DOI:10.1111/j.1750-2659.2011.00257.x
www.influenzajournal.com

Original Article

Pandemic influenza in Africa, lessons learned from 1968: a systematic review of the literature

Justin R. Ortiz,[a] Kathryn E. Lafond,[b] Tiffany A. Wong,[c] Timothy M. Uyeki[b]

[a]Department of Medicine, University of Washington, Seattle, WA, USA. [b]Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA. [c]Masagung Graduate School of Management, University of San Francisco, San Francisco, CA, USA.
Correspondence: Justin R. Ortiz, International Respiratory and Severe Illness Center (INTERSECT), Division of Pulmonary and Critical Care Medicine, University of Washington Medical Center, Box 356522, 1959 NE Pacific Street, Seattle, WA 98195-6522, USA. E-mail: jrortiz@u.washington.edu

Accepted 28 March 2011. Published online 3 May 2011.

Background To help understand the potential impact of the 2009 H1N1 pandemic in Africa, we reviewed published data from Africa of the two previous influenza pandemics.

Methods We conducted a systematic search of three biomedical databases for articles in any language on 1957 H2N2 or 1968 H3N2 pandemic influenza virus infection in Africa published from January 1950 through August 2008.

Results We identified 1327 potentially relevant articles, and 298 warranted further review. Fourteen studies on 1968 H3N2 influenza met inclusion criteria, while two studies identified describing 1957 H2N2 were excluded for data limitations. Among these 14 studies, community attack rates for symptomatic infection during all 1968 pandemic waves were around 20%. However, the proportion infected in communities ranged from 6% in isolated communities to 100% in enclosed populations. A total of 22–64% of sampled clinic patients and 8–72% of hospitalized patients had evidence of 1968 H3N2 virus infection. After the second pandemic wave, up to 41–75% of persons tested had serological evidence of 1968 H3N2 virus infection.

Conclusion The 1968 H3N2 influenza pandemic, generally regarded as mild worldwide, appears to have had a substantial impact upon public health in Africa. Without more epidemiologic data the impact of the 2009 H1N1 pandemic in Africa cannot be assumed to have been mild. Assessment of the burden of 2009 H1N1 virus and future influenza pandemics in Africa should attempt to assess disease impact by a variety of methods, including substudies among specific populations.

Keywords Africa, influenza, pandemic.

Please cite this paper as: Ortiz *et al*. (2012) Pandemic influenza in Africa, lessons learned from 1968: a systematic review of the literature. Influenza and Other Respiratory Viruses 6(1), 11–24.

Introduction

As of April 2010, 2009 pandemic influenza A (H1N1) (2009 H1N1) virus had spread rapidly to every continent and been confirmed in more than 209 territories and countries.[1] However, very limited epidemiologic data have been collected which describe the impact of the 2009 H1N1 virus on African populations. Influenza data collected prior to the 2009 pandemic from tropical countries in West Africa,[2–4] Asia,[5–8] and South America suggest that influenza virus activity occurs at moderate to high levels with morbidity comparable to that in developed nations.[9,10] Furthermore, hospital studies from Africa suggest that the burden of influenza among young children and the elderly may be substantial.[11–17] In Africa, access to health care, poor nutrition, chronic infections such as HIV, inadequate sanitation, lack of clean water, indoor air pollution, and family crowding with large numbers of children could contribute to increased influenza morbidity and mortality.[18–20] Furthermore, modeling studies suggest that the burden of pandemic influenza could be substantial in Africa.[21] While recent efforts have been made to increase the influenza surveillance capacity in Africa, many challenges remain.[22–24] A more complete characterization of seasonal and pandemic influenza activity in Africa can help public health policy makers to prioritize disease surveillance and control efforts in the region.

In light of the limited data currently available from the 2009 influenza pandemic in Africa, we undertook this study to determine the impact of the two previous mild-to-moderate influenza pandemics upon African populations. We aimed to review attack rates, disease severity, and geographic and temporal activity data during the 1957 and 1968 influenza pandemics in the continent.

Methods

In August 2008, we created an Africa influenza article database including all published articles pertaining to influenza virus infection of humans in Africa since 1950. We conducted a systematic search of all articles in any language related to influenza virus infection of humans in Africa using the following electronic databases for primary studies: Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/, 1950 to August 2008), EMBASE (http://www.embase.com, 1974 to August 2008), and Web of Science (http://isiknowledge.com, 1945 to August 2008) (details of the complete search strategy are provided in Table S1). We also searched journals and contacted experts in the field. Eligible abstracts were reviewed independently by two authors to determine whether they included data about human influenza research in the African continent (excluding surveillance and news reports), laboratory-confirmation of influenza virus infection, and reported laboratory methods. All relevant articles were obtained for inclusion in the database. When there was disagreement about the relevance of an article, it was also obtained for inclusion in the database.

In December 2009, during the influenza A (H1N1) pandemic, we used the Africa Influenza Article Database to complete a systematic review to gain insight into the impact of previous pandemics on the African continent. We did not publish a review protocol, and we did not seek to register this systematic review. Two of the authors independently reviewed all complete articles in the database to identify studies containing data on human infection with influenza A/Asian/57 (H2N2) (1957 H2N2) or influenza A/Hong Kong/68 (H3N2) (1968 H3N2) viruses collected during the 2 years after the emergence of each virus. Disagreement was settled by a third author. Data were extracted by persons fluent in the publication language. Extracted data included locale, study type, case definitions used, sample population characteristics, influenza laboratory testing methods and definitions of positive tests, and other collected epidemiologic data. Risk of bias in individual articles was assessed by the absence of the following key study characteristics: defined specimen collection criteria, defined subject recruitment criteria, defined laboratory methods using WHO-approved reagents or confirmatory tests, defined positive laboratory values, and reported the number of persons tested and the number of tests positive. Studies were expected to be heterogeneous, and the *a priori* analysis plan was to compare findings without aggregating data.

Results

Description of included studies

In August 2008, we created a database of all published articles pertaining to influenza virus infection of humans in Africa since 1950. A total of 1326 unique potentially relevant articles were identified for the database (Figure 1). Biomedical database queries identified 1284 potentially relevant articles, and an additional 42 potentially relevant articles added after discussion with experts and additional literature review. Of these, 1029 citations did not meet the inclusion criteria (primary studies of human infection by human influenza virus in Africa) and were excluded after first screen of titles and abstracts. The remaining 297 articles comprised the Africa influenza article database.

In December 2009, we reviewed the Africa influenza article database for studies pertaining to the 1957 and 1968 influenza pandemics. Of the 297 articles, 83 articles potentially described data on human infection by either 1957 H2N2 or 1968 H3N2 influenza virus based on a screen of titles and abstracts. Next, the complete 83 potentially relevant articles were read, and 16 were found to have data on human infection with 1957 H2N2 or 1968 H3N2 virus occurring within 2 years of the emergence of each virus, the inclusion criteria for this study.[25–40] Only two articles had data on the 1957 H2N2 pandemic,[39,40] while 14 had data from the 1968 H3N2 pandemic. Due to the limited number of articles on 1957 H2N2 pandemic influenza as well as a lack of a defined study population in either article, these two articles were excluded from further review (summary data from these articles are available in Table S2).

The 14 reviewed articles reported findings for laboratory-confirmed pandemic 1968 H3N2 virus infection in four African Regions: North (14%) (Table 1), West (21%) (Table 2), East (36%) (Table 3), and Southern Africa (29%) (Table 4). Articles included investigations conducted among hospitalized patients (14%), outpatient clinic patients (7%), general communities (50%), and mixed populations (36%). Study design categories included: cross-sectional (36%); prospective (43%); vaccine effectiveness studies (14%); and a combination of study designs (7%). None of the articles reported detailed epidemiologic or clinical data of the subject population, defined subject recruitment criteria, or defined specimen collection criteria. All of the studies reported laboratory methods using WHO-approved reagents or confirmatory tests. The primary diagnostic methods were isolation of virus by viral culture from respiratory specimens (7%), and serological detection of 1968 H3N2 virus antibodies by hemagglutination inhibition (HAI) assays (79%) or by single radial diffusion (SDR) assay (14%). A majority of articles (57%) also included 1968 H3N2 virus culture confirmation during clinical illness in a subset of subjects. The primary outcomes included symptomatic influenza virus infection by demonstrating rise in antibody titers between tests (paired serology) (29%), evidence of prior influenza virus infection by single serology (21%), evidence of acute influenza virus

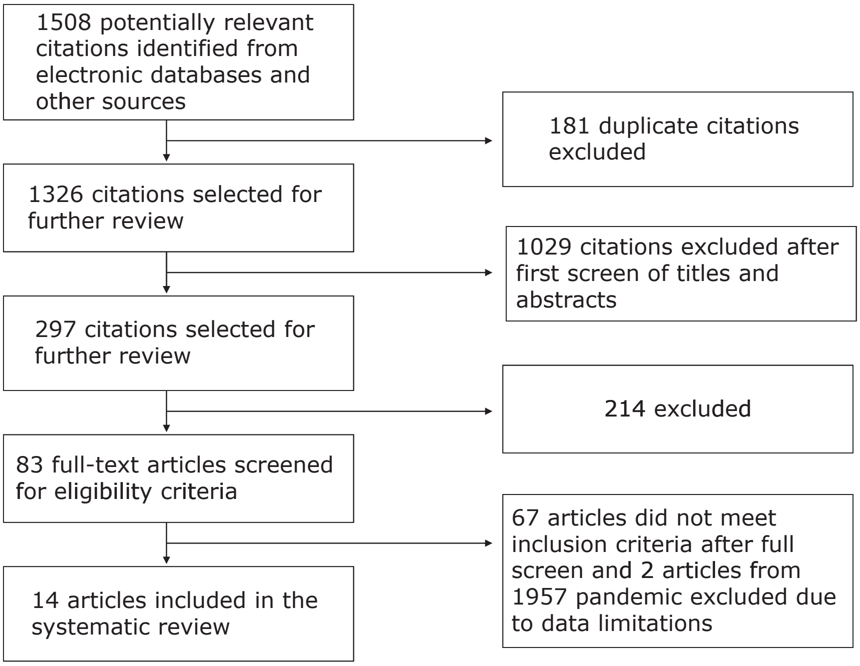

Figure 1. Study flow chart. *Note*: (i) All articles identified by our search of biomedical databases were considered potentially relevant. (ii) Articles selected for further review (first screen) had abstracts and titles suggesting that the studies included data about human research in the African continent, had laboratory-confirmation of influenza virus infection, and described laboratory methods. (iii) Citations selected for further review were confirmed to meet criteria from the first screen after review of complete articles. (iv) Articles were then screened for eligibility criteria (second screen) by review of abstracts and titles suggesting that the studies included data on human infection with influenza A/Asian/57 (H2N2) (1957 H2N2) or influenza A/Hong Kong/68 (H3N2) (1968 H3N2) viruses during the two years after the emergence of each virus. (v) Articles included in the systematic review were confirmed to meet criteria from the second screen after review of complete articles.

infection by culture (7%), influenza-like illness (ILI) with culture-confirmed influenza virus infection in a subset (7%), and a combination of these outcomes (36%).

Timing of 1968 H3N2 pandemic influenza activity in Africa

During the first wave of the pandemic in 1968–1969, the timing of influenza activity in Africa varied considerably across the continent (Figure 2). The earliest evidence of pandemic influenza was in West Africa, where peak activity differed substantially between countries. In Gambia, the timing of the epidemic, defined by the timing of elevated antibodies in the population suggests that pandemic H3N2 peaked between November 1968 and March 1969.[33,38] While a study from Senegal reported that the number influenza cases first increased between July and September 1969.[26] In North Africa, a prospective series of serologic studies from Egypt reported the highest rise in 1968 H3N2 antibody titers during December 1968, suggesting a peak in viral activity near that time.[30] In East Africa, Sudan experienced an increase in ILI cases (in a sub-study without influenza testing) from February 1969 through June 1969, whereas Kenya, Tanzania, and Uganda experienced increases in influenza cases slightly later, from April 1969 to August 1969.[34–36] Finally, cases peaked in South Africa between May and June 1969.[27,29,32]

A second wave of pandemic H3N2 activity occurred later in the 1969–1970 season (Figure 2). East Africa had the earliest evidence of a second wave of influenza from October 1969 to February 1970 in Kenya, Tanzania, and Uganda; however, influenza activity lasted into June 1970 in Sudan.[34,35] In North Africa, a study from Algeria reported that pandemic influenza activity started in November 1969, while monthly sampling in Egypt identified the highest rise in influenza antibody titers during January 1970. In West Africa, Gambia did not have influenza activity until between March and November 1970.[30] There were no data among included articles on the timing of the second wave in South Africa.

Pandemic influenza A (H3N2) virus infection in Africa

The proportion of persons infected among specific populations can be determined from most of the articles, however, due to study design limitations, population-based pandemic influenza incidence among the general population cannot be determined.

Table 1. North Africa 1968 pandemic influenza A (H3N2) articles included in review

Article and study type	Location	Time period	Specimen collection definition	Outcome measured	Population	Pandemic H3N2 attack rate
• Hosny AH, *et al.*, J Egypt Public Health Assoc. 1972 Prospective Cohort	Multiple locations in Egypt	1968–1970	None reported	Evidence of past influenza virus infection	1549 persons in 1968/69 had single serology 1103 persons in 1969/70 had single serology	73% (1134/1549) 73% (808/1103)
• Bouguermouh A, *et al.*, Arch Inst Pasteur Alger. 1970 Cross-sectional survey	Algeria	November to December 1969	Undefined ILI	Symptomatic influenza virus infection by culture	Unreported number of symptomatic persons identified in the community	Cannot be determined

Paired serology, acute and convalescent sera; single serology, cross-sectional single serum; ILI, influenza-like illness. Geographic categories are based on United Nations geographic subregions.[49]

Northern Africa

Two articles were identified from North Africa (Table 1). In one study, pandemic influenza was confirmed from an unreported number of Algerians with febrile acute respiratory illness from whom clinical specimens were collected for viral culture.[28] Another study reported HAI titers against pandemic H3N2 during the 1969–1970 and 1970–1971 influenza seasons in an undefined population which included at least some hospitalized patients.[30] In a substudy during the 1968–1969 season, 1134/1549 (73%) sera from an undefined population were positive for H3N2 antibodies, suggesting high rates of pandemic infection in the study population during the first wave. After the second wave of the pandemic in 1969–1970, the proportion of seropositive serum samples remained unchanged at 808/1103 (73%) suggesting a much lower incidence during the second wave among persons studied.

In a different sub-study, paired sera from 80 children clinically diagnosed with influenza were tested by HAI during 1968–1969. While only summary geometric mean titers (GMT) were reported, these data demonstrated a fourfold rise in GMT between acute (94 GMT) and convalescent (379 GMT) phases of illness. These data demonstrate large increases in antibody titers associated with clinical influenza illness among children studied during the first wave of the pandemic.

West Africa

Three articles were identified from West Africa (Table 2). In the first article, pandemic H3N2 virus infection was confirmed among an unreported number of Senegalese persons with febrile acute respiratory illness from May to September 1969 by culture of respiratory specimens and testing of paired sera.[26]

Two articles from Gambia reported data from the same communities during 1967 through 1975.[33,38] In the first study, serial blood draws were performed on persons in two nearby villages.[38] Evidence of antibody seroconversion to pandemic H3N2 influenza was determined by SDR assay. In one village, between November 1968 and March 1969, 10/32 (31%) persons had evidence of acute H3N2 virus infection, a rise from 0/32 during the preceding 4 months. In the second village, 6/27 (22%) seroconversions were identified during January to March 1969. Both villages had observed increases in ILI during the periods, but influenza virological data were not available.

In the second, larger study performed by the same investigators, similar methods were used to assess new pandemic H3N2 virus infections.[33] A village cohort had sera collected twice yearly, and 17/277 (6%) of seroconversions occurred from March to November 1969. Children aged 1–4 years had the highest seroconversion (15%), followed by children aged 5–14 years (5%) and persons aged >14 years (5%). Sera were collected annually from persons in three other villages, with reported seroconversion from March 1969 to March 1970 ranging from 20% to 45% among children aged 5–14 years, and 12–38% among persons aged >14 years.

The Gambia studies also provided data on H3N2 virus infections during the second wave of the pandemic;

Table 2. West Africa 1968 pandemic influenza A (H3N2) articles included in review

Article and study type	Location	Time period	Specimen collection definition	Outcome measured	Population	Pandemic H3N2 attack rate
• Barme M, *et al.*, Bull Soc Med Afr Noire Lang Fr. 1969 Cross-Sectional Survey	Senegal	May to September 1969	Undefined ILI	Symptomatic influenza virus infection by culture and paired serology in a subset	Unreported number of symptomatic children and health care workers	Cannot be determined
• Schild GC, *et al.*, Bull World Health Organ, 1977 Prospective Cohort	Two rural Gambia villages	Village 1: November 1968 to March 1969	Undefined ILI	Symptomatic influenza virus infection by paired serology	Village 1: 32 symptomatic persons had paired serology	Village 1: 31% (10/32)
		Village 2: January 1969 to March 1969			Village 2: 27 symptomatic persons had paired serology	Village 2: 22% (6/27)
• McGregor IA, *et al.*, Br Med Bull, 1979 Prospective Cohort	Four rural Gambia villages	Village 1: March 1969 to November 1969; and March 1970 to November 1970	Undefined ILI	Symptomatic influenza virus infection by paired serology	Village 1: 277 symptomatic persons had paired serology	Village 1: 6% (17/277)
					Village 1: 312 symptomatic persons had paired serology	Village 1: 14% (43/312)
		Village 2–4: March 1969 to March 1970; and March 1970 to March 1971			Village 2–4: unreported number of symptomatic persons had paired serology categorized by age group	5–14 years Village 2: 45% Village 3: 20% Village 4: 41% 15+ years Village 2: 38% Village 3: 12% Village 4: 34%
					Village 2–4: unreported number of symptomatic persons had paired serology categorized by age group	5–14 years Village 2: 3% Village 3: 5% Village 4: 2% 15+ years Village 2: 3% Village 3: 6% Village 4: 5%

Paired serology, acute and convalescent sera; single serology, cross-sectional single serum; ILI, influenza-like illness. Geographic categories are based on United Nations geographic subregions.[49]

between March 1970 and November 1970 seroconversions ranged from 16% to 23%.[33,38]

East Africa

Only one article included data on the first wave of pandemic influenza in East Africa from 1968 to 1969[35] (Table 3). Testing of paired sera collected from Ugandans with ILI demonstrated evidence of acute H3N2 virus infection among 67/88 (76%) persons incarcerated in Soroti Prison during October 1969, as well as 11/11 (100%) in Kampala University students in January and February 1969. Viral culture performed on a subset of specimens collected from the ILI patients was positive for H3N2 virus in 100% from Soroti Prison and 25% from Kampala University.

Cross-sectional serologic surveys demonstrated evidence of prior infection by pandemic H3N2 virus in several Ugandan cohorts. In West Nile, 19/115 (17%) of serum specimens collected from a convenience sample of patients

Table 3. East Africa 1968 pandemic influenza A (H3N2) articles included in review

Article and study type	Location	Time period	Specimen collection definition	Outcome measured	Population	Pandemic H3N2 attack rate
• Montefiore D, *et al.*, Trop Geogr Med. 1970 Mixed study design	Multiple locations in Uganda including prison, university, clinics, and hospitals	May 1969 to February 1970	Undefined ILI among symptomatic persons No symptoms reported among single serology	Symptomatic influenza virus infection by culture AND/Or paired serology; and evidence of past influenza virus infection by single serology	88 symptomatic prisoners with culture AND/OR paired serology	100% viral culture (2/2), and 76% paired serology (67/88)
					12 symptomatic students with culture AND/OR paired serology	25% viral culture (4/12), and 100% paired serology (11/11)
					89 random dispensary patrons with single serology (at beginning of first pandemic wave)	0% (0/89)
					115 convenience sample of patients with blood drawn as part of unrelated study with single serology	17% (19/115)
					73 randomly selected staff embers and patients attending outpatient clinic with single serology	22% (16/73)
					49 randomly selected patients and staff at hospital in isolated community with single serology	9% (4/49)
					12 symptomatic patients with paired serology	42% (5/12)
• Montefiore D, *et al.*,Bull World Health Organ. 1970 Cross-Sectional Survey	Hospitals in Kenya, Tanzania, and Uganda (two sites)	January to February 1970	None reported	Evidence of past influenza virus infection by single serology	Randomly selected hospital patients with single serology	Kenya 37% (21/57); Tanzania 72% (65/90); Uganda 22% (16/73) and 8% (4/49)

Table 3. *Continued*

Article and study type	Location	Time period	Specimen collection definition	Outcome measured	Population	Pandemic H3N2 attack rate
• Salim AR. Bull World Health Organ. 1971 Prospective Cohort	University, Sudan	January 1970	Undefined ILI	Symptomatic influenza virus infection by culture AND/OR paired serology	33 symptomatic students with viral culture AND/OR paired serology	27% viral culture (9/33); and 72% paired serology (18/25)
• Salim AR, Trop Geogr Med, 1974 Prospective Cohort	University and community, Sudan	Paired serology January to February 1970 Single serology May 1970	For paired sera undefined ILI, and for complement fixing antibodies ''blood draw for any clinical reason''	Symptomatic influenza virus infection by culture AND/Or paired serology; and evidence of past influenza virus infection by single serology	50 symptomatic students with paired serology 192 convenience sample had single serology tested by complement fixation	74% (37/50) 64% (123/192)
• Anderson N, Trop Geogr Med, 1972 Cross-Sectional Survey	Northern Kenya	July to August 1970	None reported	Evidence of past influenza virus infection by single serology	144 persons from two separate isolated villages	41% (59/144)

Paired serology, acute and convalescent sera; single serology, cross-sectional single serum; ILI, influenza-like illness. Geographic categories are based on United Nations geographic subregions.[49]

Table 4. Southern Africa 1968 pandemic influenza A (H3N2) articles included in review

Article and study type	Location	Time period	Specimen collection definition	Outcome measured	Population	Pandemic H3N2 attack rate
• Becker WB, *et al.*, S Afr Med J, 1970 Prospective cohort	South Africa factory	May to June 1969	Undefined ILI	Symptomatic influenza virus infection by culture AND/OR paired serology; and evidence of past influenza virus infection	5 symptomatic factory workers had viral culture and 14 had paired serology	100% viral culture (5/5) and 64% paired serology (9/14)
					10 symptomatic unvaccinated factory workers had single serology	90% (9/10)
					10 asymptomatic unvaccinated factory workers had single serology	50% (5/10)
					8 symptomatic unvaccinated community members had paired serology	88% (7/8)
• Eddy TS, *et al.*, S Afr Med J, 1970 Vaccine effectiveness trial	South Africa factory	May to June 1969	Trial participation	Hospitalization with ILI	1254 received active vaccine and 413 received placebo followed for hospitalization	2% vaccinated (25/1254), 11% unvaccinated (42/413), and 4% overall (67/1667)
• Joosting AC, *et al.*, S Afri Med J, 1971 Vaccine effectiveness trial	South Africa mine	March to September 1969	Respiratory hospitalization, and paired serology in a subset of participants	Antibody response to influenza virus infection or vaccination; and respiratory hospitalization with laboratory confirmed influenza	1050 received active vaccine followed for influenza-confirmed hospitalization	0·1% (1/1050)
					1050 did not receive vaccine and followed for influenza-confirmed hospitalization	1·1% (12/1050)
					60 did not receive vaccine had paired serology	75% (45/60)
• Illman D, Trop Geogr Med, 1971 Cross-Sectional Survey	Zambia	August to September 1969	None reported	Evidence of past influenza virus infection by single serology	112 persons from the remote Korekore tribe had single serology	36% (40/112)

Paired serology, acute and convalescent sera; single serology, cross-sectional single serum; ILI, influenza-like illness. Geographic categories are based on United Nations geographic subregions.[49]

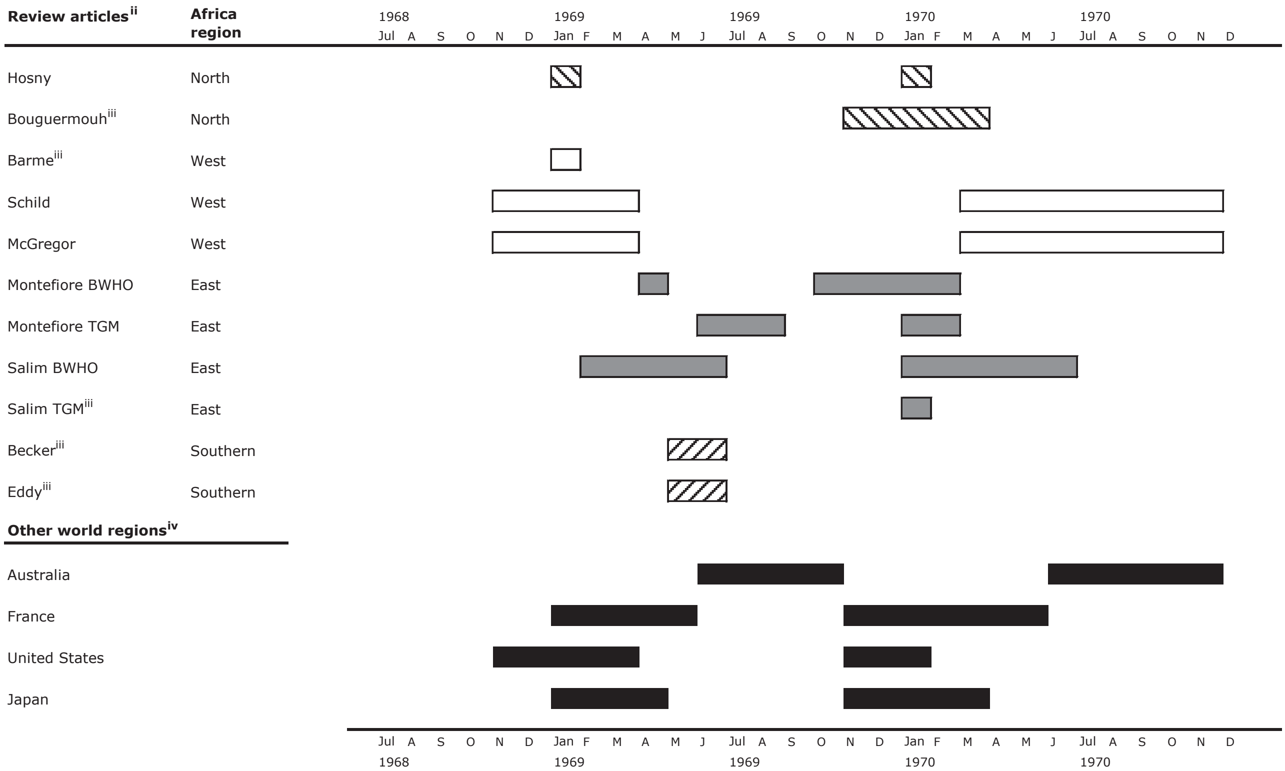

Figure 2. Timing of peak influenza activity during the 1968 pandemic, Africa and selected other countries.[i] *Note*: (i) Peaks in epidemic activity estimated from review articles. Due to study design differences, comparison of duration of influenza activity between articles and regions is not possible. Geographic categories are based on United Nations geographic subregions.[49] (ii) BWHO is Bulletin of the World Health Organization, and TGM is Tropical and Geographical Medicine. (iii) Articles did not report dates of influenza activity for both pandemic waves. (iv) Source for world region data.[41]

were positive for influenza antibodies after a wave of respiratory infections hit the community during November 1969. In Kabale Hospital in January 1970, among a random sample of staff members and patients attending an outpatient clinic (with unreported symptoms) 16/73 (22%) were seropositive. In rural Moroto during January 1970, 4/49 (9%) of a random sample of clinic patients and staff were seropositive. Finally, in Entebe Uganda, 5/12 patients (42%) who experienced ILI between June and November 1969 were seropositive after their illness.

Four additional articles from East Africa reported serologic studies conducted during and after the second wave of pandemic influenza outbreaks in Uganda, Tanzania, Kenya, and Sudan.[25,34,36,37] Among hospitalized patients with unreported symptoms, there was serologic evidence of past H3N2 virus infection among 21/57 (37%) in Kenya, 65/90 (72%) in Tanzania, and 16/73 (22%) and 4/49 (8%) in two different Uganda locations. In remote Northern Kenya, seroprevalence to pandemic H3N2 virus was 41% (59/144) after the second wave in July to August 1970.[25] Two studies from Sudan described serologic surveys in 1970 during and after the second wave of the pandemic.[36,37] In the first study, 9/33 (27%) of Khartoum University students with ILI had culture-confirmed influenza; however among a subset with paired sera, 18/25 (72%) had evidence of acute infection.[36] In another study, among a convenience sample of 200 clinic patients with blood collected for any diagnostic testing in May 1970 in Khartoum, there was evidence of prior H3N2 virus infection in 64%.[37] Furthermore, 37/50 (74%) Khartoum University students with ILI during January through February 1970 with paired sera analyzed had evidence of acute H3N2 virus infection.[37]

Southern Africa

Four articles were identified from Southern Africa (Table 4). The first two articles described different aspects of an influenza outbreak investigation among South African factory workers during the first pandemic wave.[27,29] To investigate an ILI outbreak in May–June 1969, respiratory specimens, paired sera, and single convalescent sera were collected from a variety of subjects for viral culture and serologic testing.[27] Among Bantu factory employees with ILI, 5/5 (100%) had culture-confirmed influenza. Among unvaccinated Bantu factory employees with ILI who had paired sera tested, 7/12

(58%) demonstrated seroconversion to H3N2 virus. Among unvaccinated Bantu factory employees with ILI who had single sera tested, 9/10 (90%) had evidence of prior H3N2 virus infection, and 7/8 (88%) community members with ILI also had H3N2 antibodies.

The second article from this population was a study performed to determine influenza vaccine effectiveness to decrease hospitalized ILI among ethnic Bantu factory employees.[29] During the same period, 1254 employees received vaccine against pandemic H3N2 influenza virus and 413 workers received placebo. Participants were followed for ILI requiring hospitalization. Only five of the workers with ILI had specimens tested by viral culture. All specimens yielded pandemic H3N2 virus, suggesting that most of the clinical illness in the entire cohort was also due to influenza virus infection. The overall proportion of subjects with hospitalized ILI was 4%; and 2% of vaccinated and 11% of unvaccinated persons were hospitalized.

In a separate vaccine effectiveness study conducted among South African mine workers during March to September 1969, 1100 persons (of whom 550 received vaccine) were followed for febrile respiratory illness requiring hospitalization from March to September 1969.[32] Among unvaccinated subjects with paired sera, 75% (45/60) had evidence of H3N2 virus infection. Overall, influenza-associated hospitalizations were serologically confirmed in 0·1% (1/1050) among vaccinated subjects and 1% (12/1050) among unvaccinated subjects.

Finally, a cross-sectional serologic survey conducted in a rural Zambia community during August to September 1969 determined that 36% (40/112) of participants had evidence of H3N2 virus infection.[31]

Discussion

We identified differences in timing and geographic activity of the 1968–1969 influenza A (H3N2) pandemic in African countries. The onset of peak activity differed by region. Influenza activity in North, West, and East Africa lagged behind Europe,[41] and countries as close in proximity as Senegal and Gambia experienced substantial differences in H3N2 activity. In South Africa, the first wave of the pandemic preceded activity in Australia by one month.[41] Our study was not designed to trace the spread of the 1968 pandemic across Africa, and differences in study design and case ascertainment may bias our findings. Nevertheless, forty years later, there is still no study that has described the geographic spread of inter-pandemic or pandemic influenza in Africa.

The reviewed studies reported high levels of morbidity attributable to pandemic H3N2 influenza in four different African regions. While study designs differed, attack rates during the first wave were consistently above 20%, and some communities had serologic evidence of infection in sampled populations up to 76%. These attack rates are comparable to those found in studies from temperate regions in North America, Australia, and Europe.[42] Serologic data from ill outpatients and hospitalized patients with respiratory disease suggest that a large proportion of these patients had pandemic influenza. Of sampled ill outpatients, 22% to 41% in Uganda had evidence of influenza virus infection, and enclosed populations such as Ugandan university students and prisoners had greater than 70% attack rates. Among hospitalized patients, 9% in Uganda to 73% in Egypt had evidence of infection.

The limited data available from the second wave of the pandemic from 1969 to 1970 also suggest high morbidity in African populations. Peak cases of ILI in Uganda during the second wave were about 150% of the 1968–1969 case counts.[35] Laboratory-diagnosed influenza attack rates in community-based populations ranged from 16% in Gambia to 41% in Kenya, while 64% of randomly selected outpatients in Sudan had evidence of H3N2 virus infection. Serologic testing of randomly selected hospital patients found evidence of H3N2 antibodies ranging from 8% in Uganda to 72% in Tanzania. By the end of the second wave, there was evidence that up to 73% of sampled persons in Egypt and 75% of sampled persons in South Africa had been infected with H3N2 virus since the beginning of the pandemic.

Strengths and limitations of the review

There were potential biases pertaining to all of the included studies, as none clearly defined specimen collection criteria or defined subject recruitment criteria. In addition, as with all systematic reviews, it is possible that our search methodologies missed relevant articles. Nevertheless, our methods included sensitive search terms for articles published in any language from three different biomedical journal databases, and we contacted regional experts to ensure that we did not overlook any relevant articles. Furthermore, publication bias is a known problem with systematic reviews. It is possible that serologic surveys on 1957 or 1968 influenza pandemics that showed low attack rates were not published. Nevertheless, to our knowledge, this is the most thorough published review of influenza epidemiology studies from the African continent of this time period. Cross-reactivity between the pandemic 1957 H2N2 virus and the pandemic 1968 H3N2 virus (non-specific or detection of N2 antibody) might have resulted in overestimates of levels of prior infection in cross-sectional serologic surveys. However, the majority of reviewed studies primarily assessed paired sera which are more likely to be representative of acute influenza virus infection. Nevertheless, caution should be used when comparing data among the different studies since different assays were used to detect influenza

Table 5. General recommendations for influenza surveillance and burden of disease studies in Africa during the 2009 H1N1 pandemic

General recommendations	
Study design	• Multiple studies in diverse sites will help to better understand geographic and temporal differences in virus activity across the continent. • Assess A various outcomes to understand different aspects of influenza-associated disease. • The most cost-effective and informative design methodologies (serologic surveys and sentinel surveillance) are discussed in further detail in Table 6.
Population	• Participant populations should include diverse groups; however persons at increased risk for severe influenza-associated disease should be well-represented. • Demographic and epidemiologic features of participants should be described in any research report. • Studies in health care settings (outpatient clinics and hospitals) can help to understand the proportion of severe illness associated with infection. • Ideally, surveillance populations will be well-described with accurate denominator data for incidence calculations.
Specimen collection criteria	• Specimen collection criteria should be specified in publications to allow extrapolation of influenza test results to a larger population. Ideally, specimen collection criteria should be standardized. Consideration should be given to using explicitly defined influenza-like illness in acute care settings[50], and severe acute respiratory illness (SARI) in acute care settings[18]. • Specimen collection criteria should be explicitly described in reports.
Laboratory testing	• Sensitive and specific laboratory tests should be used to diagnose influenza virus infection according to international guidelines; such as hemagglutination inhibition serological assay and RT-PCR[51]. • Results should clearly cite laboratory protocols used as well as thresholds for positive laboratory tests.
Outcomes measured	• Standard surveillance and study outcomes should be used. These include incidence of influenza virus infection (generally by serology on paired sera), or incidence of symptomatic influenza illness in community, outpatient, or hospital settings (generally by serology on paired sera or RT-PCR on upper respiratory specimens). In the case of outbreaks of a novel influenza virus, cross-sectional studies assessing evidence of past influenza virus infection can also be valuable. • Research and surveillance focus should be on the impact of influenza upon public health, and not merely collection of specimens for virologic surveillance.
Analysis	• Analysis methods and data used to calculate disease attack rates should be clearly defined and presented in all reports. • Subgroup analyses of persons at increased risk of influenza-associated disease (age extremes or certain chronic diseases) should be performed when possible.
Additional analyses	• Collection of epidemiologic and clinical data to determine risk factors of disease among persons in community incidence studies or burden of severe illness studies. • Collection of cost of care data as part of influenza burden of illness studies

virus infection. Serologic surveys in communities may detect asymptomatic and clinically mild infections that are missed when only outpatients and hospitalized patients are tested. Finally, while we describe 11 cohorts with greater than 100 persons tested for evidence of pandemic influenza A (H3N2) virus infection, the remaining participant cohorts are small, limiting the interpretation and the generalization of observed attack rates.

There were a surprisingly large number of articles identified that described influenza morbidity among Africans during the 1968 influenza pandemic. The 14 articles we identified can be put into perspective when compared to the number of influenza epidemiology articles published in Africa over the last decade. Using a similar methodology to this review, we could only detect 17 articles published about influenza in Africans from 1998 through 2008, a period with increased concern about avian and pandemic influenza.

Implications

Through mid-August 2010, relatively few cases of 2009 H1N1 had been reported to the World Health Organization from the African continent.[43] While influenza surveillance capacity has increased in the region since the 1968 pandemic, WHO weekly surveillance reports continue to provide little data from Africa. By most indicators, the 2009 H1N1 pandemic has been milder than most pandemic planning assumptions. For example, in New Zealand during the summer of 2009, 30 per 1 000 000 persons required ICU-level care for severe 2009 H1N1 pandemic influenza associated disease.[44] Given that severe disease is a relatively rare event and that Africa has high rates of community-acquired pneumonia from all causes,[45] it is possible that 2009 H1N1 activity has already occurred in many African countries, but was not adequately captured by existing surveillance systems. In South Africa, the country with arguably the most robust influenza surveillance in the

Table 6. Specific recommendations for influenza surveillance and burden of disease studies in Africa during the 2009 H1N1 pandemic

Influenza virus infection incidence in the community	Serologic tests are useful to determine the approximate proportion of persons in a community infected by influenza virus
Study design	• Prospective, paired serologic surveys before and after the first and subsequent waves of the pandemic • Cross sectional serologic surveys after the first and subsequent waves of the pandemic
Population	• Ideally, well described populations with high risk groups over-represented.
Specimen collection criteria	• All persons included without specimen collection criteria
Laboratory testing	• 2009 H1N1 specific hemagglutination inhibition assay
Outcomes measured	• Evidence of influenza virus infection by serology
Analysis	• Incidence of infection within a community (population based, if possible), incidence of infection by age group and by chronic disease diagnosis
Burden of severe influenza illness	Sentinel surveillance in health care settings (outpatient clinics and hospitals) can help to understand the proportion of severe illness associated with infection.
Study design	• Prospective surveillance
Population	• Outpatient clinics and hospitals
Specimen collection criteria	• Influenza-like illness for clinic patients Fever >38·0° AND (cough or sore throat)[50] • Severe Acute Respiratory Illness for hospitalized patients Fever >38·0° AND (cough or sore throat) AND difficult breathing[18]
Laboratory testing	• RT-PCR assay for evidence of active 2009 H1N1 virus infection
Outcomes measured	• Medically attended, laboratory confirmed, influenza-associated illness
Analysis	• Incidence of influenza illness requiring outpatient care or hospitalization
Other studies	
Vaccine effectiveness	• Licensed influenza vaccine compared to inactive comparator vaccine with robust prospective surveillance for medically attended, laboratory confirmed, influenza-associated illness • Vaccine probe studies; control group can provide data on disease burden
Risk factors of disease	• Collection of epidemiologic and clinical data to determine risk factors for severe disease among persons in community incidence studies or burden of severe illness studies
Costs to society	• Collection of cost of care data as part of influenza burden of illness studies; direct and indirect costs

Many additional methodologies exist to investigate influenza burden of disease. The above study designs are not exhaustive, but they do represent the authors' recommendations for the preferred study methodologies given resource limitations.

continent, severe and fatal outcomes with 2009 H1N1 virus infection have been documented.[46,47]

The studies included in this review provide an overview of influenza activity in multiple regions of Africa during the 1968 pandemic. Lessons can be learned from the reviewed articles to inform recommendations for current and future investigations of influenza disease burden in Africa (Tables 5 and 6). A combination of health-care based surveillance and serologic surveys among populations with defined denominators are needed to assess the impact of pandemic and interpandemic influenza in Africa. Ideally, studies should attempt to estimate the incidence of disease in the general population as well as among important subgroups including clinic patients, hospitalized patients, urban and rural communities, persons with chronic infections (e.g. HIV, tuberculosis), and among persons with other chronic comorbid diseases.

WHO is increasing efforts to coordinate and strengthen influenza surveillance and research in Africa, however many challenges remain.[48] Regular reporting of influenza surveillance data to public health systems and WHO, as well as publication of data should be encouraged. This analysis suggests that there was a substantial impact of the 1968 influenza pandemic on Africans. Hence, more data regarding the burden of seasonal influenza and the 2009 H1N1 pandemic are needed to inform future public health resource allocation, prevention, and control strategies in African countries. In particular, the impact of influenza vaccination in targeted high-risk groups in Africa should be assessed.

Conclusions

Despite being generally regarded as a mild influenza pandemic compared to 1918 H1N1 or 1957 H2N2, available published data suggest that the 1968 H3N2 pandemic may have had a substantial impact upon public health among African populations. More than one H3N2 wave occurred, and timing of peak activity varied by geographic region. In the absence of comprehensive influenza surveillance, utilization of serologic data from cross-sectional and longitudinal surveys was helpful to assess the extent of H3N2 virus infection in communities and health care settings.

CDC disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Funding

JRO reports receiving research funding from NHLBI Respiratory Research Training Grant [HL007287]] and Robert Wood Johnson Harold Amos Medical Faculty Development Program (Grant 67423). The remaining authors (KEL, TAW, TMU) received no specific funding. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

The authors report no competing interests exist.

Acknowledgements

We would like to thank the following people for their assistance with the completion of this study: Althea Burton, Jane Goett, Jean-Michel Heraud, Mark Katz, Tony Mounts, Kathy Neuzil, Olga Shargorodska, Vivek Shinde, and Chris Victor.

References

1 World Health Organization. Pandemic (H1N1) 2009 – update 82. World Health Organization, 2009.
2 David-West TS, Cooke AR. Laboratory and clinical investigation of the 1974 influenza epidemic in Nigeria. Bull World Health Organ 1974; 51:103–105.
3 Dosseh A, Ndiaye K, Spiegel A, Sagna M, Mathiot C. Epidemiological and virological influenza survey in Dakar, Senegal: 1996–1998. Am J Trop Med Hyg 2000; 62:639–643.
4 Ortiz JR, Katz MA, Mahmoud MN *et al.* Lack of evidence of avian-to-human transmission of avian influenza A (H5N1) virus among poultry workers, Kano, Nigeria, 2006. J Infect Dis 2007; 196:1685–1691.
5 Chow A, Ma S, Ling AE, Chew SK. Influenza-associated deaths in tropical Singapore. Emerg Infect Dis 2006; 12:114–121.
6 Katz MA, Tharmaphornpilas P, Chantra S *et al.* Who gets hospitalized for influenza pneumonia in Thailand? Implications for vaccine policy. Vaccine 2007; 25:3827–3833.
7 Nguyen HL, Saito R, Ngiem HK *et al.* Epidemiology of influenza in Hanoi, Vietnam, from 2001 to 2003. J Infect 2007; 55:58–63.
8 Nguyen HT, Dharan NJ, Le MT *et al.* National influenza surveillance in Vietnam, 2006–2007. Vaccine. 2009; 28:398–402.
9 Bellei N, Carraro E, Perosa A, Watanabe A, Arruda E, Granato C. Acute respiratory infection and influenza-like illness viral etiologies in Brazilian adults. J Med Virol 2008; 80:1824–1827.
10 Thomazelli LM, Vieira S, Leal AL *et al.* Surveillance of eight respiratory viruses in clinical samples of pediatric patients in southeast Brazil. J Pediatr (Rio J). 2007; 83:422–428.
11 Berkley JA, Munywoki P, Ngama M *et al.* Viral etiology of severe pneumonia among Kenyan infants and children. JAMA 2010; 303:2051–2057.
12 Ijpma FF, Beekhuis D, Cotton MF *et al.* Human metapneumovirus infection in hospital referred South African children. J Med Virol 2004; 73:486–493.
13 Forgie IM, Campbell H, Lloyd-Evans N *et al.* Etiology of acute lower respiratory tract infections in children in a rural community in The Gambia. Pediatr Infect Dis J 1992; 11:466–473.
14 Johnson AW, Osinusi K, Aderele WI, Gbadero DA, Olaleye OD, Adeyemi-Doro FA. Etiologic agents and outcome determinants of community-acquired pneumonia in urban children: a hospital-based study. J Natl Med Assoc 2008; 100:370–385.
15 Madhi SA, Ludewick H, Abed Y, Klugman KP, Boivin G. Human metapneumovirus-associated lower respiratory tract infections among hospitalized human immunodeficiency virus type 1 (HIV-1)-infected and HIV-1-uninfected African infants. Clin Infect Dis 2003; 37:1705–1710.
16 Mulholland EK, Ogunlesi OO, Adegbola RA *et al.* Etiology of serious infections in young Gambian infants. Pediatr Infect Dis J 1999; 18(10 Suppl):S35–S41.
17 Cohen C, Simonsen L, Kang JW *et al.* Elevated influenza-related excess mortality in South african elderly individuals, 1998–2005. Clin Infect Dis 2010; 51:1362–1369.
18 Ortiz JR, Sotomayor V, Uez OC *et al.* Strategy to enhance influenza surveillance worldwide. Emerg Infect Dis 2009; 15:1271–1278.
19 World Health Organization. Risk factors estimates for 2004. 2004: Available from: http://www.who.int/entity/healthinfo/global_burden_disease/CRA_DALY6_2004.xls.
20 World Health Organization. Global Action Plan for the Prevention and Control of Pneumonia in children aged under 5 years. Wkly Epidemiol Rec 2009; 84:451–452.
21 Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. Lancet 2006; 368(9554):2211–2218.
22 Ortu G, Mounier-Jack S, Coker R. Pandemic influenza preparedness in Africa is a profound challenge for an already distressed region: analysis of national preparedness plans. Health Policy Plan 2008; 23:161–169.
23 Oshitani H, Kamigaki T, Suzuki A. Major issues and challenges of influenza pandemic preparedness in developing countries. Emerg Infect Dis 2008; 14:875–880.
24 Breiman RF, Nasidi A, Katz MA, Kariuki Njenga M, Vertefeuille J. Preparedness for highly pathogenic avian influenza pandemic in Africa. Emerg Infect Dis 2007; 13:1453–1458.
25 Anderson N, Mufson MA. Viral antibodies among the Turkana people of Northern Kenya. Trop Geogr Med 1972; 24:168–177.
26 Barme M, Ly M, Gueye I. A2-Hong Kong influenza in Dakar in 1969. Bull Soc Med Afr Noire Lang Fr 1969; 14:729–734.
27 Becker WB, Kipps A, Ranchod M, Keen A. Laboratory investigation of a closed epidemic of Hong Kong influenza. S Afr Med J 1970; 44:217–218.
28 Bouguermouh A, Issatchenko V, Ait-Mesbah O. The 1969–1970 flu epidemic in Algeria: a study of the viruses isolated. Arch Inst Pasteur Alger 1970; 48:189–191.
29 Eddy TS, Davies NA. The effect of vaccine on a closed epidemic of Hong Kong influenza. S Afr Med J 1970; 44:214–216.
30 Hosny AH, Imam IZ, Nour AA, el-Beltagy AM. Influenza in the Arab Republic of Egypt from 1966 to 1972 (with special reference to the

''Hong Kong'' epidemic of 1968). J Egypt Public Health Assoc 1972; 47:170–181.
31 Illman D, Mufson MA. Viral antibodies in the Korekore Tribe of Northern Rhodesia. Trop Geogr Med 1971; 23:64–70.
32 Joosting AC, Harwin RM, Sweetnam B *et al.* A trial of an influenza vaccine in miners. S Afr J Med Sci 1971; 36:33–37.
33 McGregor IA, Schild GC, Billewicz WZ, Williams K. The epidemiology of influenza in a tropical (Gambian) environment. Br Med Bull 1979; 35:15–22.
34 Montefiore D, Drozdov SG, Kafuko GW, Fayinka OA, Soneji A. Influenza in East Africa, 1969–70. Bull World Health Organ 1970; 43:269–273.
35 Montefiore D, Drozdov SG, Kafuko GW, Fayinka OA, Soneji A. Influenza A2-HongKong-68 virus in Uganda. Trop Geogr Med 1970; 22:452–458.
36 Salim AR. Hong Kong influenza in the Sudan. Bull World Health Organ 1971; 44:713–716.
37 Salim AR. Serological evidence of A2 Hong Kong influenza in Sudan. Trop Geogr Med 1974; 26:210–213.
38 Schild GC, Newman RW, McGregor IA, Williams K. The use of transportable single-radial-diffusion immunoplates in seroepidemiological studies of influenza in the Gambia. The occurrence and persistence of antibody to influenza A/Hong Kong/68 (H3N2) virus in selected inhabitants of two rural villages. Bull World Health Organ 1977; 55:3–13.
39 Depoux R, Orio J. Note on the epidemic of Asiatic influenza at Brazzaville. Bull Soc Pathol Exot Filiales 1958; 51:38–40.
40 Sureau P. Etude sérologique d'une épidémie de grippe (septembre–décembre 1957). Arch Inst Pasteur Madagascar 1958; 26:165–170.
41 Viboud C, Grais RF, Lafont BA, Miller MA, Simonsen L. Multinational impact of the 1968 Hong Kong influenza pandemic: evidence for a smoldering pandemic. J Infect Dis 2005; 192:233–248.
42 Jackson C, Vynnycky E, Mangtani P. Estimates of the transmissibility of the 1968 (Hong Kong) influenza pandemic: evidence of increased transmissibility between successive waves. Am J Epidemiol 2010; 171:465–478.
43 World Health Organization. World Health Organization. Influenza – Update 1142010: Available from: http://www.who.int/csr/don/2010_08_20/en/print.html.
44 Webb SA, Pettila V, Seppelt I *et al.* Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 2009; 361:1925–1934.
45 World Health Organization. The global burden of disease: 2004 update. World Health Organization, Geneva, Switzerland, 2004.
46 Archer B, Cohen C, Naidoo D *et al.* Interim report on pandemic H1N1 influenza virus infections in South Africa, April to October 2009: epidemiology and factors associated with fatal cases. Euro Surveill 2009; 14:pii=19369.
47 Koegelenberg CF, Irusen EM, Cooper R *et al.* High mortality from respiratory failure secondary to swine-origin influenza A (H1N1) in South Africa. QJM 2010; 103:319–325.
48 Steffen C, Diop OM, Gessner BD *et al.* Afriflu – international conference on influenza disease burden in Africa, 1–2 June 2010, Marrakech, Morocco. Vaccine 2011; 29:363–369.
49 United Nations Statistics Division. Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings, 2010. Available from: http://unstats.un.org/unsd/methods/m49/m49regin.htm#africa.
50 World Health Organization. WHO Recommended Surveillance Standards, 2nd edn. Geneva, Switzerland: World Health Organization, 1999 [cited 2006 4/22/07]; Available from: http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_CSR_ISR_99_2_EN/en/.
51 Dwyer DE, Smith DW, Catton MG, Barr IG. Laboratory diagnosis of human seasonal and pandemic influenza virus infection. Med J Aust 2006; 185(10 Suppl):S48–S53.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Strategy to search Pubmed to identify studies for this systematic review.

Table S2. Africa 1957 pandemic influenza A (H2N2) articles.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.