Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis

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Summary

Background **The global burden of disease attributable to seasonal influenza virus in children is unknown. We aimed to estimate the global incidence of and mortality from lower respiratory infections associated with influenza in children younger than 5 years.**

Methods **We estimated the incidence of influenza episodes, influenza-associated acute lower respiratory infections (ALRI), and influenza-associated severe ALRI in children younger than 5 years, stratified by age, with data from a systematic review of studies published between Jan 1, 1995, and Oct 31, 2010, and 16 unpublished population-based studies. We applied these incidence estimates to global population estimates for 2008 to calculate estimates for that year. We estimated possible bounds for influenza-associated ALRI mortality by combining incidence estimates with case fatality ratios from hospital-based reports and identifying studies with population-based data for influenza seasonality and monthly ALRI mortality.**

Findings **We identified 43 suitable studies, with data for around 8 million children. We estimated that, in 2008, 90 million (95% CI 49–162 million) new cases of influenza (data from nine studies), 20 million (13–32 million) cases of influenza-associated ALRI (13% of all cases of paediatric ALRI; data from six studies), and 1 million (1–2 million) cases of influenza-associated severe ALRI (7% of cases of all severe paediatric ALRI; data from 39 studies) occurred worldwide in children younger than 5 years. We estimated there were 28 000–111 500 deaths in children younger than 5 years attributable to influenza-associated ALRI in 2008, with 99% of these deaths occurring in developing countries. Incidence and mortality varied substantially from year to year in any one setting.**

Interpretation **Influenza is a common pathogen identified in children with ALRI and results in a substantial burden on health services worldwide. Sufficient data to precisely estimate the role of influenza in childhood mortality from ALRI are not available.**

Funding **WHO; Bill & Melinda Gates Foundation.**

Introduction

Acute lower respiratory infections (ALRI) such as pneumonia and bronchiolitis are a leading cause of morbidity and mortality in young children.[1] Around 156 million new episodes of ALRI occur worldwide every year and about 1·56 million young children died as a result of such infections in 2008.[2,3] Respiratory viruses are commonly associated with ALRI episodes in young children.[4–10] We previously estimated that respiratory syncytial virus (RSV) is present in 22% of such episodes, making it the most prevalent pathogen in children with ALRI.[11] Influenza has long been regarded as an important disease in the elderly because of its high incidence and concomitant high rate of hospital admissions and mortality in individuals older than 65 years.[12] However, studies in the past decade suggested that the burden of disease due to hospital admissions for influenza-associated ALRI in young and very young children is also substantial.[13–16]

Previously, no estimates of the global burden of disease from seasonal influenza virus-associated ALRI in young children have been made. We identified only two systematic reviews of the incidence of influenza-associated pneumonia,[17,18] neither of which provided summary incidence rates. Recent estimates of global ALRI incidence and mortality associated with *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and RSV[11,19,20] do not fully explain the paediatric ALRI burden, and so the role of other pathogens needs to be explored. Influenza is associated with a large but unknown number of hospital admissions in young children globally and is vaccine preventable. Globally, there is an increasing capacity for laboratory-confirmed diagnosis of influenza infection which led to increased recognition (especially) of severe

Lancet 2011; 378: 1917–30

Published Online November 11, 2011 DOI:10.1016/S0140-6736(11)61051-9

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influenza-related illness in children and adults in developing countries during the influenza A H1N1 pandemic in 2009. Additionally, studies from developing countries have provided population-based estimates of burden of influenza in children that have added to the evidence of the health effects of the disease worldwide. Moreover, the influenza A H1N1 (2009) pandemic raised questions about the baseline incidence and mortality from seasonal influenza in young children so as to better assess the need for and structure of vaccination programmes.

Many data for incidence and mortality from influenza-associated ALRI in developing countries remain unpublished. Therefore, we formed an international Influenza Study Group to supplement our systematic literature review with unpublished data. We aimed to estimate the burden of disease due to influenza-associated ALRI in children younger than 5 years for 2008 globally and for six WHO regions.

Methods

Search strategy and selection criteria

We undertook a systematic literature review with various search terms (webappendix pp 3–4) and hand searched online journals and scanned reference lists of identified citations. We restricted the search to Medline (Ovid), Embase, CINAHL, Global Health, Web of Science, WHOLIS, LILACS, IndMed, grey literature (SIGLE), and Chinese language databases and to studies published between Jan 1, 1995, and Oct 31, 2010. Panel 1 shows study eligibility criteria. No language or publication restrictions were applied. Two authors (HN and VE) independently did the literature search and extracted data. Any disagreements were resolved after discussion. The Influenza Study Group agreed on a common approach to data analysis and formulated common case definitions. We invited participation of other researchers and contacted authors of published studies who had done similar population-based studies of paediatric influenza (webappendix pp 6–7).

Definitions

Most investigators used modified versions of the case definitions for clinical pneumonia, severe pneumonia, and influenza surveillance that were established by WHO and the US Centers for Disease Control and Prevention (CDC; webappendix pp 8–29).[21,22] We chose to use the terms ALRI and severe ALRI because a proportion of children with lower respiratory complications of influenza might not only present with pneumonia but also with bronchiolitis. We defined influenza-associated ALRI as cough or difficulty in breathing (with fast breathing for age) in a child with influenza virus identified with valid diagnostic tests. We defined influenza-associated severe ALRI as identification of influenza virus with valid diagnostic tests in a child with either cough or difficulty in breathing with indrawing of the lower chest wall (with or without fast breathing for age) or hospitalisation for a respiratory ailment. We also included a category of influenza episodes that included the entire spectrum of respiratory burden from influenza-positive influenza-like illness (webappendix p 56), influenza-associated ALRI, and influenza-associated severe ALRI.

We used a modification of the definition for influenza season that was provided by Izurieta and colleagues.[23] The influenza season included any month in which at least 10 samples were analysed and the virus was detected in more than 5% of specimens. We designated countries as developed or developing on the basis of the Global Burden of Disease Study regions[24] as previously described[11] and child population estimates for every region for 2008 as in *The State of the World's Children Special Edition*.[25]

Data imputation

For studies that did not report disease incidence in children aged 0–4 years, we used imputation to calculate missing data by use of the median incidence rate ratio (for details see webappendix p 5).[11,26] If the duration of the study was not in exact multiples of 1 year, we calculated and reported a yearly incidence. We also decided that, if only a proportion of eligible cases were sampled (with a systematic method) and data for all eligible cases were available, the incidence could be adjusted by scaling for the proportion sampled. Figure 1 summarises our overall approach and associated rationale for decisions adopted.

***Panel 1:* Study eligibility criteria**

Inclusion criteria

- Studies with data for laboratory-confirmed influenza (eg, mild influenza or influenza like illnesses, acute respiratory infections, acute lower respiratory infections, or severe acute lower respiratory infections)
- Studies of children younger than 5 years, or data reported separately for this age group
- Studies published between Jan 1, 1995, and Oct 31, 2010
- Study should have been carried out for at least 1 year (apart from in temperate regions where influenza seasonality is more clearly defined and for studies reporting case fatality ratio); this criterion is important since influenza is a seasonal disease
- Studies reporting influenza incidence or mortality for at least the first year of life

Exclusion criteria

- Studies in which influenza was studied as co-infection rather than primary outcome
- Case definition not clearly defined or not applied consistently
- Case ascertainment done only during the epidemic period
- Incidence and mortality estimated with modelling techniques

Statistical analysis

We did a meta-analysis of data for disease incidence and case fatality and report pooled estimates and 95% CIs. We used the random-effects model (DerSimonian-Laird method) if there was significant heterogeneity in the data ($p<0·05$).[27] Investigators who use a passive case ascertainment usually report substantially lower incidence of influenza-associated ALRI than do those who use an active approach, which is expected in developing countries in which access to health services is restricted. Therefore, we based our incidence estimates of influenza episodes and influenza-associated ALRI for developing countries on a selection of data from developing country studies that did active case ascertainment only (webappendix pp 35–46), consistent with the approach adopted in our previous global estimate of ALRI associated with RSV.[11] We estimated incidence for developed and developing countries and then applied these incidence estimates to the population of children younger than 5 years in 2008 to yield the number of new episodes of all three categories in 2008.[25] We also calculated the incidence of influenza-associated severe ALRI for WHO regions on the basis of incidence meta-estimates for the individual regions.

Because data were scarce, we did not attempt to model a point estimate for influenza-associated ALRI mortality. Instead, we used two approaches to assess the probable upper and lower bound of mortality that could be plausibly attributed to influenza. First, we applied the meta-estimate of influenza-associated case fatality ratio from hospital-based reports to incidence data for influenza-associated severe ALRI reporting to hospitals or clinics (calculated separately for developing and developed countries). Because access to hospital care in most developing countries is poor, we defined this result as the lower bound for mortality.

Our second approach was much the same as the method previously used[11] to estimate mortality from ALRI associated with RSV in children. We assumed that all excess mortality from ALRI in children younger than 5 years during the influenza season was caused by seasonal influenza virus, and that non-influenza mortality is equal within and between periods of influenza epidemics. Because this approach is an extreme case scenario, we assumed that this method yielded an upper bound for influenza-associated ALRI mortality. We defined the duration in months of the influenza season for every

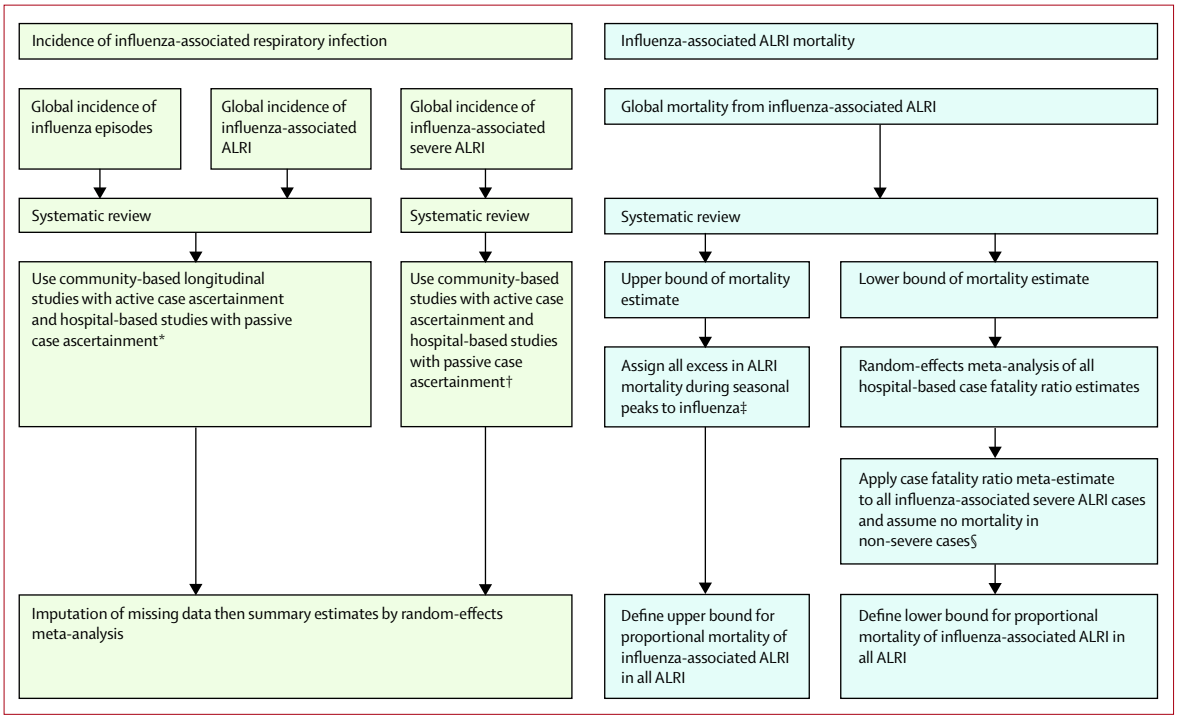

Figure 1: **Approaches for estimation of global influenza incidence and mortality in children aged 0–4 years**

*Approach justified by large difference in reported incidence between studies using active and passive case ascertainment in the case of developing countries; studies with passive case ascertainment reported much lower estimates than did those with active ascertainment. †Approach justified by the decision that hospital-based data would be most useful for population-based projections, since all severe episodes are likely to need hospital treatment; also, we noted no difference in reported incidence of influenza-associated severe ALRI between studies with active and passive case ascertainment. ‡Approach based on the assumptions that baseline proportional mortality of influenza-associated ALRI in all ALRI would be similar to proportional incidence of influenza-associated severe ALRI in all severe ALRI, and that there is no overall effect from all other respiratory pathogens; then if all excess ALRI mortality during influenza seasonal peaks is assigned to influenza as the only cause in a setting (with many seasonal peaks) and this mortality is added to baseline mortality estimates, this approach is likely to overestimate the contribution of influenza to mortality from all ALRI. §Approach deemed to yield a lower bound for influenza-associated ALRI mortality because an unknown proportion of influenza-associated ALRI mortality occurs outside the hospital. ALRI=acute lower respiratory infections.

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See **Online** for webappendix

	Case ascertainment	Study population (n)	Specimen and diagnostic tests	Incidence of influenza episodes (per 1000 children per year)*			Incidence of influenza-associated ALRI (per 1000 children per year)*			Incidence of influenza-associated severe ALRI (per 1000 children per year)*		
				Aged <1 year	Aged <2 years	Aged <5 years	Aged <1 year	Aged <2 years	Aged <5 years	Aged <1 year	Aged <2 years	Aged <5 years
Western Europe												
Kiel, Germany; urban; 1996–2000[42]	Passive, hospital (inpatient)	Census-derived estimate	NPA; RT-PCR	NA	NA	NA	NA	NA	NA	2	(1)	1
Madrid, Spain; urban; 1997–2003[43]	Passive, hospital (inpatient)	Census-derived estimate (n=149 602)	Nasal or throat aspirate; viral culture and subsequent fluorescent staining with monoclonal antibodies	NA	NA	NA	NA	NA	NA	(1)	(1)	(1)
Multicentre, Germany; mixed urban-rural; 1999–2001[44]†	Passive, hospital (inpatient)	Census-derived estimate	NPA; PCR	NA	NA	NA	11	12	(11)	2	2	(1)
Berne, Switzerland; urban; 1999–2004[45]	Active, community based	Defined population base (n=187)	Nasal swab; RT-PCR	21	(24)	(22)	NA	NA	NA	NA	NA	NA
Turku, Finland; urban; 2000–02[30]†	Passive, clinic (outpatient)	Defined population base (n=1270)	Nasal swab; viral culture and subsequent immunoperoxidase staining with monoclonal antibodies	188	186	186	NA	NA	NA	NA	NA	NA
Leicester, UK; mixed urban-rural; 2001–02[31]	Passive, hospital (inpatient)	NHS database (n=56 395)	Nasal and throat swabs; PCR	NA	NA	NA	NA	NA	NA	2	2	2
Gipuzoka, Spain; mixed urban-rural; 2001–04[32]	Passive, hospital (inpatient)	Census-derived estimate	NPA; viral culture and RT-PCR	NA	NA	NA	NA	NA	NA	3	2	1
East London, UK; urban; 2002–04[46]	Passive, hospital (inpatient)	Census-derived estimate (n=15 177)	NPA; IF and PCR	(18)	19	16	NA	NA	NA	(3)	3	2
East sub-Saharan Africa												
Manhiça district, Mozambique; rural; 2006–07 (Roca and colleagues)	Passive, hospital (inpatient)	Defined population base (n=13 291 cyo)	NPA; multiplex RT-PCR	NA	NA	NA	NA	NA	NA	4	3	2
Kilifi district, Kenya; rural; 2007 (Berkley and colleagues)	Passive, hospital (inpatient)	Defined population base (n=44 544)	Nasal wash; multiplex real-time PCR	NA	NA	NA	NA	NA	NA	3	2	1
Bondo district, Kenya; rural; 2007–09 (Ope and colleagues)	Passive, hospital (inpatient)	Census-derived estimate (n=55 117)	Nasopharyngeal and/or oropharyngeal wash, real-time RT-PCR	NA	NA	NA	NA	NA	NA	1	2	1
Kibera, Nairobi, Kenya; urban; 2008 (Katz and colleagues)	Passive, hospital (outpatient)	Census-derived estimate (n=3434 cyo)	Nasopharyngeal and oropharyngeal swabs; real-time RT-PCR	NA	NA	NA	NA	NA	NA	5	6	9
Lwak, Kisumu, Kenya; rural; 2008 (Katz and colleagues)‡	Passive, clinic (outpatient)	Census-derived estimate (n=3825 pyo)	Nasopharyngeal and oropharyngeal swabs; real-time RT-PCR	NA	NA	NA	NA	NA	NA	1	1	1
West sub-Saharan Africa												
The Greater Banjul area and Upper River Region, The Gambia; periurban and rural; 2007–08 (Howie and colleagues)§	Passive, hospital (inpatient and outpatient)	Defined population base (n=24 378)	NPA; mass-tag PCR	NA	NA	NA	14	6	3	0	1	0
Southern sub-Saharan Africa												
Soweto, South Africa; urban; 1998–2004 (Madhi and colleagues)¶	Passive, hospital (inpatient)	Defined population base (n=39 876)	NPA; DFA	NA	NA	NA	NA	NA	NA	2	2	1
South Asia												
Mirzapur, Bangladesh; rural; 1993–1996[47]	Active, community based	Defined population base (n=252)	NPA; ELISA	NA	NA	NA	NA	NA	NA	(2)	2	(1)
Ballabgarh, India; rural; 2001–05 (Broor and colleagues)	Active, community based	Defined population base (n=281)	Nasopharyngeal wash; DFA	180	178	(184)	33	44	(34)	NA	NA	NA
Kamalapur, Bangladesh; urban; 2004–07[41]	Active, community based	Defined population base (n=5000)	Nasopharyngeal wash; viral culture	132	117	99	11	31	27	1	1	1

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	Case ascertainment	Study population (n)	Specimen and diagnostic tests	Incidence of influenza episodes (per 1000 children per year)*			Incidence of influenza-associated ALRI (per 1000 children per year)*			Incidence of influenza-associated severe ALRI (per 1000 children per year)*		
				Aged <1 year	Aged <2 years	Aged <5 years	Aged <1 year	Aged <2 years	Aged <5 years	Aged <1 year	Aged <2 years	Aged <5 years
(Continued from previous page)												
Kamalapur, Bangladesh; urban; 2008 (Brooks and colleagues)‡	Active, community based	Defined population base (n=5710)	Nasopharyngeal wash; RT-PCR and tissue culture	75	188	204	35	61	46	2	2	1
Southeast Asia												
Bohol, Philippines; mixed urban-rural; 2000–04 (Lucero and colleagues)‡	Passive, hospital (inpatient and outpatient)	Defined population base (n=20 516 pyo)	NPA; viral culture and PCR	NA	NA	NA	5	4	(5)	2	2	(1)
Sa Kaeo and Nakhon Phanom, Thailand; rural; 2005–08 (Simmerman and colleagues)‡	Passive, hospital (inpatient)	Census-derived estimate (n=83 200)	Nasopharyngeal swabs; RT-PCR and viral culture	NA	NA	NA	NA	NA	NA	6	7	5
Nha Trang, Vietnam; urban; 2007–08[33]	Passive, hospital based (inpatient)	Census-derived estimate (n=13 952)	NPA; PCR	NA	NA	NA	NA	NA	NA	17	18	9
East Asia												
Hong Kong, China; urban; 1997–99[34]‖	Passive, hospital (inpatient)	Census-derived estimate (n=324 538)	NPA; IF followed by viral culture and serology	NA	NA	NA	NA	NA	NA	5	5	3
Hong Kong, China; urban; 2003–06[35]	Passive, hospital (inpatient)	Census-derived estimate	NPA; DFA and viral culture	NA	NA	NA	NA	NA	NA	7	7	7
Suzhou district, China; mixed urban-rural; 2007–08[36]**	Passive, hospital (inpatient)	Census-derived estimate (n=481 470)	NPA; DFA	NA	NA	NA	NA	NA	NA	1	0	0
High-income Asia-Pacific												
Soma, Japan; urban; 2002–08 (Sato and colleagues)	Passive, hospital (inpatient and outpatient)	Defined population base (n=5692)	Nasal swab; immunochromatography	39	45	45	NA	NA	NA	6	6	5
Australasia												
South Australia, Australia; mixed urban-rural; 1996–2006[48]**	Passive, hospital (inpatient)	Census-derived estimate	Details of specimen not available; viral culture, PCR	NA	NA	NA	NA	NA	NA	2	(1)	1
High-income North America												
Nashville, TN, USA; urban; 1974–99[15]	Passive, clinic (outpatient) and hospital (inpatient)	Defined population base (n=3041 cyo)	Nasal wash; viral culture	93	102	95	11	11	8	3	3	2
Boston, MA, USA; urban; 1993–2004[49]	Passive, hospital (ED)	Census-derived estimate (n=40 640)	NPA; DFA and viral cultures	NA	NA	NA	(15)	21	(15)	NA	NA	NA
Milwaukee, WI, USA; mixed urban-rural; 1996–98[50]	Passive hospital (inpatient)	Census-derived estimate	Nasopharyngeal swabs, bronchoalveolar lavage, throat swabs, endotracheal aspirates; MPCR, tissue culture, EIA	NA	NA	NA	NA	NA	NA	(3)	(3)	1
Monroe County, (NY) and Davidson County (TN), USA; urban; 2000–01[37]	Passive, hospital (inpatient)	Defined population base	Nasal swab and throat swab; viral culture and RT-PCR	NA	NA	NA	NA	NA	NA	2	1	1
Nashville, Rochester (NY) and Cincinnati (OH) USA; urban; 2000–04[16]	Passive, clinic (outpatient); hospital (ED and inpatient)	Defined population base	Nasal swab and throat swab; viral culture and RT-PCR	(71)	(73)	73	NA	NA	NA	(2)	(2)	1
Philadelphia, PA, USA; urban; 2000–04[51]**	Passive, hospital (inpatient)	Census-derived estimate (n=87 216)	Nasal aspirate; solid-phase immunoassay, DFA and viral culture	NA	NA	NA	NA	NA	NA	(4)	4	2
Colorado, USA; mixed urban-rural; 2000–08 (Simões and colleagues)**	Passive, hospital (inpatient)	Census-derived estimate (n=334 810)	Nasal wash; viral culture, ELISA, RT-PCR	NA	NA	NA	NA	NA	NA	3	3	1

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	Case ascertainment	Study population (n)	Specimen and diagnostic tests	Incidence of influenza episodes (per 1000 children per year)*			Incidence of influenza-associated ALRI (per 1000 children per year)*			Incidence of influenza-associated severe ALRI (per 1000 children per year)*		
				Aged <1 year	Aged <2 years	Aged <5 years	Aged <1 year	Aged <2 years	Aged <5 years	Aged <1 year	Aged <2 years	Aged <5 years
(Continued from previous page)												
Salt Lake County, UT, USA; mixed urban-rural; 2001–04[38]**	Passive, hospital (inpatient)	Census-derived estimate (n=71 784)	NPA; DFA	NA	NA	NA	NA	NA	NA	2	2	1
Davidson County, TN, USA; mixed urban-rural; 2003–04[52]	Passive, hospital (inpatient)	Census-derived estimate (n=37 813)	Nasal and throat swabs; viral culture, RT-PCR, rapid tests, IFA, serology	NA	NA	NA	NA	NA	NA	(5)	5	2
Multistate, USA; mixed urban-rural; 2003–04[39]**†	Passive, hospital (inpatient)	Census-derived estimate (n=1 164 869)	Viral culture, DFA, IFA, rapid antigen test, RT-PCR	NA	NA	NA	NA	NA	NA	2	2	1
Navajo and WMA reservations, USA; rural; 2003–05 (Bhat and colleagues)‡	Passive, hospital (inpatient)	Defined population base (n= 857)	NPA; viral culture and serology	NA	NA	NA	NA	NA	NA	(3)	(3)	(2)
Davidson County (TN), Monroe County (NY) and Hamilton County (OH), USA; mixed urban-rural; 2004–05[53]	Passive hospital (inpatient)	Census-derived estimate (n=141 338)	Nasal and throat swabs; viral culture, RT-PCR, rapid tests, IFA, serology	NA	NA	NA	NA	NA	NA	(4)	3	2
Multistate, USA; mixed urban-rural; 2004–08[40]†	Passive, hospital (inpatient)	Census-derived estimate (n=5 633 069)	Nasopharyngeal and oropharyngeal swabs; viral culture, DFA, IFA, rapid antigen test, RT-PCR	NA	NA	NA	NA	NA	NA	1	1	0
Central Latin America												
Santa Rosa, Guatemala; mixed rural and small towns; 2008 (Lindblade and colleagues)	Passive, hospital and clinics (inpatient and outpatient)	Census-derived estimate (n=34 465)	Nasopharyngeal and oropharyngeal swabs; real-time RT-PCR	(91)	(93)	93	NA	NA	NA	(1)	(1)	1
Tropical Latin America												
Rio de Janeiro, Brazil; urban; 1987–89[54]	Passive, hospital (inpatient)	Defined population base (n=262)	NPA; IFA, viral culture	NA	NA	NA	NA	NA	NA	(5)	(5)	3
Managua, Nicaragua; urban; 2007–08 (Gordon and colleagues)**	Passive, hospital and clinics (outpatient)	Defined population base (n=1024)	Nasal and throat swabs; RT-PCR	(203)	(205)	(205)	(18)	(17)	(13)	(4)	(4)	(3)

For more details of the unpublished studies see webappendix pp 6–7. ALRI=acute lower respiratory infection. NPA=nasopharyngeal aspirate. NA=not available. IF=immunofluorescence assay. cyo=child-years observed. pyo=person-years observed. DFA=direct immunofluorescence. MPCR=multiplex PCR. EIA=enzyme immunoassay. IFA=indirect immunofluorescence assay. ED=emergency department admission. WMA=White Mountain Apache. *Data in parentheses are computed incidence estimates from data imputation. †Detailed age-specific incidence estimates obtained directly from authors. ‡Some included patients were hospitalised. §Included children aged 2 months to 4 years. ¶Included children aged 6 weeks to 4 years. ||Incidence estimated with hospital discharge records and laboratory data. **Included children aged 2–4 years.

Table 1: **Incidence estimates of influenza episodes, influenza-associated-ALRI, and influenza-associated severe ALRI in children younger than 5 years from published and unpublished studies by Global Burden of Diseases, Injuries and Risk Factors regions**

calendar year of the study (MonFLU). For every year, we calculated the average number of total ALRI deaths in the community that occurred per month during (AvgFLU) and outside (AvgOTHER) the influenza season, and the total number of deaths (TOTAL) during the year. The proportion of yearly deaths due to influenza was then calculated as:

$$\frac{(\text{AvgFLU} - \text{AvgOTHER}) \times \text{MonFLU}}{\text{TOTAL}}$$

Population-based data to define influenza season and monthly death records (with reported causes of death based on verbal autopsy data) from the same populations for 3 years were available from Ballabgarh, Haryana in India and Nairobi in Kenya.[28,29] However, the Kenyan data were not suitable for our analytical approach because influenza virus was circulating throughout 2003–05, making an influenza season impossible to define (webappendix p 53). Application of the second approach to the estimated mortality of children younger than 5 years from ALRI in India in 2008[3] provided an estimate of all ALRI deaths attributable to influenza if community-based case ascertainment was used. We then applied the ratio between influenza-associated ALRI deaths (determined with this approach) and influenza-associated ALRI deaths in hospitalised cases in India (determined with the first approach) to the lower bound of influenza-associated ALRI mortality in developing countries to estimate an upper bound of

global ALRI mortality attributable to influenza in children younger than 5 years.

We did all data analyses with Stata version 11.1.

Role of the funding source

The funding sources supported a meeting of the Influenza Study Group in Edinburgh, UK (Feb 3–4, 2010). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. HN had full access to all the data in the study and HN and HC had final responsibility for the decision to submit for publication.

Results

We identified 43 studies[15,16,30–54] with suitable data (table 1, figure 2): 18 were population-based studies reporting incidence of influenza-associated severe or non-severe ALRI in populations under surveillance; 10 were studies estimating incidence on the basis of hospital-discharge records or laboratory reports and a census-based denominator of children at risk; and 15 were population-based studies with unpublished data, reporting a clear denominator of children at risk (figure 3). Only 24 studies (13 published[15,30–41] and 11 unpublished; webappendix p 5) reported disease incidence for children aged 0–4 years and data were imputed for 19 studies. Most studies were passive hospital-based (inpatient), but five used active community-based case ascertainment and ten used a passive hospital or clinic-based (outpatient) approach.

Most studies reported the highest incidence of influenza episodes, influenza-associated ALRI, and influenza-associated severe ALRI in the first year of life (table 1). Data from studies included in the meta-analyses were heterogeneous ($p<0·0001$).

Three studies from developing countries estimating incidence of influenza-associated ALRI used active community-based case ascertainment[41] in which children with ALRI or severe ALRI identified by field workers during weekly home visits were referred to an on-site clinic where the child was examined by a doctor.[41,55] Incidence of influenza episodes and influenza-associated ALRI was highest in children after the first year of life. We estimated that about 90 million (95% CI 49–162 million) new cases of influenza and 20 million (13–32 million) episodes of influenza-associated ALRI (both severe and non-severe) occurred worldwide in children aged 0–4 years in 2008 (table 2).

We based the estimate of influenza-associated severe ALRI incidence on studies with either active or passive case-ascertainment as the incidence estimates for influenza-associated severe ALRI were much the same (table 2, webappendix pp 47–52). Thus, we estimated that 1 million (95% CI 1–2 million) new episodes of influenza-associated severe disease occurred worldwide in children younger than 5 years in 2008 (table 2). The incidence of influenza-associated severe ALRI varied widely from year to year, dependent on the (sub)type of circulating influenza virus (webappendix pp 31–32). Table 3 shows the estimated incidence of influenza-associated severe ALRI and the number of new episodes of severe disease in 2008 by WHO region (excluding the eastern Mediterranean region, from which data were not available).

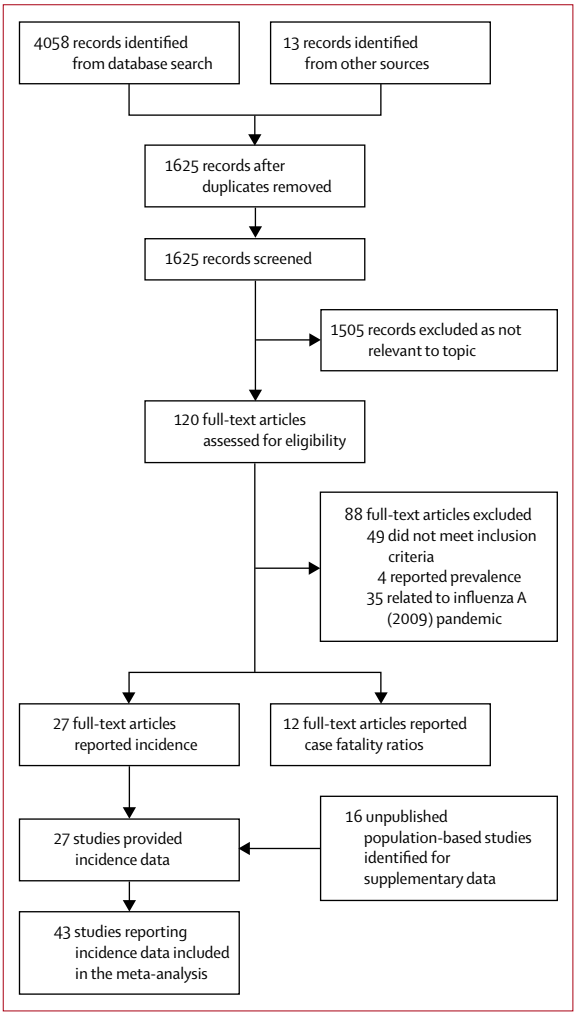

Figure 2: **Flow diagram for selection of studies**

We identified 12 published and eight unpublished studies providing data for case fatality ratios for deaths in children who were admitted to hospital with influenza-associated severe ALRI (table 4).[31,32,34,38,40,48,51,56–60] We estimated the case fatality ratio meta-estimate from these studies and found that the meta-estimate for developing countries was roughly more than 17 times those for developed countries.

Approach 1 was based on the estimated number of new cases of influenza-associated severe ALRI from hospital-based or clinic-based studies in the year 2008 (table 2) and the case fatality ratios from children admitted with severe disease reported in hospital-based studies calculated separately for developing and developed countries

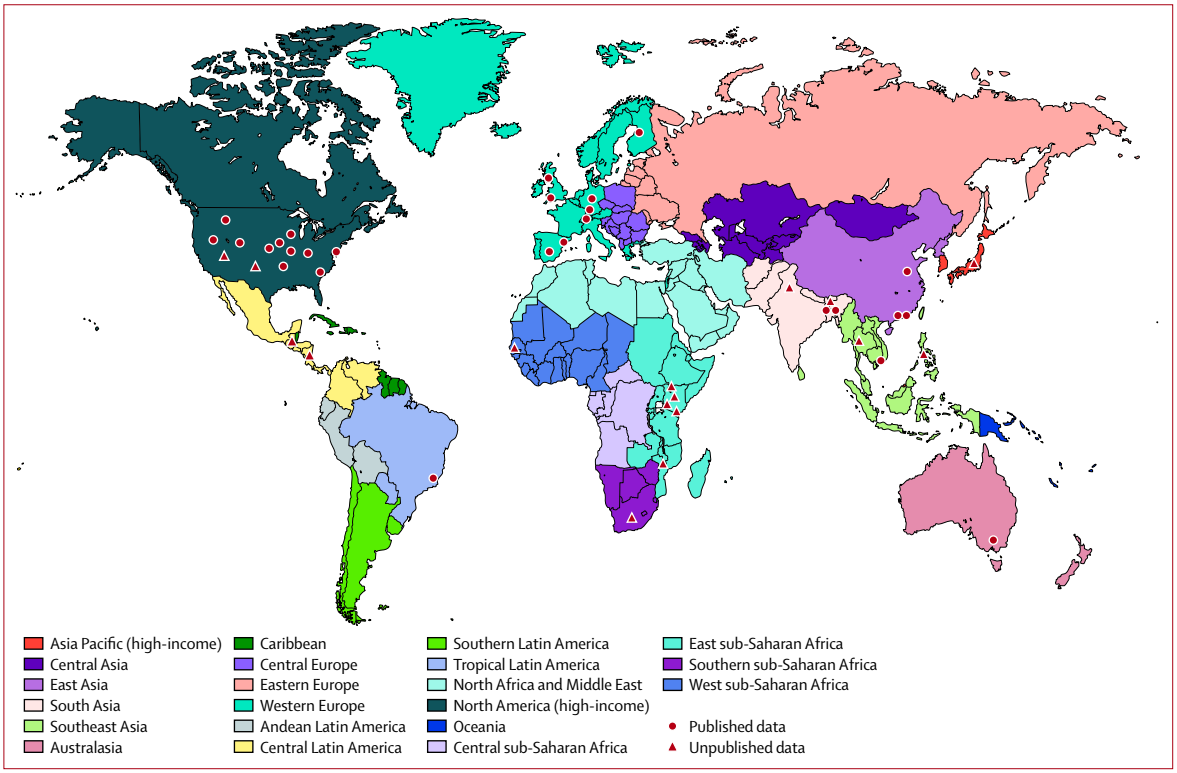

Figure 3: **Location of the 43 studies by Global Burden of Diseases, Injuries and Risk Factors region**

(table 4). With the first approach, we estimated that 27 800 (95% CI 7400–48 000) children younger than 5 years died because of influenza-associated severe ALRI in 2008 (panel 2). We did not have sufficient data to calculate case fatality ratio estimates in younger age categories. Because this estimate includes only children admitted to hospital we judged it to represent a plausible lower bound of influenza-associated severe ALRI mortality.

Approach 2 used cause of death data in children not admitted to hospital, assigned by verbal autopsy, and concurrent influenza virus isolations in the same population. Such data were available only from Ballabgarh in India for 2006–08.[40] Influenza isolation data from a sample of the same population accessing outpatient services for influenza-like illnesses were available from the referral hospital at Ballabgarh (figure 4).

We estimated that the number of deaths calculated with approach 2 was about four times higher than the number estimated with approach 1 (table 5, panel 2). Available data suggest that RSV circulated entirely outside the influenza season with no overlap. Furthermore, the site has low malaria activity.[61] If we assume that these data are broadly representative of India, then 6·5% of all paediatric ALRI deaths in India were associated with influenza in 2006–08. If extrapolated to other developing countries, this approach yields a crude estimate (for developing countries) of 111 500 (range 21 000–245 000) deaths attributable to influenza-associated ALRI in young children in 2008 (panel 2). However, this method probably overestimates deaths because it assumes that all excess ALRI mortality during the influenza season is because of influenza. This assumption is probably untrue because of the shared seasonality of other respiratory pathogens and the likelihood that influenza deaths occur outside the defined influenza season in tropical and subtropical regions.[35,59]

Our rough data-derived estimate of the plausible lower and upper bounds for influenza-associated ALRI mortality in young children are consistent with influenza being associated with 2–7% of deaths from ALRI in children. Data from India (table 5 and figure 4) and Kenya (webappendix p 53), show substantial yearly variation in magnitude of influenza epidemic activity and associated ALRI deaths, suggesting that national, regional, and global influenza mortality could also vary widely from year to year.

Discussion

Our study is the first to estimate global incidence of influenza-associated ALRI and resultant mortality in children younger than 5 years. We estimated that, in 2008, there were about 90 million (95% CI 49–162 million) new cases of influenza episodes, 20 million (13–32 million) cases of influenza-associated ALRI, and 1 million (1–2 million) cases of influenza-associated severe ALRI in this group, causing 28 000–111 500 deaths. Estimates are very variable within countries or regions and between

	Influenza episodes			Influenza-associated ALRI			Influenza-associated severe ALRI		
	Aged <1 years	Aged <2 years	Aged <5 years	Aged <1 years	Aged <2 years	Aged <5 years	Aged <1 years	Aged <2 years	Aged <5 years
Developing countries									
Active									
Studies*	3 (0)	3 (0)	3 (1)	3 (0)	3 (0)	3 (1)	3 (1)	3 (0)	3 (1)
Incidence (95% CI)†	119 (77–186)	156 (108–227)	154 (84–275)	23 (9–57)	44 (26–74)	35 (22–55)	1 (1–2)	2 (1–2)	1 (1–1)
Passive									
Studies*	2 (2)	2 (2)	2 (1)	3 (1)	3 (1)	3 (2)	16 (3)	16 (3)	16 (2)
Incidence (95% CI)†	140 (64–306)	142 (66–307)	142 (66–307)	10 (4–25)	7 (4–12)	5 (3–9)	3 (2–5)	3 (2–4)	2 (1–3)
Active and passive									
Studies*	5 (2)	5 (2)	5 (2)	6 (1)	6 (1)	6 (3)	19 (4)	19 (3)	19 (3)
Incidence (95% CI)†	128 (90–183)	153 (115–205)	150 (98–229)	15 (7–31)	18 (7–44)	14 (6–3)	3 (2–4)	3 (2–4)	2 (1–3)
Developed countries									
Active									
Studies*	1 (0)	1 (1)	1 (1)	0	0	0	0	0	0
Incidence (95% CI)†	NA	NA	NA	NA	NA	NA	NA	NA	NA
Passive									
Studies*	5 (2)	5 (1)	5 (0)	3 (1)	3 (0)	3 (2)	20 (6)	20 (6)	20 (3)
Incidence (95% CI)†	60 (30–117)	65 (34–124)	62 (31–127)	15 (14–16)‡	15 (9–23)	12 (7–18)	2 (2–3)	2 (2–3)	1 (1–2)
Active and passive									
Studies*	6 (2)	6 (2)	6 (1)	3 (1)	3 (0)	3 (2)	20 (6)	20 (6)	20 (3)
Incidence (95% CI)†	52 (28–99)	57 (31–105)	56 (28–106)	15 (14–16)‡	15 (9–23)	12 (7–18)	2 (2–3)	2 (2–3)	1 (1–2)
Global									
Developing countries									
Incidence (95% CI)§	119 (77–186)	156 (108–227)	154 (84–275)	23 (9–57)	44 (26–74)	35 (22–55)	3 (2–4)	3 (2–4)	2 (1–2)
Number of new cases (thousands)	14 634	..	87 198	2763	..	19 807	341	..	934
Developed countries									
Incidence (95% CI)	52 (28–98)	57 (31–105)	55 (28–106)	15 (14–16)‡	15 (9–23)	12 (7–18)	2 (2–3)	2 (2–3)	1 (1–2)
Number of new cases (thousands)	588	..	3056	165	..	650	26	..	66
Total									
Number of new cases (thousands)¶	15 222 (9684–23 883)	..	90 254 (49 257–161 694)	2927 (1244–7176)	..	20 457 (13 009–32 174)	368 (254–532)	..	1000 (665–1503)

ALRI=acute lower respiratory infection. *Data are number of studies and number of studies with imputed data in parentheses. †Data are incidence meta-estimates from random effects model; incidence estimates are per 1000 children per year ‡Incidence estimates are based on fixed effects model as data were not significantly heterogeneous (p=0·25). §Incidence estimates for influenza episodes and influenza-associated ALRI based on meta-estimate for studies with active case ascertainment only and for severe ALRI based on the meta-estimate for studies with both active and passive case ascertainment. ¶Number of new cases globally in the year 2008 is the sum of new cases in children residing in developing and developed countries in 2008; data in parentheses are 95% CIs.

Table 2: **Estimates of incidence (per 1000 children per year) and number of new cases of influenza episodes, influenza-associated ALRI, and influenza-associated severe ALRI in children younger than 5 years from studies with active and passive case ascertainment, by Global Burden of Diseases region**

regions (table 1, table 4), partly due to methodological differences and partly due to variation in influenza epidemiology between study populations and yearly variations in influenza severity. The real uncertainty in estimates is wider than that expressed in a standard 95% CI. There were insufficient data to provide global incidence estimates by type or subtype of influenza virus although incidence of influenza A was generally higher than was that for influenza B. Influenza A (particularly H3N2 subtype) results in higher morbidity and mortality than does influenza B.[62,63] Several factors affect estimates, including the method of case ascertainment, precise case definitions for severe or non-severe ALRI, the proportion of eligible patients tested for influenza virus, and differences in sensitivity and specificity of influenza assays. Hospital-based passive case ascertainment probably yields substantial underestimates of influenza-associated ALRI incidence, especially in developing countries, partly due to poor access to health care.[64,65] Studies in Kenya and The Gambia have shown two-fold to 10-fold decreases in hospital pneumonia admissions in areas farthest from hospital.[64,66,67] In one study,[68] investigators attempted to reduce this effect through provision of reimbursements for travel costs; nonetheless, about 25% of referred children did not attend the hospital. This finding supports our decision to base estimates of influenza episodes and influenza-associated ALRI incidence in developing countries on active case-ascertainment studies.

The studies that we included used various standard case definitions, nasal sampling methods, and diagnostic assays and some only sampled a random proportion of eligible cases or did not include children in the full 0–4 year age

	Countries	Incidence* (95% CI)	Children younger than 5 years in 2008 (thousands)	New episodes in children younger than 5 years in 2008 (thousands)†
Americas	15	1 (1–2)	76 903	94 (63–140)
Western Pacific	7	2 (1–5)	121 005	255 (105–620)
Europe	6	1 (1–2)	51 875	55 (37–82)
Southeast Asia	4	1 (0–6)	180 892	256 (65–1020)
Africa	7	1 (1–3)	131 307	180 (97–332)
Summed regional estimate‡	..	..	..	841 (367–2194)
Developing countries	..	2 (1–2)	566 411	935 (617–1410)
Developed countries	..	1 (1–2)	56 038	66 (48–92)
Global estimate	..	..	622 449	1001 (665–1503)

ALRI=acute lower respiratory infection. *Per 1000 children younger than 5 years per year. †Data in parentheses are 95% CIs. ‡No regional estimate exists for the Eastern Mediterranean region as there are no data from this region; this absence contributes to the difference in summed regional estimates and global estimates.

Table 3: **Incidence and number of new episodes of influenza-associated severe ALRI in children younger than 5 years, by WHO region**

	Study dates	Case fatality for influenza-associated severe ALRI
Developed countries		
South Australia, Australia[48]	1996–2006	4/626 (0·64%)
Hong Kong[34]*	1997–99	7/5471 (0·13%)
Philadelphia, PA, USA[51]	2000–04	5/573 (0·87%)
Leicester, UK[31]	2001–02	0/33
Gipuzoka, Spain[32]	2001–04	0/70
Salt Lake County, UT, USA[38]	2001–04	1/325 (0·31%)
Sydney, Australia[60]	2003	1/16 (6·25%)
Canada[56]	2003–04	1/424 (0·23%)
Multicentre, USA[40]	2003–08	7/2998 (0·23%)
Hong Kong, China[57]*	2005	1/86 (1·16%)
Developing countries		
Paraná State, Brazil[58]	1996–2001	3/45 (6·67%)
Soweto, South Africa (Madhi and colleagues)	1998–2004	10/178 (5·61%)
Bohol, Philippines (Lucero and colleagues)†‡	2000–04	3/40 (7·50%)
Kuala Lumpur, Malaysia[59]	2002–07	3/116 (2·59%)
Sa Kaeo and Nakhon Phanom, Thailand (Simmerman and colleagues)	2005–08	1/430 (0·20%)
Kilifi, Kenya (Berkley and colleagues)	2007	1/41 (2·43%)
Bondo district, Kenya (Ope and colleagues)	2007–09	3/67 (4·48%)
SARI Sentinel sites, Jordan, Oman, and Egypt (Dueger and colleagues)	2008	2/80 (2·50%)
Santa-Rosa, Guatemala (Lindblade and colleagues)‡§	2008	2/7 (28·57%)
Takeo town, Cambodia (Vong and colleagues)	2008	1/20 (5·00%)

For more details of the unpublished studies see webappendix pp 6–7 and 33. For developed countries, the case fatality ratio (CFR) meta-estimate was 0·17% (95% CI 0·08–0·26; p for heterogeneity=0·76). For developing countries, the CFR meta-estimate was 2·96% (0·79–5·13; p for heterogeneity=0·06). ALRI=acute lower respiratory infection. *Although China is classed as a developing country, Hong Kong was regarded as a developed country as socioeconomic and demographic indicators are much the same as those in developed countries. †Children in this study were aged 0–<2 years; the CFR meta-estimates if this study were excluded was 2·75%. ‡The CFR meta-estimate if Philippines and Guatemala studies were excluded was 2.71%. §The CFR meta-estimate if this study were excluded was 2·92%

Table 4: **Case fatality because of influenza-associated severe ALRI in children younger than 5 years who were admitted to hospital**

Panel 2: **Estimated mortality caused by influenza-associated acute lower respiratory infections (ARLI) in children younger than 5 years**

Approach 1: Case fatality ratio and incidence rate

a Estimated new cases per year of influenza-associated severe ALRI in children younger than 5 years in developed countries: 66 000

b Estimated case fatality ratio for children younger than 5 years caused by influenza-associated severe ALRI yearly in developed countries: 0·17%

c Estimated mortality from influenza-associated severe ALRI in children younger than 5 years in developed countries: $a \times b = 112$

d Estimated new cases per year of influenza-associated severe ALRI in children younger than 5 years in developing countries: 934 600

e Estimated case fatality ratio for children younger than 5 years caused by influenza-associated severe ALRI yearly in developing countries: 2·96%

f Estimated mortality from influenza-associated severe ALRI in children younger than 5 years in developing countries: $d \times e = 27\,664$

g Estimated global mortality caused by influenza-associated severe ALRI in children younger than 5 years: $c + f = 27\,776$

Approach 2: ALRI mortality during influenza season based on data from Ballabgarh, India

h Average proportion of ALRI mortality attributable to influenza during 3 years: 0·06

i Estimated mortality caused by ALRI in Indian children younger than 5 years: 371 605

j Estimated mortality due to influenza-associated ALRI in children younger than 5 years: 24 179 (mean of the three yearly estimates)

k Estimated mortality due to influenza-associated ALRI in Indian children (from Approach 1, with incidence rates from table 2 and case fatality ratio for developing countries): 5998

l Proportion of mortality from this approach compared to approach 1: $j \div k = 4{\cdot}03$

m Estimated global mortality due to influenza-associated ALRI (by extrapolating Indian model): $4{\cdot}03 \times f = 111\,486$

range. These factors would also have contributed to some residual variation in reported incidence estimates (webappendix pp 8–29 and p 34). There are several reasons why we might have overestimated true influenza incidence. First, estimates of influenza-associated ALRI are based on only three studies with active community-based case ascertainment from south Asia. Second, influenza virus has been previously isolated from asymptomatic children,[69] although this proportion is probably very low.[9,70] Third, incidence estimation depends on the relative sensitivity and specificity of the WHO respiratory rate cutoffs for true ALRI. This definition was developed for community case

management of paediatric ALRI in developing countries and is thus highly sensitive but has comparatively low specificity (86% for infants and 93% for children aged 1–4 years).[71]

There are several reasons why we might have underestimated true influenza incidence. First, seven studies identified infection either by rapid tests such as ELISA or immunofluoresence alone and 12 used them in combination with either PCR or viral culture. Immunofluorescence assays have variable and lower sensitivity (40–100%) and specificity (86–99%) than does PCR.[72–76] However, the overall effect of this discrepancy depends on relative sensitivity and specificity of the assays, which were unknown for most studies. Second, although we based our estimates of influenza-associated ALRI on data from community-based studies with active case ascertainment, which encouraged referral of patients to hospital, they could have still missed an unknown proportion of cases. Finally, access to hospital care is typically poor in most low-income settings and thus studies using passive hospital-based case ascertainment would have underestimated the true burden of severe disease.

Substantial uncertainty surrounds case fatality estimates from developing countries. First, many studies only tested a random sample of eligible patients. Some sites reported that some eligible children were not sampled because they were critically ill, refused participation, or were discharged or died before sampling (webappendix p 33). Thus, we might have obtained falsely low estimates because mortality tends to be highest in these groups. Second, the degree to which studies are representative of wider population groups is unknown. Finally, infection with influenza virus has been shown to predispose to bacterial infection, particularly pneumococcal pneumonia.[77–81] Results from a study[77] of a nine-valent pneumococcal vaccine probe in South Africa suggest that at least 45% of influenza-associated severe ALRI have co-infection with *S pneumoniae*. Although bacterial infections have higher case fatality ratios in developing countries, the sensitivity of bacterial diagnostic tests is low.[65,82,83] To fairly interpret childhood pneumonia deaths, mortality should be coattributed to influenza and bacterial pneumonia in cases of co-infection.

We show a more than 15-fold difference in meta-estimates of influenza-associated case fatality ratio between developing and developed regions. This difference could be attributable to epidemiological factors such as population immunity, circulation of *S pneumoniae*, or circulating type or subtype of influenza virus; clinical factors such as availability of oxygen, mechanical ventilation, antivirals, and trained nursing staff; and access to care. We based our estimate of lower bound on reported incidence of influenza-associated severe ALRI and on reported case fatality ratio in patients in hospital. The incidence estimates for developing countries are probably underestimated. Furthermore, hospital-based case fatality ratios cannot be regarded as representative of whole population groups and in most resource-poor settings might be higher than are these reported estimates. However, our estimates for children aged 0–4 years in the USA were consistent with estimates reported elsewhere[84] in 1990–99.

Our estimate of the upper bound was made on the basis of only one study and so replication in other settings is needed. Moreover, although we attributed all excess ALRI mortality during influenza season to influenza (strengthened by the lack of co-circulation with RSV), several other viral pathogens (eg, parainfluenza virus and human metapneumovirus) causing ALRI have unknown seasonal patterns and could account for as much as a third of the ALRI admissions with an equivalent case fatality ratio.[85–89] Conversely, our assumption that no influenza mortality in young children occurred outside the influenza season is unlikely to be true in developing countries in tropical and subtropical areas, leading to an underestimate.[35,59] Furthermore, a substantial proportion

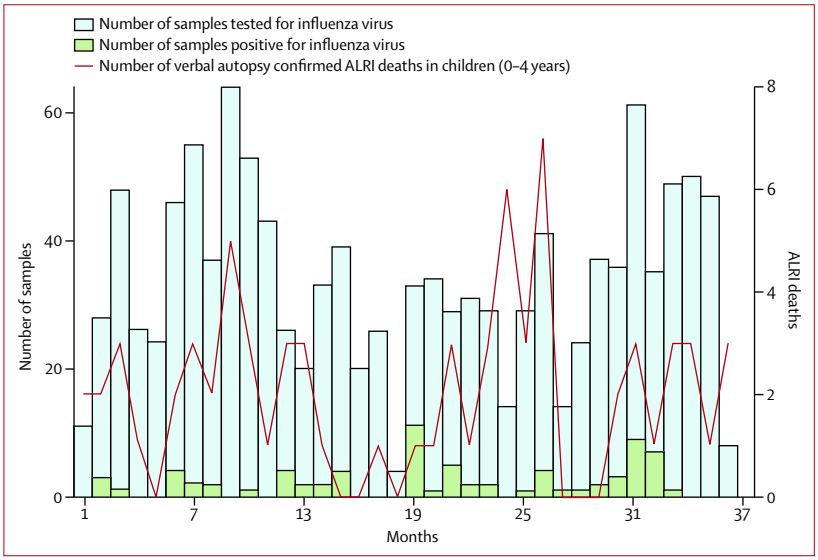

Figure 4: **Pattern of verbal autopsy confirmed ALRI deaths in children younger than 5 years by circulation of influenza virus in the community in Ballabgarh, India (2006–08)**
Month 1 is January, 2006, and month 36 is December, 2008. ALRI=acute lower respiratory infections.

	Duration of influenza season (months)	Mean number of deaths per month during influenza season	Mean number of deaths per month outside influenza season	Overall ALRI deaths per year	Proportion of ALRI deaths caused by influenza	Influenza-associated ALRI deaths in India
2006	3	2·33 (0·58)	2·22 (1·48)	27	0·01	4588
2007	7	1·70 (1·25)	1·60 (2·51)	20	0·04	14 864
2008	5	2·60 (2·70)	1·86 (1·46)	26	0·14	53 086
Mean per year	..	..	..	..	..	24 179 (25 556)

Data are n or mean (SD). ALRI=acute lower respiratory infection.

Table 5: **Estimated influenza-associated ALRI deaths in India based on verbal autopsy confirmed ALRI deaths occurring in the community in children younger than 5 years in Ballabgarh, India**

of the upper bound of influenza mortality that has been attributed to influenza might be the result of co-infection or subsequent infection with a bacterial pathogen (although influenza could have predisposed the child to bacterial infection).[80,81]

The burden on health services of hospitalisation is substantial in influenza, with 1 million episodes of influenza-associated severe ALRI (accounting for 7% of all paediatric severe ALRI episodes) in 2008. Nonetheless, the evidence to support valid and precise estimates of global influenza-associated ALRI mortality is sparse and of low quality. Some sites might have started to improve data collection after the emergence of pandemic influenza A H1N1 (2009). However, this improvement needs to be sustained and expanded to other areas, especially where no data are presently available. Development and consistent application of standardised case definitions and study protocols (at least regionally) would make an important contribution towards addressing gaps in the data and substantially improving these estimates. Further large-scale unselected case series reporting age-specific case fatality ratios from many well described clinical settings in developing countries and large-scale post-mortem studies of ALRI cases that include investigation of influenza virus as a possible cause would also substantially improve the evidence base for this estimate. Influenza is the second most common pathogen identified in children with ALRI and contributes substantially to the burden of hospitalisation and mortality in young children. Our estimates should inform public health policy and vaccine strategy, especially in developing countries. Our report should also help inform donor agencies in assigning funding priorities for novel vaccine development and implementation or other influenza prevention strategies. Until the widespread implementation of an effective influenza vaccine is achievable, reliable provision of effective case management (including oxygen therapy for hypoxaemia and antibiotic treatment of secondary bacterial infections) will substantially reduce sequelae and mortality associated with this disease.

Contributors

HN led the literature search, data analysis, data interpretation, and report writing and contributed to study design and data collection. WAB, MK, AR, SAM, JMS, SH, KAL, OC, DG, WA, RFB, SJO, PFW, SB, and EAFS contributed to study design, data collection, data analysis, data interpretation, and review of manuscript. JAB, AG, AK, MO, ML, WO, ED, SV, MC, PB, EH, MV, TB, RT, DF, and KPK contributed to data collection, data analysis, data interpretation, and review of manuscript. PC-L, LK, NB, and AB contributed to data analysis, data interpretation, and review of manuscript. ET contributed to data interpretation and review of manuscript. MS, MK, and COG-C contributed to data collection, data analysis, and review of manuscript. VE contributed to literature search, data collection, and data analysis. BG did experimental work in the laboratory and contributed to data analysis. M-AW contributed to study design, data analysis, data interpretation, and review of manuscript. AWM, BDG, and IR contributed to study design, data interpretation, and review of manuscript. HC conceptualised the study, provided oversight to literature review, data collection, data analysis, and data interpretation and contributed to report writing and critical review of manuscript.

Conflicts of interest

SAM has received research funding from Wyeth for the Soweto study that contributed to the data. He has received consultancy from Pfizer, GSK, and Novartis and speaker fees from Pfizer and GSK. However, no honoraria were received for work included in this study. BDG has received consultancy from WHO and a travel grant from Sanofi Pasteur to attend a conference on influenza in 2010. He is employed by Agence de Médecine Préventive, which has received funding from WHO, Pfizer, GlaxoSmithKline, and Merck. In 2010, the Agence de Médecine Préventive was hired by Sanofi Pasteur to organize a conference on influenza. However, no grants or honoraria were received for work included in this study. EAFS has received speaker fees and consultancy from MedImmune and research grants from Roche and MedImmune. However, no grants or honoraria were received for work included in this study. NB is employed by Johns Hopkins University which has received funding from Aventis Pasteur and Evans-Powderject. All other authors declare that they have no conflicts of interest.

Acknowledgments

Financial support for this work was provided by WHO Global Influenza Program (grant number HQGIP1002906) and the Bill & Melinda Gates Foundation (grant number 51285). The study in Ballabgarh, India, received financial support from US Centers for Disease Control and Prevention (CDC) and Indian Council of Medical Research. This work was done as part of the wider programme of the Child Health Epidemiology Working Group (CHERG) to establish the major causes of global childhood disease burden. Walter Ochieng sadly died suddenly and unexpectedly while this paper was being prepared for publication. We would like to acknowledge his important contribution to this study and his role in strengthening influenza surveillance in Kenya. We thank Johannes Forster (Department of Paediatrics, St Josefskrankenhaus Freiburg and University of Freiburg, Freiburg, Germany), Gabriele Ihorst (Clinical Trials Center, University Medical Centre Freiburg, Freiburg, Germany), Terho Heikkinen (Turku University Hospital, Turku, Finland), Alex Ezeh, Samuel Oti, and Catherine Kyobutungi (African Population and Health Research Centre, Nairobi, Kenya), and the Influenza Emerging Infections Program Network, USA for providing additional data from their published papers; Vivek Gupta and Sanjay K Rai (Comprehensive Rural Health Services Project, Ballabgarh and All India Institute of Medical Sciences, New Delhi, India); Samander Kaushik and Yashpal Singh (Department of Microbiology, All India Institute of Medical Sciences, New Delhi, India); National Institute of Virology, Pune, India; Wallace D Bulimo (National Influenza Centre, Nairobi, Kenya); Respiratory and Zoonosis group, Department of Medical Virology, University of Pretoria, South Africa; D James Nokes (KEMRI, Kilifi, Kenya); Locadiah Kuwanda (Chris Hani Baragwanath Hospital, Johannesburg, South Africa); Pedro L Alonso, Ll Quinto, Q Bassat (CRESIB, Hospital Clínic/IDIBAPS, Universitat de Barcelona, Barcelona, Spain and Centro de Investigação em Saúde da Manhiça, Ministerio de Saúde, Maputo, Mozambique); Jens Levy (Influenza Division and International Emerging Infections Program, US CDC–Thailand MOPH Collaboration, Nonthaburi, Thailand); Alejandra Estevez, Fabiola Moscoso, and Jennifer Gray (Centro de Estudios en Salud, Universidad del Valle de Guatemala); Lissette Reyes, Juan Carlos Moir (Ministerio de Salud Pública y Asistencia Social, Guatemala); Alicia M Fry (Influenza Division, CDC, Atlanta, USA); Hanna Nohynek, Taneli Puumalainen and Petri Ruutu (National Institute for Health and Welfare, Finland); Leilani Nillos (Research Institute for Tropical Medicine, Department of Health, Alabang, Muntinlupa, Philippines) and ARIVAC consortium; Ian Lipkin (University of Columbia, New York); Gerard Morris (University Witwatersrand, South Africa); Grant Mackenzie, Readon Ideh, Bernard Ebruke, Claire Oluwalana (MRC, Gambia) and the Gambia Severe Pneumonia Studies Group; Karen Fowler (University of Alabama at Birmingham, Birmingham, AL, USA); Katherine O'Brien (Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA) for their assistance; Jian Shayne F Zhang (Centre for Population Health Sciences, The University of Edinburgh, UK) for doing the literature search in Chinese language databases; Carolyn B Bridges (Influenza Division, National Center for Immunizations and Respiratory Disease, CDC, Atlanta, GA, USA) for critically reviewing the manuscript and providing helpful comments. The findings and conclusions in this report are those

of the authors and do not necessarily represent the views of the US CDC or WHO.

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