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Influenza-associated morbidity and mortality in sub-saharan Africa

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Abstract

Influenza is one of the major infectious disease threats to the world. New Global Burden of Disease estimates attribute nearly 2% of all-cause mortality during the first five years of life to influenza. In tropical developing countries, the pattern of influenza circulation may differ markedly from those in temperate, developed settings. Of influenza deaths, 99% are estimated to occur in low and middle income countries. Studies on seasonal influenza occurrence, morbidity and mortality in sub-Saharan Africa published from January 1st, 2000 to December 31st, 2015 were reviewed in order to assess the burden of seasonal influenza in the Region. The starting date of January 1st, 2000 has been selected because of the increasing number and quality of studies in later years. Relevant studies were identified using combinations of Medical Subject Headings (MeSH) and text terms as follows: ("influenza" AND "Africa") OR ("Africa" AND ("pneumonia" OR "acute respiratory infection")) OR ("influenza" AND each individual sub-Saharan African country). The study seems to show that seasonal influenza could have a greater toll on morbidity and mortality in Africa, compared with more-developed continents considering the frequency of predisposing factors such as HIV and TB and the absence of influenza vaccination programs in most of the African countries. Available data suggest both the respiratory disease and influenza-associated mortality may be increased in low-income settings such as sub-Saharan Africa.

Keywords: influenza, morbidity, mortality, sub-saharan Africa, respiratory, predisposing

Abbreviations: AIDS, acquired immune deficiency syndrome; AR, attack rate; ARI, acute respiratory infections; aOR, adjust odd ratio; CFP, case fatality proportion; CFR, case fatality rate; CI, confidence interval; DNA, deoxyribonucleic acid; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; ILI, influenza-like illness; NICD, national institute for communicable disease; PCR, polymerase chain reactions; PIV, parainfluenza virus; PTB, pulmonary tuberculosis; RR, relative risk; rRT-PCR, reverse real time PCR; RSV, respiratory syncytial virus; SARI, severe acute respiratory infection; TB, tuberculosis; TIV, trivalent inactivated influenza; US CDC, US centers for disease control and prevention; NAMRU, naval medical research unit; WHO, World health organization

Introduction

Influenza is a highly communicable acute respiratory disease. It is one of the most prevalent vaccine-preventable diseases. The influenza virus can cause illness in individuals of all ages, results in repeated infections throughout life, and is responsible for annual worldwide epidemics of varying severity. The World Health Organization (WHO) estimates that influenza affects between 3 and 5million individuals each year, causing between 250,000 and 0.5million deaths.[1] New Global Burden of Disease estimates attribute nearly 2% of all-cause mortality during the first five years of life to influenza.[2]

In tropical countries, the pattern of influenza circulation may differ markedly from those in temperate, developed settings. Also, populations in low and middle income countries like many of those in sub-Saharan Africa are more vulnerable to influenza related complications because of the high prevalence of underlying medical conditions such as Human Immunodeficiency Virus (HIV) infection, tuberculosis (TB), malaria and malnutrition, and limited access to healthcare. Of influenza deaths, 99% are estimated to occur in low and middle income countries.[3] This study aims at assessing the morbidity and mortality related to seasonal influenza in sub-Saharan Africa.

Review methods

Information sources

Searches of the PubMed database were completed to identify studies on seasonal influenza in sub-Saharan Africa published in English and French from January 1st, 2000 to December 31st, 2015. The starting date of January 1st, 2000 has been selected because of the increasing number and quality of studies in later years.

Literature search

Relevant studies were identified using combinations of Medical Subject Headings (MeSH) and text terms as follows: ("influenza" AND "Africa") OR ("Africa" AND ("pneumonia" OR "acute respiratory infection")) OR ("influenza" AND each individual sub-Saharan African country). References of identified articles have been examined for additional articles, titles and abstracts of additional articles have been screened and studies have been selected if they included some aspect of seasonal influenza in sub-Saharan Africa.

Study selection

Studies that reported data on the occurrence of influenza in sub-Saharan Africa and on its contribution to morbidity and mortality have been included. Studies that reported results from outside sub-Saharan Africa, that only had data on avian or animal influenza, that only reported data on pandemic influenza, that duplicated data on other more comprehensive reports have been excluded.

Results and discussion

Results

Nine hundred and forty five articles titles and abstracts have been screened, out of which 70 reports have been retrieved and assessed for eligibility criteria, of which 28 did not meet inclusion criteria. Forty-two articles were included in this study[4–45] (Figure 1).

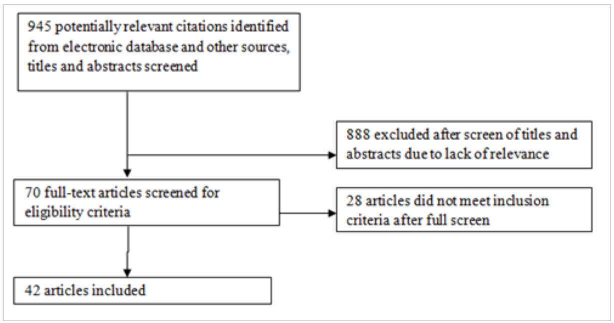

Figure 1 Flow chart for studies selection.

Morbidity and co-morbidity

Morbidity: Influenza surveillance conducted in 15 countries in Africa from 2006 to 2010 have shown 21.7% of influenza-like illness (ILI) cases (5165/69 860) tested positive for influenza, ranging from 6.7% in Angola to 40.4% in Madagascar.[4] In Senegal, from June 1996 to December 1998, the proportion of influenza virus isolation varied from 17.5% to 40% during the peak period (July/September) of acute respiratory infections (ARI) in Dakar.[5] These data are in contrast to temperate regions where influenza occurs during winter season. Clinical and virological surveillance of acute respiratory infections among children less than 5years old living in rural areas in Senegal showed that influenza represented 45.6% of positive viral detection in patients with ARI.[6] The recent enhancement of the surveillance network in the country has showed that co-infection and co-circulation of viruses were frequent and were responsible of ILI peaks.[7] The first months of implementation of the enhanced surveillance system confirmed that Influenza viruses were among the most frequent cause of ILI (20%). The other viruses were adenoviruses (21%), rhinoviruses (18%) and enteroviruses (15%).[7] In Antananarivo, Madagascar, influenza epidemiologic and virologic surveillance from 1995 to 2002 had shown that the virus had been continually spreading all year long.[8] In another study conducted from July 2008 to June 2009, Influenza A and B accounted respectively for 27.3% and 3.9% of ILI cases. Of all viral detection, influenza A was the most common virus.[9] In Mozambique, viral ARI are frequent among infants visited in Manhiça District Hospital, the influenza viruses represented 15% of viral detection in infants younger than 12months.[10] The most frequent virus was the rhinovirus (26%).[10] However, in Cote d'Ivoire, the most affected people were from 15 to 59years (47%) followed by those from 0 to 5years (34%).[11]

Recently, many West African countries have published their first data on influenza surveillance. In Togo and Niger, the highest influenza positive percentage was observed in 5 - 14years old with respectively (30%) among ILI in Togo[12] and 25% among ILI patients and 10% among severe acute respiratory infection (SARI) patients in Niger.[13] In Burkina Faso, of the 881 patients with ILI enrolled and sampled in the sentinel surveillance system, 58 (6.6%) tested positive for influenza viruses.[14] In contrast to the findings in Togo and Niger, the most affected were patients within 0 – 5years (41.4%), the 6 – 14years old were the second (22.4%).[14] In Sierra Leone also the majority (36%) of ILI and SARI cases was detected in children under the age of four.[15]

Surveillance of ILI in Central Africa began only recently. The surveillance systems in Gabon and Central African Republic have provided valuable data on the circulation of influenza viruses and other respiratory viruses. In Gabon, three-quarters of the patients were children under five years old.[16] The most common viruses were adenoviruses (17.5%), followed by parainfluenza viruses (PIVs) (16.8%), influenza viruses were detected only in 11.9% of tested specimens.[16] In Central African Republic, influenza viruses were the most common viruses (8.8%) followed by RSV (3.0%).[17] However, the study included only infants and children aged 0–15years.[17]

In Djibouti, East Africa, in response to local reports of a possible outbreak during the A(H1N1)pdm09 pandemic, enhanced surveillance for ILI was conducted at Camp Lemonnier. rRT-PCR and DNA sequencing revealed that 25 (78%) of the 32 clinical samples collected were seasonal H3N2 and only 2 (6%) were A(H1N1)pdm09 influenza.[18] In South Africa, a country with a marked influenza season, the annual detection rate amongst specimens tested at the National Institute for Communicable Diseases (NICD) during the influenza seasons ranged from 32% in 2008 to 47% in 2005 and 2007.[19]

Severe morbidity: Influenza related-hospitalizations

Several studies have reported high frequency of severe influenza among persons with ARI. In two recent studies from South Africa (Pretoria and Cape Town), influenza was detected respectively in 3.5%[20] and 0.9%[21] of children <5years of age hospitalized for ARI. Another study from the pediatric service of Tygerberg Children's Hospital in Western Cape, has found influenza A and B respectively in 13% and 15% of children hospitalized for ARI.[22] In a study conducted in Cape Town from June 1st, 1995 to August 31st, 1996, influenza B was isolated in 0.6% of children <2years of age hospitalized for ARI.[23] A severe acute institutional influenza outbreak was reported from Pretoria, in a police residential college amongst new recruits and staff members at the end of May 2003. The outbreak had an attack rate (AR) per dormitory building from 27% to 47%, with an overall AR of 34%.[24]

In a recent study conducted in two-long term refugee camps in Kenya, influenza associated-SARI hospitalizations were 4.8/1000 in <5years old and 11.1/1000 in year old.[25] Influenza virus was also detected in 6% of children younger than 13years of age admitted for clinical pneumonia to a Kenyan rural hospital.[26] In a population-based study conducted in rural western Kenya, of the 2079 patients with tested swabs, infection with influenza virus was confirmed in 204 (10%). Am <1ong those tested for influenza virus, 6.8% of the children aged < 5years and 14.0% of the patients aged ≥ 5years were found positive. The annual rate of hospitalization (per 100 000 population) was 56.2 among patients with influenza. The rate of influenza-associated hospitalization was highest among children aged less than 5years.[27]

In Nigeria, in a 30-month study of under 5-admissions for ARI, influenza A was found in 17.3% of children admitted with severe pneumonia radiologically-confirmed.[28] In a hospital-based study in the same age group in Ghana, influenza accounted only for 1% of respiratory viruses; the most common virus was RSV (14.1%).[29] A clinic and hospital-based sentinel influenza surveillance in Uganda, had showed that patients aged 5–14years had the highest influenza-positive percentage (19.6%).[30] Influenza circulated throughout the year, but the percentage of influenza-positive specimens peaked during June–November, coinciding with the second rainy season in Uganda.[30]

Co-morbidity: influenza-HIV, influenza-chronic lung disease, influenza-meningitis, influenza-malaria

The association between influenza and HIV has been studied in children aged from 2months to 5years admitted at Chris Hani-

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Baragwanath Hospital in Soweto, South Africa. The study has shown that children with HIV have an 8times higher risk of admission to hospital from influenza-associated ARI than HIV negative children.[31] Children aged ≥5Years and adults infected with HIV experienced a 13–19times greater SARI incidence than HIV-uninfected individuals ($p<0.001$).[32] In another study from Kenya, HIV-infection was associated with hospitalization due to influenza (aOR=3.56; 95% CI 1.25-10.1). Chronic lung disease was also associated with hospitalization due to influenza (aOR=6.83; 95% CI 1.37-34.0).[33] In the absence of highly active antiretroviral therapy (HAART), adults aged 25-54years with AIDS experience a substantially elevated risk of influenza-associated death, 150 to 200-fold higher than the general population of the same age, and 2-4 folds higher than seniors age 65 and over.[34]

In Burkina Faso which is a country located in the heart of the African meningitis belt, the association between respiratory infections and meningococcal carriage has been studied. The study suggested that viral respiratory tract infections, including influenza, might contribute to increased transmission and nasopharyngeal carriage of virulent meningococci.[35]

Although children <5years old in sub-Saharan Africa are vulnerable to both malaria and influenza, little is known about coinfection. A retrospective, cross-sectional study in western rural Kenya has addressed this issue. The study found that 45% (149/331) of influenza-positive patients were coinfected with malaria, whereas only 6% (149/2408) of malaria-positive patients were coinfected with influenza.[36] Coinfection with malaria and influenza was uncommon but associated with longer hospitalization than single infections among children 24-59months of age.[36]

Mortality

A recent study of elderly South Africans estimated that the risk of influenza-associated death in that country was three to four times higher than in the United States.[37] A three-year study of influenza and respiratory syncytial virus associated adult mortality in Soweto, has shown that Influenza seasons were significantly associated with excess mortality in adults across all 3years. Excess mortality was highest in those ≥65years of age: 82.8/100,000 populations in the mild 1997 season and 220.9/100,000 in the severe 1998 season.[38]

Some papers reported case fatality-rate during influenza outbreak or through population based studies. In 2002, an influenza outbreak in Madagascar had a case-fatality rate of 3%; most fatalities occurred in young children.[39,40] Similarly high (3.5%) case-fatality rates among children <5years of age were observed during an influenza outbreak in the Democratic Republic of Congo in 2002.[41] In the population based-study conducted in rural western Kenya, the case-fatality rate among admitted patients with PCR-confirmed infection with influenza virus was 2.0%.[27]

In a study of mortality amongst patients with influenza-associated SARI in Soweto, South Africa, the estimated incidence of influenza-associated SARI deaths per 100,000 population was highest in children <1year (20.1, 95%CI 12.1-31.3) and adults aged 45–64years (10.4, 95%CI 8.4–12.9).[42] Adjusting for age, the rate of death was 20-fold (95%CI 15.0–27.8) higher in HIV-infected individuals than HIV-uninfected individuals.[42] This study has documented that influenza cause's substantial mortality in Soweto, South Africa. An analysis of data from the same surveillance program found that the relative risk of influenza-associated hospitalization was 4–8times higher in HIV-infected compared to HIV-uninfected individuals.[42]

The role of influenza in severe acute respiratory illness deaths in Sub-Saharan Africa was studied in 8 African countries. The data were collected from 37 714 SARI cases, and 3091 (8.2%; range by country, 5.1%-25.9%) tested positive for influenza virus.[43] There were 1073 deaths (2.8%; range by country, 0.1%-5.3%) reported, among which influenza virus was detected in 57 (5.3%).[43] Case-fatality proportion (CFP) was higher among countries with systematic death reporting than among those with sporadic reporting. The influenza-associated CFP was 1.8% (57 of 3091), compared with 2.9% (1016 of 34 623) for influenza virus–negative cases ($P < .001$) [43]. Among 834 deaths (77.7%) tested for other respiratory pathogens, rhinovirus (107 [12.8%]), adenovirus (64 [6.0%]), respiratory syncytial virus (60 [5.6%]), and Streptococcus pneumoniae (57 [5.3%]) were most commonly identified. Among 1073 deaths, 402 (37.5%) involved people aged 0-4 years, 462 (43.1%) involved people aged 5-49years, and 209 (19.5%) involved people aged ≥50years.[43]

A study of the influenza-associated mortality among individuals with PTB in South Africa from 1999–2009 observed an increased risk of influenza-associated mortality in persons with PTB compared to non-tuberculosis respiratory deaths.[44] In the same period of time (1999-2009), in South Africa, the mortality associated with seasonal and pandemic influenza among pregnant and non-pregnant women of childbearing age in a high HIV-prevalence setting was conducted. The estimated mean annual seasonal influenza–associated mortality rates were 12.6 (123 deaths) and 7.3 (914 deaths) among pregnant and non-pregnant women respectively.[45] Among pregnant women, the estimated mean annual seasonal influenza–associated mortality rates were 74.9 (109 deaths) among HIV infected and 1.5 (14 deaths) among HIV–uninfected individuals.[45] Among non-pregnant women, the estimated mean annual seasonal influenza–associated mortality rate was 41.2 (824 deaths) among HIV-infected and 0.9 (90 deaths) among HIV-uninfected individuals.[45] The study suggested that pregnant women experienced an increased risk of seasonal influenza–associated mortality compared with non-pregnant women (relative risk [RR], 2.8; 95% confidence interval [CI], 1.7-3.9).[45]

Discussion

The burden of seasonal influenza in children under 5years of age and those from 5 to 14years appears far greater than in the elderly.[11–16] This corroborates findings elsewhere that younger children experience a high influenza attack rate and a higher rate of influenza-related complications.[46] In the study of Brooks et al.,[47] 28% of influenza positive children developed pneumonia during their illness. The average annual incidence of influenza pneumonia was greatest among children < 5years of age (236 per 100 000).[47] Children are not only affected by influenza themselves; they play also an important role in introducing and spreading respiratory illness into households and communities.[48] They shed influenza virus for longer periods of time as compared to adults.[49,50] Also, children characteristically exercise suboptimal hand hygiene and sneezing/coughing precautions, making them efficient vectors of influenza spread throughout the community. Focusing influenza vaccination efforts on children may therefore be an effective and practical method of reducing the burden of influenza in sub-Saharan Africa.

The burden of ARI, already very large in stable settings, increases considerably in crises. Crises due to armed conflict, forced displacement and natural disasters result in excess morbidity and mortality due to infectious diseases. Risk factors related to overcrowding due to displacement into camps or into host households with overcrowded living and sleeping quarters could increase risk of

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influenza transmission. Interestingly, the study from Kenya[25] provided evidence that influenza is a major contributor to pneumonia cases in refugee populations.

The high prevalence of co-morbid conditions, including HIV infection, tuberculosis, and pregnancy, may contribute to increased disease severity and mortality from influenza in Africa.[51] There are approximately 30 million persons infected with HIV worldwide, including 5million in South Africa only.[34] Published studies suggest that in the absence of highly active antiretroviral therapy (HAART), adults with AIDS experience a substantially elevated risk of influenza-associated death.[34] Also, children with HIV have higher risk of admission to hospital from influenza-associated ARI than HIV negative children.[31] HIV remains a substantial risk factor for severe influenza-related disease in sub-Saharan Africa. These findings support the ongoing importance of influenza prevention measures in persons with HIV/AIDS. The trivalent inactivated influenza (TIV) vaccine is protective against laboratory-confirmed symptomatic influenza in persons with moderate or asymptomatic HIV infection.[52] However, further evaluation of effectiveness is warranted in severely immune-compromised HIV-infected adults and those with co-morbidities such as tuberculosis.

On the other hand the absence of influenza vaccination program in most of the African countries may increase the risk of transmission of the virus. In developed countries the vaccination of risk groups reduces the prevalence of seasonal influenza; there is also a context of herd immunity which gives protection to unvaccinated people.

When thorough documentation was available the mortality related to influenza has been found also substantial in sub-Saharan Africa. Interestingly, based on the experience in Madagascar, that island was one of the few places in sub-Saharan Africa where a large outbreak was well documented with 114,000 deaths out of a population of 3,250,000.[53] Thus, the worldwide distribution of these reports indicates that under conditions where high mortality was clustered in time and place, the impact of influenza could easily be recognized.[53]

There are now established influenza surveillance systems in several African countries with support from the World Health Organization (WHO) and different organizations such as the US Centers for Disease Control and Prevention (US CDC), Naval Medical Research Unit (NAMRU), and Institut Pasteur.[54] Although many gaps remain, much more is known about seasonal influenza in sub-Saharan Africa now than ever before. Strengthening influenza surveillance, along with conducting special studies on the burden of influenza-associated hospitalization and mortality in relation to other etiologies of pneumonia as well as risk groups for severe and complicated disease, and the economic burden of influenza are important to guide policy-makers in their allocation of scarce resources for related public health interventions.

Conclusion

The burden of seasonal influenza in sub-Saharan Africa seems unlikely to be less than in other areas as usually though. Seasonal influenza is a major contributor to childhood pneumonia. But, its contribution to early childhood pneumonia appears still under-appreciated in high pneumonia-endemic tropical settings such as sub-Saharan Africa for several reasons. Also, there is good reason to believe that seasonal influenza could also have a greater toll on morbidity and mortality in Africa, compared with more-developed continents considering the frequency of predisposing factors such as HIV and TB and the absence of influenza vaccination program. When documentation was available, the mortality related to the disease has been found also substantial.

Despite the growing successes of the influenza surveillance systems in sub-Saharan Africa, they need to be strengthened and expanded in order to address some of the data gaps. The strengthening of national surveillance capacity supports the long-term goal of generating improved data for national decision-making.

Study limitations

The authors acknowledge the following limitations of the study: Firstly, the studies reviewed did not use standardized case definitions of ILI and SARI. Secondly, data on outpatient and inpatient proportional morbidity and mortality may not be representative of population patterns due to differences in health care utilization by type of illness. Studies varied substantially on the basis of the number of years of assessment, age-groups included, number of influenza isolates obtained, and testing methods implemented.

Conflicts of interest

Author declares there are no conflicts of interest.

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