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Review

The burden of influenza in East and South-East Asia: a review of the English language literature

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Abstract While human infections with avian influenza A (H5NI) viruses in Asia have prompted concerns about an influenza pandemic, the burden of human influenza in East and Southeast Asia has received far less attention. We conducted a review of English language articles on influenza in 18 countries in East and Southeast Asia published from 1980 to 2006 that were indexed on PubMed. Articles that described human influenza-associated illnesses among outpatients or hospitalized patients, influenza-associated deaths, or influenza-associated socioeconomic costs were reviewed. We found 35 articles from 9 countries that met criteria for inclusion in the review. The quality of articles varied substantially. Significant heterogeneity was noted in case definitions, sampling schemes and laboratory methods. Early studies relied on cell culture, had difficulties with specimen collection and handling, and reported a low burden of disease. The recent addition of PCR testing has greatly improved the proportion of respiratory illnesses diagnosed with influenza. These more recent studies reported that 11–26% of outpatient febrile illness and 6-14% of hospitalized pneumonia cases had laboratory-confirmed influenza infection. The influenza disease burden literature from East and Southeast Asia is limited but expanding. Recent studies using improved laboratory testing methods and indirect statistical approaches report a substantial burden of disease, similar to that of Europe and North America. Current increased international focus on influenza, coupled with unprecedented funding for surveillance and research, provide a unique opportunity to more comprehensively describe the burden of human influenza in the region.

Keywords Disease burden, East Asia, influenza, South-East Asia.

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Introduction

An improved understanding of disease burden in East and South-East Asia is needed to support decisions involving the allocation of limited resources toward influenza control programs. In the absence of a robust body of literature that describes the health and socioeconomic burden of disease, influenza has been seldom considered an important cause of respiratory illness, and control programs have advanced slowly or not at all. In the United States and Europe, many research studies and surveillance systems have documented a significant disease burden in terms of morbidity, mortality, and economic losses.[1–5] These data have supported the development and expansion of influenza surveillance and vaccination programs.[6–8] This review was undertaken to identify and summarize published articles that describe the burden of human influenza in East and South-East Asia. Recommendations for standardizing and improving methods for disease burden estimation, and outlining future directions for research that will support influenza control strategies in this region are discussed.

Methods: Search strategy and selection criteria

A three-step approach was used to identify articles describing the human health, social, and economic burden of human influenza in East and South-East Asia (Figure 1). First, we conducted a literature search of English-language articles in the PubMed database (http://www.ncbi.nlm.nih.gov/sites/entrez) that were published from January 1980 through December 2006 and contained original research data. Papers that included data from any of the 18 internationally recognized countries located in East and South-East Asia were included in the search (Table 1). The search terms used were 'influenza' and the name of each country. For example, the

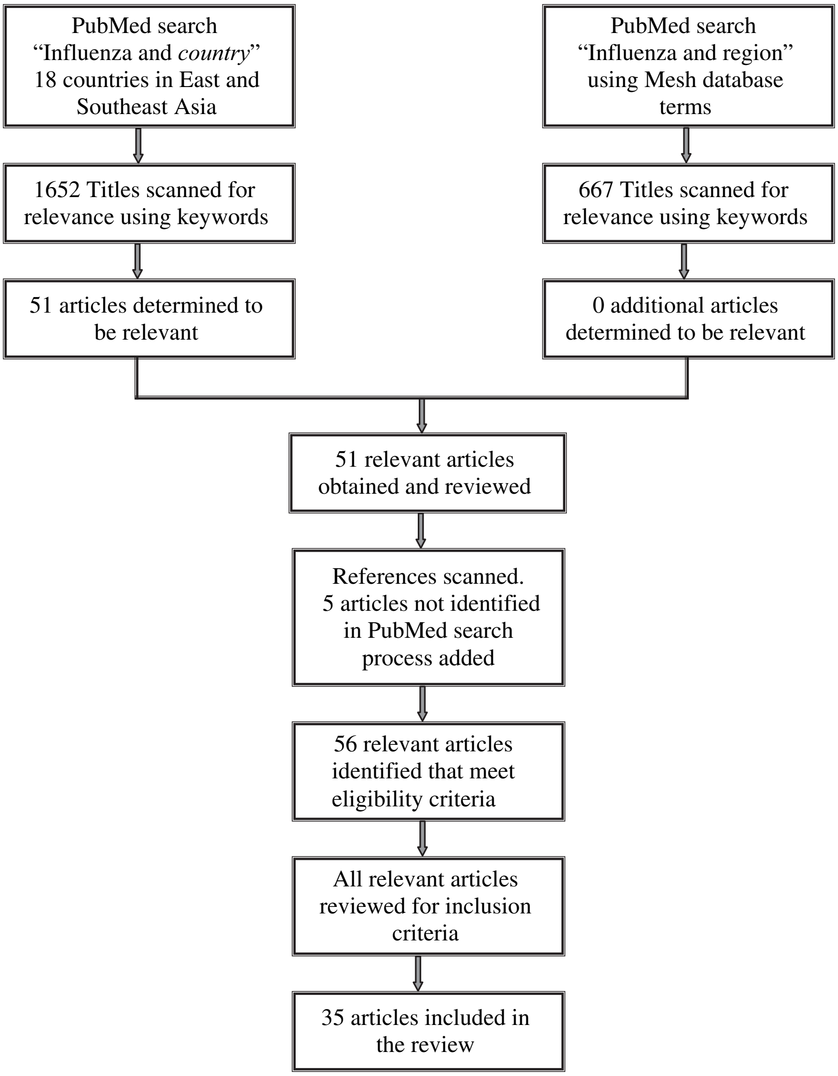

Figure 1. Methods.

Table 1. Countries included in this review

South-East Asian countries	East Asian countries
Brunei*	Japan
Cambodia	South Korea
East Timor*	North Korea*
Indonesia	Republic of China*
Laos*	Hong Kong (PRC)
Malaysia	Mongolia*
Myanmar	Macau (PRC)*
Philippines*	Taiwan (ROC)
Singapore	
Thailand	
Vietnam*	

PRC, People's Republic of China; ROC, Republic of China.
*No articles meeting criteria for inclusion.

terms 'influenza and Thailand,' 'influenza and Japan,' and so forth were entered. Next, geographic descriptors included in the PubMed Medical Subject Headings (MeSH) (http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh) database were used to search for influenza publications with a regional focus. Specifically, the terms 'Asia, Southeastern and influenza' and 'Far East and influenza' were entered.

Second, the titles of all citations returned from the PubMed database searches were scanned for relevance. Titles were reviewed for the presence of any of the following key words; 'epidemiology,' 'surveillance,' 'burden,' 'mortality,' 'deaths,' 'etiology,' 'pneumonia,' 'influenza-like illness,' 'acute upper or lower respiratory infection,' 'hospitalization or hospital admission,' 'seizure,' 'outpatient,' and 'social or economic cost.' Articles with titles that included at least one of these words were considered 'possibly relevant' and the abstract was reviewed. If an abstract contained information on disease burden such as estimates of influenza incidence, mortality, the contribution of influenza to hospitalized pneumonia cases or outpatient illness, or social and economic costs, it was considered 'relevant' and the complete article was obtained for further review. If there was doubt as to whether the article was relevant based on the review of the title and abstract, the article was considered 'possibly relevant' and the complete article was obtained for review.

Third, articles that were considered 'relevant or possibly relevant' were included in the final analysis if they met specific eligibility criteria. To be included, the article must have provided a description of the time period under study, the research or surveillance methods employed, the sampled population including age groups, the case definition and a description of the laboratory testing methods used. We excluded articles from studies that did not use any type of laboratory confirmation. We also excluded articles published only in non-English languages. In a few cases only an article's abstract was published in English. In these instances, the article was included only if the English language abstract contained sufficient information to determine whether it met the eligibility criteria. Finally, references cited in eligible articles were scanned for additional articles not identified through the PubMed search. These articles were subjected to the same process as described above to determine inclusion eligibility.

Results

The PubMed search returned 1652 records. Fifty-one of these articles were determined to be relevant. The search by geographic region returned 175 records for 'influenza and Asia, southeastern' and 492 records for 'influenza and Far East.' No additional relevant articles were identified using the geographic search terms. A manual review of the references cited from all relevant articles identified five additional relevant articles. Among the 56 relevant articles identified, 35 met the eligibility criteria and were included in the review. Articles included data from Thailand (9), Taiwan (6), Hong Kong (6), Japan (4), Korea (3), Indonesia (1), Myanmar (1), Malaysia (1), and Singapore (4).

The amount of information included in the articles varied widely with few providing detailed descriptions of the sampling approaches or laboratory methods. Frequently, nonsystematic or convenience sampling schemes were used. The majority of studies focused on children and a variety of influenza-like illness (ILI) and pneumonia case definitions were used. Most studies involving inpatients were designed to identify the causes of pneumonia in children and only five studies estimated influenza incidence. Most articles published prior to 1997 focused on the virological or other laboratory aspects of influenza including antigenic characterization of influenza viruses and vaccine development. Several articles documented influenza outbreaks at schools, military camps, and remote hill tribe communities. The majority of articles published between 1997 and 2006 focused on avian influenza A (H5N1) and pandemic preparedness.

Fifteen articles focused on the etiology of pneumonia requiring hospitalization (Table 2). Twelve articles assessed the contribution of influenza virus infection to outpatient illness (Table 3). Six studies focused on influenza-associated hospitalization while two studies estimated influenza-associated mortality and a single study examined both topics (Table 4). Three studies examined the contribution of influenza virus infection to fever of unknown origin requiring hospitalization or febrile seizures. Two studies enrolled both outpatients and inpatients.[9,10] Two studies estimated the direct medical or social costs (lost work or school days) of influenza.[9,11]

Influenza-associated pneumonia and fever requiring hospitalization

The 15 studies that provided data on the contribution of influenza virus infection to pneumonia requiring hospitalization included a total of 18,156 patients in six countries during 1982–2004. Twelve studies were among pediatric patients, and 10 of these reported data from a single, urban hospital. Most studies enrolled patients year-round for one or more years, with the exception of two Japanese studies where enrollment was limited to winter months.[12,13] All studies collected nasopharyngeal specimens, either aspirates or swabs, from acutely ill participants. Fourteen studies utilized cell culture as their primary influenza diagnostic approach. Eight studies also used serologic methods to detect a significant rise in influenza antibody titers between acute and convalescent serum specimens. Across the 15 studies, respiratory viruses were identified in 22–46% of the study participants.

Influenza type A viruses were identified in 0–12% of study participants. Influenza type B virus infection was detected in 0–3% of pneumonia cases except for a single Japanese study that reported 12% of pneumonia cases associated with influenza type B.[12] Overall, 0–14% of all hospitalized pneumonia cases were attributable to influenza type A or B virus infections when cell culture, immunofluorescent antibody staining antigen (IFA) and/or antibody testing methods were used. Two studies of patients hospitalized with fever in Thailand found serologic evidence of influenza virus infection in 5% and 6% of patients, respectively.[14,15] In the only study to use reverse transcriptase polymerase chain reaction (RT-PCR) testing, 80 (11%) of 761 pneumonia patients were found to have evidence of influenza.[9] In that study from Thailand, RT-PCR identified 56 (70%) of 80 influenza-positive patients while 38 (48%) were identified by serology, and 16 (20%) were confirmed by cell culture.

Table 2. Influenza-associated pneumonia and fever requiring hospitalization

Author	Country	Year(s)	Study description	Age group	Sample size	Specimen type	Laboratory methods	Influenza A, *n* (%)	Influenza B, *n* (%)	Key findings
Simmerman *et al.*[9]	Thailand	2003–04	Prospective, population-based eight rural hospitals	All ages	761	NP swabs, serum	PCR virus isolation, HI serology	80 (11)	Not reported	Infants, elderly most affected 12,575 to 75,801 influenza positive pneumonia hospitalizations nationwide Est. 118,335–941,567 lost work days Est. US$3·8–20·7 mil in medical costs
Siritantikorn *et al.*[51]	Thailand	1998–01	Prospective, single rural hospital	<5 years	472	NP aspirates	IFA	6 (1)	Not reported	
Sunakorn *et al.*[52]	Thailand	1988–89	Prospective, single urban hospital	<5 years	226	NP secretions	IFA	0	1 (0·4)	
Ekalaksananan *et al.*[53]	Thailand	1992–94	Prospective, single urban hospital	<5 years	74	NP aspirates	IFA virus isolation	0	0	No influenza infections identified
Puthavathana *et al.*[54]	Thailand	1986–87	Prospective, single urban hospital	<5 years	600	NP aspirates	IIF virus isolation, HI serology	33 (5)	14 (2)	
Lauderdale *et al.*[55]	Taiwan	2001–02	Prospective, 13 hospitals	>16 years	448	Serum	HI serology	11 (2)	Not reported	
Tsai *et al.*[56]	Taiwan	1997–99	Prospective, eight hospitals	<13 years	2077	Throat swabs or NP aspirates	Virus isolation	50 (2)	24 (1)	
Chan *et al.*[57]	Malaysia	1982–97	Retrospective review at university hospital	<25 months	5691	NP secretions	Virus isolation	59 (1)	18 (0·3)	'75% of influenza viruses isolated in infants <12 months'
Yun *et al.*[58]	Korea	1990–94	Prospective, single urban hospital	<15 years, 93% <7 years	712	Nasal aspirates	Virus isolation, IFA	31 (4)	11(2)	'Influenza may be an important cause of pneumonia'
Sonoda *et al.*[59]	Japan	1986–92	Prospective, single urban hospital	<15 years, 46% <2 years	1512	NP secretions	Virus isolation, HI serology	62 (4·1)	26 (1·7)	Peak season Nov–Feb
Numazaki *et al.*[60]	Japan	2000–01	Prospective, population based, multicenter	<15 years	921	NP swabs, serum	Virus isolation, serology	110 (12)	Not reported	69% of influenza occurred in <5 years
Sugaya *et al.*[12]	Japan	1989–90, winter months	Prospective, single urban hospital	<16 years	244	Throat swabs, serum	Virus isolation, HI serology	24 (10)	29 (12)	Mean hospital stay 8·2 days 41 (77%) had no underlying disease
Sugaya *et al.*[13]	Japan	1991–98, winter months	Prospective, single urban hospital	<16 years	1959, Mean 280/year	NP aspirates, serum	Virus isolation, HI serology	203 (10)	71 (4)	Most patients were infants, children <6 Impact of seasonal influenza epidemics greater than generally thought
Kim *et al.*[61]	Korea	1995–98	Prospective, pediatric wards of five hospitals	<11 years	1389	NP aspirates	Virus isolation, IFA	66 (5)	18 (1)	

Table 2. Continued

Author	Country	Year(s)	Study description	Age group	Sample size	Specimen type	Laboratory methods	Influenza A, *n* (%)	Influenza B, *n* (%)	Key findings
Ahn *et al.*[62]	Korea	1996–98	Prospective, single urban hospital	<15 years	1070	NP aspirates	Virus isolation, IFA	50 (5)	33 (3)	Peak Feb–March
Suttinont *et al.*[14]	Thailand	2001–02	Prospective, FUO study, five rural hospitals	Adults	845	Serum	Serology, not defined	39 (4·6); type not specified		
Leelarasamee *et al.*[15]	Thailand	1991–93	Prospective, FUO study, 10 community hospitals	>2 years	1137	Serum	HI serology	68 (6); type not specified		
Chiu *et al.*[42]	Hong Kong	1997–98	Retrospective febrile seizures, large urban hospital	6 months–5 years	416	NP aspirate	IFA, virus isolation	Not reported	Not reported	'Clear increase of febrile seizures associated with influenza A season'

FUO, fever of unknown origin.

Contribution of influenza to outpatient illness

Thirteen articles focused on influenza virus infection among outpatients. Overall, these studies included more than 55 000 patients with ILI from five countries in hospital outpatient departments and community health centers during 1972–2004. The studies used a wide variety of case definitions to identify patients with ILI. Six studies enrolled only pediatric patients while seven studies also included some adult patients. Cell culture was used for confirmation of influenza virus infection in all studies. Three studies published since 2004 utilized rapid influenza antigen tests and 2 of these also used RT-PCR methods.[9,16,17] Eleven to 26% of outpatients with ILI had laboratory-confirmed influenza on an annualized basis across all studies. Studies conducted in northern latitudes (Taiwan, Japan) reported increases in influenza activity during the winter months while most studies from tropical and subtropical countries reported year-round influenza activity with increases during the rainy months (May–September). Outbreaks of influenza type B viruses were reported to occur during the cooler months (January–March).[18]

Influenza-associated hospitalization and mortality

Studies that addressed influenza-associated hospitalizations or mortality were conducted in Hong Kong or Singapore. These studies used indirect statistical modeling methods to analyze hospital discharge, cause of death, and virological surveillance data to estimate influenza disease burden. In Hong Kong, increased influenza activity was found to be significantly correlated with pneumonia and cardiac deaths as well as excess hospital admissions in the elderly and in young children.[19–22] In Singapore, 3·8% of all deaths were attributable to influenza with the proportion of influenza-associated deaths 11·3 times higher in persons over 65 years of age than in the general population.[23] Incidence rates for influenza-associated hospitalization and mortality from all studies were similar to those reported in the United States using similar methods.[1,24]

Discussion

Outside of a few high income countries in the region, the English-language literature describing the burden of human influenza in East and South-East Asia is limited. Most articles published before 1997 focused on virological strain surveillance or outbreaks while the majority of more recent articles address avian influenza A (H5N1) and pandemic preparedness. Only nine of 18 countries had articles that met the eligibility criteria, and only five articles provided estimates of influenza incidence on a population basis. In most of the region, published data on influenza-associated outpatient visits, hospital admissions, and mortality, as well

Table 3. Influenza-associated outpatient illness

Author	Country	Year(s)	Study type	Age group	Sample size	Specimen type	Laboratory methods	Influenza A, *n* (%)	Influenza B, *n* (%)	Seasonality	Key findings
Puthavathana *et al.*[54]	Thailand	1986–87	Prospective, single urban hospital OPD	<5 years	138	NP aspirates	IIF, virus isolation, HI serology	15 (10·9)	6 (4·3)		
Puthavathana *et al.*[63]	Thailand	1979–83	Influenza surveillance, single urban hospital OPD	<13 years	2036	Throat swabs	Virus isolation	54 (2·9)	4 (0·002)		'Influenza is uncommon in young children'
Simmerman *et al.*[64]	Thailand	1993–02	Review of routine national surveillance	All	4305	Throat swabs	Virus isolation	Not reported	Not reported	Peak May – August	34% of 4305 surveillance specimens influenza positive 64–91/100 000/year passively reported
Simmerman *et al.*[9]	Thailand	2003–04	Prospective, population-based five rural hospital OPDs	All ages	1092	NP swabs	Rapid test, PCR, Virus isolation	252 (23); type not specified		Strong peak June–September	Estimated 924 478 OPD visits Estimated 3·1 million days of lost work
Shih *et al.*[65]	Taiwan	2000–04	National surveillance, 11 laboratories	All ages	32 775	Throat swabs NP aspirates	Virus isolation	1969 (6)	1275 (4)	'No clear seasonal pattern'	
Tsai *et al.*[56]	Taiwan	1997–99	Prospective, 11 OPD clinics	<13 years	4909	Throat swabs or NP aspirates	Virus isolation	334 (0·07)	157 (0·03)	Peaks in winter months	
Lin *et al.*[66]	Taiwan	1995–97	Prospective, single pediatric hospital OPD	<18 years	910	Throat swabs	Virus isolation	54 (0·06)	58 (0·06)		
Tseng *et al.*[67]	Taiwan	1979–95	Surveillance, 3 OPD clinics	All ages, 80% <12 years	5882	Throat swabs	Virus isolation	214 (0·04)	99(0·02)	'Isolated every month, peak in winter'	
Hasegawa *et al.*[17]	Myanmar	2003–04	Sentinel surveillance, one hospital OPD, two private clinics	All ages, 79% <10 years	616	Throat or nasal swabs	Rapid test, virus isolation	133 (21·6)	6 (1)		'71% of rapid test positive specimens grew virus'
Beckett *et al.*[16]	Indonesia	1999–03	Prospective sentinel surveillance	>4 years. 85% >14 years	1544	Throat and nasal swabs	Rapid tests, RT-PCR and virus isolation	172 (11); type not specified		'Isolated year round with rainy season peaks'	
Doraisingham *et al.*[18,68]	Singapore	1972–86	Sentinel surveillance, 91% outpatients from government clinics	All ages	20 specimens per week	Throat swabs	Virus isolation			'Annual outbreaks (April – June) against a background of almost year-long transmission'	Influenza type B outbreaks every 16–24 months Young children most affected
Ng *et al.*[11]	Singapore	1988–99	Estimates using survey, hospital, vital statistics and virological surveillance data	All ages	N/A	Throat swabs	Virus isolation	Average 15%; type not specified			Estimated 630 000 cases of influenza, 520 000 clinic visits, 315 000 days of illness absence annually

Table 4. Influenza-associated hospitalization and mortality

Author	Country	Year(s)	Study description	Age group	Sample Size	Specimen type	Laboratory Method	Key findings
Wong *et al.*[19]	Hong Kong	1996–00	Excess hospitalization. Poisson regression of weekly hospital bed counts and virological data	All	95% of all hospital bed days 3098–8333 specimens/year	Not specified	Virus isolation	10·5% average influenza positive by week 29·3/100,000 all ages excess P&I hospitalizations annually 'Influenza has a major impact on hospitalization due to cardiorespiratory diseases'
Wong *et al.*[69]	Hong Kong	1996–99	Excess deaths. Poisson regression of weekly deaths and virological data	All	Vital stats data 6–7000 specimens/year	Not specified	Virus isolation	>64 year age group contributed 70–90% of all deaths 3–16% of all deaths were influenza-associated 7·3 deaths/100 000/year from C&R disease among 40–65 years and 102·0 deaths per 100 000/year among >65 year 'Mortality rates similar to the US using same methodology'
Li *et al.*[20]	Hong Kong	1999–00	Excess deaths and hospitalizations using correlation and regression models, virological data	All	84% of all hospital admissions Vital stats data 15–17 000 specimens/year	Not specified	Virus isolation	Year-round with peaks in Jan–March; 613 annual excess deaths, 4051 excess hospitalizations for P&I, and 15 873 for respiratory and circulatory diseases 'Statistically significant correlations between influenza activity and P & I deaths' 'Significant mortality and morbidity due to influenza infection'
Yap *et al.*[21]	Hong Kong	1998–01	Excess hospital admissions. Retrospective regression analyses with virological data	>64 years	Hospital admission data 7000 specimens/year	NP aspirates	Virus isolation	Adjusted excess influenza-associated admissions were 58·5, 20·0, 29·2, and 13·4 per 10 000 populations >65 years in 1998, 1999, 2000, and 2001, respectively 'Influenza activity is associated with significant excess hospital admissions among elderly persons, comparable to data from western countries'
Chiu *et al.*[22]	Hong Kong	1997–99	Retrospective comparison of hospitalization rates different periods of influenza activity	<16 years	Hospital admission data. 6–7000 specimens/year	NP aspirates	Virus isolation	Adjusted excess influenza attributable hospitalization: 278·5 and 288·2 per 10 000 children <1 year in 1998 and 1999, respectively; 218·4 and 209·3 per 10 000 children 1–2 years 125·6 and 77·3 per 10 000 children 2–5 years 57·3 and 20·9 per 10 000 children 5–10 years 'Influenza is an important cause of hospitalization among children, with rates exceeding those reported for temperate regions'

Table 4. Continued

Author	Country	Year(s)	Study description	Age group	Sample Size	Specimen type	Laboratory Method	Key findings
Chow *et al.*[23]	Singapore	1996–03	Influenza-associated mortality. Regression model using vital statistics and virological data	All	57 060 specimens	Respiratory specimens Serum	Virus isolation, IFA, HI serology	Annual influenza-associated mortality from all causes, P & I, C & R of 14·8, 2·9, and 11·9/100 000/year, respectively 3829(7%) influenza + (range 3–10%) 3·8% of total annual deaths were influenza-associated 'Influenza A had significant and robust effects on monthly all-cause deaths'

as the direct and indirect economic costs related to influenza, are limited or not available. However, several studies from middle and high income countries (Thailand, Hong Kong, Singapore, Japan) reported that the estimated burden of human influenza is greater than previously appreciated and similar to that of the United States and European countries.[9,13,19,21,23,25]

Methodological issues

Influenza surveillance and research studies in the region have utilized widely varying case definitions and the ability to make comparisons is further limited by the substantial variability in data collection and diagnostic testing methods used.[26–28] To facilitate disease burden comparisons over time and across regions, researchers should use simple, precisely defined case definitions, employ representative sampling methods, carefully collect and manage clinical specimens, and employ sensitive PCR methods to detect influenza virus infection. The World Health Organization (WHO) has developed a definition for ILI that, if used, would facilitate year to year and country to country comparisons.[29] While the WHO case definition will not capture all influenza cases across all ages, collection of data from a wide range of patients (e.g., age, sex, underlying medical conditions, date of illness onset, symptoms) can help develop more specific case definitions for different age groups.

Sampling methodologies in the reviewed studies tended to be based upon incompletely described convenience samples. Approaches that provide a sample representative of a defined target population allow for estimation of population-based incidence rates, a key parameter to measure disease burden. The collection of denominator data is also important and will allow determination of the proportion of influenza infections among outpatients with ILI and the proportion of hospitalized pneumonia cases with influenza.

Reviewed studies used a variety of laboratory diagnostic methods. Older studies relied predominantly upon chick embryo or tissue cell viral culture. However, reliance on these methods likely under-detects influenza virus infections because the yield is highly dependent on obtaining samples as close to illness onset as possible, proper specimen collection and handling, and differences in the duration and titer of shed viruses between adults and children.[30] The use of multiple testing methods is recommended to identify a higher proportion of influenza virus infections.

Polymerase chain reaction methods are more rapid and sensitive than viral culture and technological improvements are lowering its cost.[31–33] Rapid influenza diagnostic tests are simple to use and produce quick results which can be particularly useful for socioeconomic analyses by reducing recall bias.[34] However, rapid tests have lower sensitivity than PCR or viral culture and should not be relied upon alone for estimating influenza disease burden.[35] Serologic diagnosis of acute influenza virus infection requires collection of paired sera, with the convalescent serum specimen obtained about 2 weeks after the acute sample. Determination of interpretable hemagglutinin inhibition antibody titers is dependent upon availability of antisera to circulating virus strains. Therefore, serologic testing is more applicable for research studies and is seldom used for routine surveillance.

The application of continuous quality control measures and regular external assessments of laboratory procedures is also essential.[36] Several studies reported difficulties in rigorously maintaining these laboratory practices, which probably contributed to the low proportions of influenza virus infections reported. Over time, these limitations may have led to a misperception that influenza was not a major cause of morbidity in these countries.

Future research strategies

There are many challenges to directly ascertaining the burden of influenza. A proportion of persons with influenza virus infection will be asymptomatic or have mild symptoms.[37–40] Many symptomatic individuals with influenza may not seek medical treatment despite missing work or school days.[41] Laboratory confirmation of influenza virus infection is often unavailable or not performed. Some patients with influenza will test negative for influenza if they are no longer shedding detectable levels of viruses while others might test falsely negative because of limitations of the test or improper specimen collection and handling. Some influenza patients will present with atypical symptoms and healthcare providers will not suspect influenza, including infants with sepsis-like syndrome, children with febrile seizures or otitis media, and elderly persons without fever.[42–44] Patients with serious complications from influenza may not be recognized, such as those with exacerbation of chronic diseases, secondary bacterial pneumonia or rare manifestations such as encephalopathy, rhabdomyolysis, and myocardial infarction.[45–47] Taken together, these factors suggest that even well-conducted research and surveillance systems are likely to underestimate the burden of influenza.

Indirect methods for estimating influenza disease burden have been developed to supplement studies using laboratory confirmed testing as an outcome. These include retrospective epidemiological modeling to estimate influenza-attributable morbidity and mortality based upon hospital discharge diagnoses, outpatient and emergency room records, vital statistics registry, and influenza surveillance data.[1,19,48,49] The most common examples are estimates of excess influenza-attributable hospitalizations and deaths based on pneumonia and influenza cases during periods when influenza viruses are circulating at levels significantly above baseline. These methods depend on the availability of hospitalization and cause of death data, as well as multi-year influenza virological surveillance data. Many low- and middle-income countries do not have such data, which limits indirect disease burden ascertainment in much of the region. Ideally, both direct and indirect measurements of influenza burden can complement each other and should be undertaken to provide a more complete estimate of the impact of influenza.

Limitations

We considered only articles published in peer-reviewed English language journals or those with an English language abstract that provided sufficient information to meet our eligibility criteria. We limited our search to the PubMed database. We did not include a potentially large number of influenza articles published only in Japanese, Chinese, and Korean journals. We also did not include data presented only at scientific meetings or published as conference abstracts. Nonetheless, we feel that our findings are informative and represent the most complete review to date of the influenza literature in this region. We were unable to present summary estimates of influenza incidence or aggregate data due to the variability of case definitions, methodologies, and data presented. Although we reviewed the literature from 18

Table 5. Influenza research gaps in East and South-East Asia

Surveillance to define seasonal trends in influenza activity
(a) Among urban populations
(b) Among rural populations
(c) Multiple years
(d) Year-round
(e) Among populations in different climatic zones
(f) Among all age groups
(g) Population-based
Influenza-attributable mortality
(a) To establish mortality rates, describe, and identify high-risk groups for death from complications of influenza among all age groups where the prevalence of chronic diseases or co-infections may differ from Western populations
(b) Population-based
Influenza-associated outpatient and hospitalization rates
(a) To establish morbidity rates, identify and describe high-risk groups for serious complications of influenza among all age groups where the prevalence of chronic diseases or co-infections may differ from Western populations (e.g., neurologic complications associated with influenza such as encephalopathy and encephalitis)
(b) Population-based
Economic studies
(a) Ascertain direct medical care costs
(i) Home treatment costs, over-the-counter medicines
(ii) Outpatient medical care visits (treatment, testing, provider, facility costs)
(iii) Inpatient medical care costs (treatment, testing, provider, facility costs)
(b) Estimate indirect and societal costs
(i) Lost work and school days
(ii) Reduced productivity due to illness, death

countries in East and South-East Asia, we did not include articles about influenza burden in South Asia. The burden of influenza in such large and densely populated countries as India, Pakistan, and Bangladesh merits further review.

Conclusion

The published literature on the burden of influenza in East and South-East Asia is limited but expanding. Early studies appear to have underestimated influenza disease burden because of limitations in study design and laboratory testing methods. Recent studies that have employed multiple laboratory assays and more rigorous protocols, as well as those using indirect methods of ascertainment, report a substantial burden of disease, similar to that in North America and Europe.[9,19,23] Our review revealed a number of areas where further research is needed. Major research gaps include the socioeconomic impact of influenza as well as influenza-attributable mortality (Table 5).

Recently, epidemiological and laboratory capacity in the region have been strengthened by unprecedented investments in training and infrastructure motivated by concerns of an impending pandemic. It is incumbent upon the influenza research community to capitalize on this window of opportunity to establish sustainable surveillance systems and design research studies to better describe the epidemiology and impact of human influenza. Recognition of the substantial health burden of human influenza and continued investment in influenza surveillance is essential to maintain and improve upon the capacity of the region to detect new strains of seasonal influenza, and to be prepared to detect the emergence of a new pandemic virus. With the exception of a few countries in the region (e.g., Japan, South Korea), very little influenza vaccine is used.[50] Well-designed population-based surveillance and research studies that yield representative data on the burden of influenza can be used to motivate and guide decision making on the expanded use of influenza vaccine.

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Conflict of interest

The authors deny any conflict of interest associated with the publication of this review.

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