with partial-years			Datasets with full-years		
	No. of studies (n=)	Median Percent Positive (IQR)	p-value	No. of studies (n=)	Median Percent Positive (IQR)	p-value
Age group in years						
≥14	20	9% (0.06, 0.12)	0.4649	43	9% (0.04, 0.22)	0.4765
18 to 64	7	10% (0.06, 0.21)		12	10% (0.04, 0.15)	
≥45	7	11% (0.09, 0.19)		19	9% (0.04, 0.14)	
≥65	5	10% (0.06, 0.11)		26	10% (0.07, 0.15)	
Type of study						
Unpublished surveillance	5	10% (0.08, 0.21)	0.3676	20	11% (0.06, 0.15)	0.2709
Published	17	10% (0.06, 0.13)		22	7% (0.02, 0.20)	
Timeframe for outcome data						
Pre-2009†	18	10% (0.6, 0.14)	0.2571	29	8% (0.02, 0.17)	*0.038*
Post-2009	6	13% (0.08, 0.18)		20	12% (0.08, 0.20)	
Diagnostic test						
Polymerase Chain Reaction (PCR) only	6	19% (0.10, 0.22)	0.1751	16	11% (0.07, 0.15)	0.3086
Immunofluorescence only	1	7%		0	0%	
Culture only	0	0%		1	1%	
Serology Only	5	6% (0.6, 0.10)		5	6% (0.02, 0.21)	
Multiple diagnostic tests, incl. PCR	10	9% (0.08, 0.10)		42	8% (0.03, 0.14)	
Multiple diagnostic tests, excl. PCR	0	0%		5	20% (0.07, 0.22)	
Case definition						
Acute Respiratory Infection	2	6% (0.03, 0.09)	*0.032*	3	13% (0.01, 0.17)	0.9681
Acute Lower Respiratory Infection	2	17% (0.13, 0.21)		6	12% (0.07, 0.14)	
Pneumonia	9	7% (0.06, 0.10)		15	7% (0.02, 0.20)	
Severe Acute Respiratory Illness	2	9% (0.08, 0.10)		39	10% (0.05, 0.15)	
Other	7	17% (0.16, 0.22)		6	6% (0.02, 0.24)	
Study population						
General adult population	18	9% (0.06, 0.10)	0.4309	35	10% (0.05, 0.15)	0.2257
COPD	3	16% (0, 0.22)		3	8% (0.02, 0.24)	
Immunocompromised	0	0%		2	1% (0.01, 0.02)	
Other	1	18%		2	15% (0.04, 0.25)	
WHO region						
African	1	6%	0.4022	14	9% (0.06, 0.14)	0.7672
Eastern Mediterranean	1	10%		0	0%	
European	8	10% (0.07, 0.14)		16	7% (0.02, 0.17)	
Americas	5	7% (0.04, 0.09)		7	12% (0.06, 0.18)	
Southeast Asian	2	14% (0.04, 0.23)		12	12% (0.07, 0.16)	
Western Pacific	5	17% (0.10, 0.18)		21	9% (0.03, 0.17)	
World Bank income level						
Low	2	13% (0.06, 0.21)	0.9284	8	10% (0.07, 0.14)	0.4374
Lower Middle	3	10% (0.04, 0.23)		11	11% (0.04, 0.15)	
Upper Middle	3	8% (0.07, 0.17)		5	13% (0.08, 0.20)	
High	14	10% (0.06, 0.13)		18	6% (0.02, 0.19)	
Development Status						
Developing	9	10% (0.07, 0.17)	0.4425	25	11% (0.06, 0.15)	*0.0464*
Industrialized	13	10% (0.06, 0.13)		17	5% (0.02, 0.08)	

*Thirteen eligible articles provided data for influenza A only, and were excluded from the overall positive analyses

**Kruskal-Wallis/Wilcoxon rank sum test.

†Pandemic defined as calendar year 2009. Nine studies only provided combined pre-pandemic/pandemic estimates.

7b. Influenza-positive pooled estimates for datasets stratified by partial-years

	Datasets with partial-years				Datasets with full-years			
	PCR Tested N*	PCR tested Pooled % Positive (95% CI)	N†	Pooled % Positive (95% CI)†	PCR Tested N*	PCR tested Pooled % Positive (95% CI)	N†	Pooled % Positive (95% CI)†
Age group in years								
≥14	14	12% (0.08, 0.16)	20	11% (0.08, 0.14)	48	11%(0.09, 0.14)	68	11% (0.09, 0.13)
18 to 64	7	13% (0.07, 0.24)	7	13% (0.07, 0.24)	37	12% (0.09, 0.16)	43	12% (0.09, 0.16)
≥45	6	11% (0.08, 0.15)	7	11% (0.08, 0.15)	27	10% (0.09, 0.11)	34	10% (0.09, 0.11)
≥65	5	11% (0.08, 0.14)	5	11% (0.08, 0.14)	18	10%	26	10%
Study population								
General adult population	13	11% (0.08, 0.16)	18	11% (0.08, 0.14)	46	11% (0.09, 0.14)	62	11% (0.09, 0.13)
Special population**	2	20% (0.05, 0.86)	4	14% (0.05, 0.37)	3	4% (0.008, 0.17)	5	10% (0.03, 0.39)
WHO region								
African			1		14	9% (0.07, 0.12)	14	9% (0.07, 0.12)
Americas	3	9% (0.03, 0.23)	5	8% (0.05, 0.14)			7	14% (0.07, 0.30)
Eastern Mediterranean			1					
European	5	11% (0.07, 0.18)	8	10% (0.07, 0.16)	7	21% (0.06, 0.68)	16	10% (0.04, 0.23)
Southeast Asian	2	17% (0.0002, 143)	2	17% (0.0002, 143)	12	11% (0.08, 0.16)	12	11% (0.08, 0.16)
Western Pacific	5	10% (0.06, 0.18)	5	10% (0.06, 0.18)	16	11% (0.08, 0.16)	20	11% (0.08, 0.15)
Income level								
Low Income	1		2	12% (0.00005, 254)	16	13% (0.10, 0.17)	16	13% (0.10, 0.17)
Lower Middle Income	3	14% (0.03, 0.72)	3	14% (0.03, 0.72)	22	12% (0.07, 0.19)	28	12% (0.08, 0.17)
Upper Middle Income	2	9% (0.002, 5.6)	3	9% (0.03, 0.24)	5	10% (0.04, 0.26)	7	10% (0.06, 0.17)
High Income	9	10% (0.07, 0.14)	14	9% (0.07, 0.12)	6	7% (0.03, 0.17)	18	7% (0.04, 0.12)
Development status†								
Developing	6	13% (0.07, 0.24)	9	12% (0.08, 0.19)	45	11% (0.09, 0.14)	52	11% (0.09, 0.14)
Industrialized	9	10% (0.07, 0.14)	13	9% (0.06, 0.13)	4	5% (0.02, 0.10)	17	6% (0.3, 0.11)

*Number of data points included in model, including multiple individual years from a single dataset, when available
**Includes ICU patients, acute asthma patients, COPD patients, and immunocompromised patients
†All diagnostic tests included
‡no PCR data
§Includes: ICU patients only, acute asthma patients, immunocompromised patients, and COPD patients
§Includes: ICU patients only, acute asthma patients, immunocompromised patients, and COPD patients

Appendix 8. Evaluating Impact of Multipathogen Detection

8a. Crude positive proportions

	Studies with Multipathogen detection		
	No. of studies (n=)	Median Percent Positive (IQR)	p-value
Age group in years			
≥14	37	8% (0.04, 0.15)	0.4386
18 to 64	2	14%(0.09, 0.18)	
≥45	6	8% (0.02, 0.18)	
≥65	5	7% (0.06, 0.16)	
Type of study			
Unpublished surveillance	0	0%	
Published	41	8% (0.04, 0.17)	
Timeframe for outcome data			
Pre-2009†	41	8% (0.04, 0.17)	
During 2009 ("pandemic")	0	0%	
Post-2009	0	0%	
Diagnostic test			
Polymerase Chain Reaction (PCR) only	5	17% (0.10, 0.22)	0.1922
Immunofluorescence only	1	7%	
Culture only	1	1%	
Serology Only	10	6% (0.02, 0.16)	
Multiple diagnostic tests, incl. PCR	17	8% (0.04, 0.10)	
Multiple diagnostic tests, excl. PCR	5	20% (0.07, 0.22)	
Case definition			
Acute Respiratory Infection	3	3% (0.01, 0.09)	0.2715
Acute Lower Respiratory Infection	1	13%	
Pneumonia	24	7% (0.04, 0.10)	
Severe Acute Respiratory Illness	0	0%	
Other	11	16% (0.04, 0.22)	
Study population			
General adult population	28	8% (0.05, 0.12)	0.1751
COPD	6	12% (0.02, 0.22)	
Immunocompromised	2	1% (0.01, 0.02)	
Other	3	18% (0.04, 0.25)	
WHO region			
African	1	6%	0.5452
Eastern Mediterranean	1	10%	
European	20	7% (0.02, 0.12)	
Americas	5	7% (0.04, 0.09)	
Southeast Asian	1	6%	
Western Pacific	11	17% (0.07, 0.23)	
World Bank income level			
Low	1	6%	0.7587
Lower Middle	1	6%	
Upper Middle	5	17% (0.07, 0.20)	
High	32	8% (0.03, 0.14)	
Development Status			
Developing	10	10% (0.07, 0.19)	0.1252
Industrialized	30	7% (0.02, 0.13)	

*Thirteen eligible articles provided data for influenza A only, and were excluded from the overall positive analyses
**Kruskal-Wallis/Wilcoxon rank sum test.
†Pandemic defined as calendar year 2009. Nine studies only provided combined pre-pandemic/pandemic estimates.

8b.Pooled estimates

Studies with Multipathogen detection

	PCR Tested N*	PCR tested Pooled % Positive (95% CI)	N†	Pooled % Positive (95% CI)†
Age group in years				
≥14	16	10% (0.07, 0.13)	36	8% (0.06, 0.11)
18 to 64	2	13% (0.002, 8.3)	2	13% (0.002, 8.3)
≥45	4	11% (0.03, 0.34)	6	9% (0.04, 0.22)
≥65	2	12% (0.001, 19)	5	10% (0.04, 0.28)
Study population				
General adult population	13	10% (0.07, 0.13)	28	8% (0.06, 0.11)
Special population**	5	9% (0.3, 0.30)	11	7% (0.03, 0.16)
WHO region				
African	0	0%	1	
Americas	2	6% (0.0001, 47)	5	7% (0.02, 0.18)
Eastern Mediterranean	0	0%	1	
European	8	9% (0.06, 0.13)	20	7% (0.05, 0.11)
Southeast Asian	1		2	
Western Pacific	7	13% (0.08, 0.21)	11	12% (0.07, 0.19)
Income level				
Low Income	0	0%	1	
Lower Middle Income	0	0%	2	
Upper Middle Income	2	19% (0.03, 1.0)	5	12% (0.05, 0.30)
High Income	15	9% (0.06, 0.12)	32	8% (0.06, 0.11)
Development status				
Developing	5	15% (0.09, 0.26)	10	12% (0.09, 0.19)
Industrialized	13	8% (0.06, 0.12)	30	7% (0.05, 0.10)

*Number of data points included in model, including multiple individual years from a single dataset, when available
**Includes ICU patients, acute asthma patients, COPD patients, and immunocompromised patients
†All diagnostic tests included
‡no PCR data
§Includes: ICU patients only, acute asthma patients, immunocompromised patients, and COPD patients

Appendix 9. Glossary

Terms or abbreviation followed by definition

Surface antigens of influenza virus type A
- HA – hemagglutinin
- NA – neuraminidase

Public Health Agencies
- WHO – World Health Organization
- CDC – Centers for Disease Control and Prevention

Study Timeframe
- Pre-pandemic – conducting study, collection and testing specimens prior to the 2009-calendar year
- Pandemic – collecting and testing specimens during the 2009-calendar year
- Post-pandemic – conducting study, collecting and testing specimens in 2010-calendar year and later

Diagnostic Test
- PCR – Polymerase Chain Reaction
- Multiple diagnostic tests incl. PCR – study using more than one tests including polymerase chain reaction to detect and confirm influenza
- Multiple diagnostic tests excl. PCR – study using more than one tests excluding polymerase chain reaction to detect and confirm influenza
- Immunofluorescence – a microscopy technique used to detect the presence of a protein specifically targeted by fluorescent-labeled antibodies
- Complement Fixation – immunological assay which includes serum complement for the binding of antigen-antibody complexes

Case Definitions
- SARI – Severe acute respiratory infection
- ILI – Influenza-like illness
- ARI – Acute respiratory illness
- ARLI – Acute respiratory like illness
- LRTI – Lower respiratory tract illness
- CAP – Community acquired pneumonia
- Other – includes acute febrile illness, respiratory infection, acute exacerbation of chronic illness

Study Populations
- COPD – Chronic obstructive pulmonary disease
- ICU – Intensive care unit
- Other – includes ICU patients (only), acute exacerbation of chronic illness
- Popn – population

Regional Groupings
- WHO region – six regions that WHO member states are grouped into
- World Bank income level – http://siteresources.worldbank.org/DATASTATISTICS/Resources/OGHIST.xls
- Development status – United Nations Population Division (UNPD), 2012 World Population Prospects Report

Statistical Terms

- CI – confidence intervals
- IQR – interquartile range; statistic dispersion

Exploratory Analysis

- Partial-year data - datasets which completed ongoing influenza testing beyond a 12-month period, such as 15 and 26 months
- Multipathogen detection – datasets which tested for other pathogens in addition to influenza type A and B
    - RSV – Respiratory syncytial virus
    - M.pna – *Mycoplasma pneumoniae*

Vaccines and immune status

- LAIV – Live Attenuated Influenza Vaccine
- HIV – human immunodeficiency virus
- Immunosenescence – decreased immune functionality observed or associated with aging