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Quantifying How Different Clinical Presentations, Levels of Severity, and Healthcare Attendance Shape the Burden of Influenza-associated Illness: A Modeling Study From South Africa

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Abstract

Background.—Burden estimates of medically and nonmedically attended influenza-associated illness across syndromes and levels of severity are lacking.

Methods.—We estimated the national burden of medically and nonmedically attended influenza-associated illness among individuals with different clinical presentations (all-respiratory, all-circulatory, and nonrespiratory/noncirculatory) and levels of severity (mild, fatal, and severe, nonfatal) using a combination of case-based (from laboratory-confirmed influenza surveillance) and ecological studies, as well as data from healthcare utilization surveys in South Africa during 2013–2015. In addition, we compared estimates of medically attended influenza-associated respiratory illness, obtained from case-based and ecological studies. Rates were reported per 100 000 individuals in the population.

Results.—The estimated mean annual number of influenza-associated illness episodes was 10 737 847 (19.8% of 54 096 705 inhabitants). Of these episodes, 10 598 138 (98.7%) were mild, 128 173 (1.2%) were severe, nonfatal, and 11 536 (0.1%) were fatal. There were 2 718 140 (25.6%) mild, 56 226 (43.9%) severe, nonfatal, and 4945 (42.8%) medically attended should be after fatal episodes. Influenza-associated respiratory illness accounted for 99.2% (10 576 146) of any mild, 65.5% (83 941) of any severe, nonfatal, and 33.7% (3893) of any fatal illnesses. Ecological and case-based estimates of medically attended, influenza-associated, respiratory mild (rates: ecological, 1778.8, vs case-based, 1703.3; difference, 4.4%), severe, nonfatal (rates: ecological, 88.6, vs case-based, 75.3; difference, 15.0%), and fatal (rates: ecological, 3.8, vs case-based, 3.5; difference, 8.4%) illnesses were similar.

Conclusions.—There was a substantial burden of influenza-associated symptomatic illness, including severe, nonfatal and fatal illnesses, and a large proportion was nonmedically attended. Estimates, including only influenza-associated respiratory illness, substantially underestimated influenza-associated, severe, nonfatal and fatal illnesses. Ecological and case-based estimates were found to be similar for the compared categories.

Keywords

influenza; burden; rates; South Africa

The World Health Organization (WHO) has highlighted the need for influenza disease-burden estimates from low- and middle-income countries. Such estimates would enable governments to make informed, evidence-based decisions when allocating scarce resources and planning intervention strategies to limit the impact and spread of influenza viruses [1]. Nevertheless, the estimation of the comprehensive, influenza-associated disease burden remains challenging, because influenza virus infections may result in a range of clinical illness presentations, including different levels of severity, and not all episodes may be medically attended.

Whereas estimates of influenza-associated mortality have been generated mainly from ecological studies [2–7], the majority of estimates of influenza-associated hospitalizations and outpatient consultations have been obtained from laboratory-confirmed influenza surveillance, conducted at sentinel healthcare facilities [8–18].

Ecological studies have proven valuable to estimate the burden of influenza-associated illness among patients with syndromes that are typically not included in virological surveillance for influenza (ie, circulatory or nonrespiratory/noncirculatory syndromes) [2–5, 19]. Nonetheless, ecological studies depend on the availability of time series of deaths, hospitalizations, or outpatient consultations at the national level or from well-defined populations, as well as virological surveillance data over the same period. In addition, estimates derived from ecological studies are not from laboratory-confirmed cases, potentially raising concern about the inappropriate attribution of observed illness episodes to influenza.

Burden estimates obtained from virological, case-based influenza surveillance have the advantage of laboratory confirmation of cases. Nonetheless, virological influenza surveillance is typically implemented at selected healthcare facilities [8, 10, 11], making it difficult to infer the burden at a national level or to estimate the burden for the more severe spectrum of illness (ie, deaths) because of the paucity of such events at a limited number of surveillance sites. In addition, in accordance with WHO recommendations [20], virological influenza surveillance is typically conducted among patients presenting with respiratory illnesses [8–17], hampering the ability to obtain burden estimates among patients with nonrespiratory clinical presentation.

Furthermore, burden estimates (either from ecological or case-based studies) obtained from data gathered at healthcare facilities do not capture influenza-associated disease events that are not medically attended.

In this study, we aimed to estimate the national burden of medically and nonmedically attended influenza-associated illness among patients with different clinical presentations and levels of severity, using a combination of case-based and ecological studies, as well as data from healthcare utilization surveys (HUS) [21, 22] in South Africa during 2013–2015. In addition, we sought to compare estimates of medically attended influenza-associated respiratory illness, obtained from case-based and ecological studies.

METHODS

Data Sources and Structure of the Burden Pyramid

For the burden pyramid estimation, we used 4 main data sources (Table 1) and a combination of case-case based and ecological studies (Table 1). The detailed description of the data sources is provided in the Supplementary Material. We estimated the national burden of influenza-associated illness within 18 main compartments, resulting from the combination of 2 levels of healthcare attendance (medically and nonmedically attended; Table 1), 3 levels of severity (mild, fatal, and severe, nonfatal; Table 1), and 3 syndromes (all-respiratory, all-circulatory, and all medical nonrespiratory/noncirculatory: the case definitions are provided in Table 2). In addition, we estimated the burden of influenza-associated illnesses among individuals presenting with respiratory illness and meeting the WHO influenza-like illness (ILI) and severe, acute respiratory infection (SARI) case definitions (a subset of all-respiratory illness) used for global influenza surveillance [1, 20], resulting in a total of 24 compartments.

Estimation of the National Burden of Influenza-associated Illness

The schematic of the estimation approach, used to construct the burden pyramid for each syndrome, level of severity, and healthcare attendance, is provided in Figure 1; the detailed description of the estimation approach, used to obtain the burden pyramid, and the sources of case-based and ecological estimates are provided in the Supplementary Material.

All estimates were obtained both overall and within the following age categories: <1, 1–4, 5–24, 25–44, 45–64, 65, <5, and 5 years. Rates were reported per 100 000 individuals in the population. All estimates were reported as mean annual estimates over the study period (2013–2015).

Comparison of Case-based and Ecological Estimates of Medically attended, Influenza-associated Respiratory Illness

We assumed that estimates obtained from case definitions listed in the same row in Table 2 would be comparable between case-based and ecological studies. We directly compared the ecological and case-based estimated rates for medically attended, influenza-associated severe respiratory illness (including deaths) and deaths (ie, pneumonia and influenza [P&I]-ecological vs SARI case-based and all-respiratory-ecological vs severe respiratory illness [SRI] case-based for both levels of severity).

For the comparison of medically attended, influenza-associated, mild respiratory illnesses (ie, P&I-ecological vs ILI case-based), we first adjusted the ecological estimates by the proportion of individuals with ILI that sought health care in private hospital clinics (23.1%), among those that sought health care with any private healthcare provider, including private general practitioners, using data from HUS conducted in 3 South African communities [21, 22]. All analyses were implemented using Stata 14.2 (StataCorp, College Station, TX).

Ethical Approval

The SARI and SRI protocol was approved by the University of the Witwatersrand Human Research Ethics Committee (HREC) and the University of KwaZulu-Natal Human Biomedical Research Ethics Committee (BREC), protocol numbers M081042 and BF157/08, respectively. The ILI protocol was approved by HREC and BREC protocol numbers M120133 and BF080/12, respectively. This surveillance was deemed nonresearch by the US Centers for Disease Control and Prevention (nonresearch determination number: 2012–6197). For the ecological study, we used only de-identified and aggregated data, which did not require human subjects' ethics review.

RESULTS

National Burden of Influenza-associated Illness

Overall—The estimated overall mean annual number of influenza-associated illnesses was 10 737 847 (Figure 2 and Supplementary Table S3), resulting in a symptomatic community attack rate (CAR) of 19.8%. Influenza-associated, all-respiratory illnesses accounted for 99.3% (10 663 980) of all influenza-associated illnesses (Supplementary Figure S3 and Supplementary Table S3). The ratio of all influenza-associated illnesses to influenza-associated, severe, nonfatal illnesses was 83.8:1 and to death was 930.8:1 (Figure 2 and Supplementary Table S7). This ratio was highest among influenza-associated, all-respiratory illnesses (severe, nonfatal illnesses: 127.0:1; death: 2739.3:1) and lowest among influenza-associated, circulatory illnesses (severe, nonfatal illnesses: 1.5:1; death: 6.7:1).

Mild Illness—The estimated mean annual number of influenza-associated mild illnesses was 10 598 138 (98.7% of all estimated influenza-associated illnesses; Figure 2 and Table 3). Of these mild cases, 2 718 140 (25.6%) were medically attended (Figure 2 and Table 3), and the highest number occurred among individuals aged 5–24 years (5 745 544, 54.2%; Supplementary Figure S4). Influenza-associated, all-respiratory mild illnesses accounted for 99.2% (10 576 146) of all influenza-associated, mild illnesses (Supplementary Figure S3 and Table 3). All and medically attended influenza-associated ILI accounted for 33.9% (3 593 813) and 8.7% (921 419) of all influenza-associated, mild illnesses, respectively (Supplementary Table S1). Overall, the influenza-associated, mild illness rates were highest among individuals aged 5–24 years (28 935.2 per 100 000 individuals in the population) and lowest among individuals aged ≥65 years (2707.0 per 100 000 individuals in the population; Table 3). This trend was similar among influenza-associated, all-respiratory cases, whereas the highest rates were observed in individuals aged ≥65 years and <1 year among influenza-associated, all-circulatory and nonrespiratory/noncirculatory cases, respectively (Table 3).

Severe, Nonfatal Illness

The estimated mean annual number of influenza-associated, severe, nonfatal illnesses was 128 173 (1.2% of all estimated influenza-associated illnesses; Figure 2 and Table 4). Of these severe cases, 56 226 (43.9%) were medically attended (Figure 2 and Table 4), and the highest number occurred among individuals aged 25–44 years (36 113, 28.2%; Supplementary Figure S4). Influenza-associated, all-respiratory, severe, nonfatal illnesses accounted for 65.5% (83 941) of all influenza-associated, severe, nonfatal illnesses

(Supplementary Figure S3 and Table 4). All and medically attended influenza-associated SARI accounted for 40.3% (51 621) and 19.7% (25 237) of all influenza-associated, severe, nonfatal illnesses, respectively (Supplementary Table S1). Overall, the influenza-associated, severe, nonfatal illness rates were higher among individuals aged <1 year (1550.9 per 100 000 individuals in the population) and ≥65 years (761.3 per 100 000 individuals in the population); the lowest rates were among individuals aged 5–24 years (58.4 per 100 000 individuals in the population; Table 4). Such a U-shaped distribution was observed for all the syndromes evaluated in this study (Table 4).

Deaths—The estimated mean annual number of influenza-associated deaths was 11 536 (0.1% of all estimated influenza-associated illnesses; Figure 2 and Table 5). Of these deaths, 4945 (42.8%) occurred in a hospital (Figure 1 and Table 6), and the highest number occurred among individuals aged ≥65 years (4195, 36.1%; Supplementary Figure S4). Influenza-associated, all-respiratory deaths accounted for 33.7% (3893) of all influenza-associated deaths (Supplementary Figure S3 and Table 5). All and in-hospital influenza-associated SARI deaths accounted for 19.8% (2291) and 9.7% (1126) of all influenza-associated deaths, respectively (Supplementary Table S1). Overall, the influenza-associated death rates were higher among individuals aged <1 year (80.3 per 100 000 individuals in the population) and ≥65 years (137.9 per 100 000 individuals in the population); the lowest rates were among individuals aged 5–24 years (2.0 per 100 000 individuals in the population; Table 5). This U-shaped distribution was similar for influenza-associated, all-respiratory deaths, whereas the highest rates were observed in individuals aged ≥65 years and <1 year for influenza-associated, all-circulatory and nonrespiratory/noncirculatory deaths, respectively (Table 5). The estimated case fatality rate among individuals with influenza-associated severe illness was 8.3% overall and 4.4%, 18.6%, and 12.9% among individuals with influenza-associated all-respiratory, all-circulatory, and nonrespiratory/noncirculatory severe illnesses, respectively (Supplementary Table S6).

Comparison of Case-based and Ecological Estimates of Medically Attended Influenza-associated Respiratory Illness

The percentage difference of ecological and case-based rate estimates of medically attended, influenza-associated mild respiratory illness was 4.4% (rates: P&I-ecological, 1778.8, vs ILI case-based, 1703.3 per 100 000 individuals in the population; Table 6). This percent difference was 10.0% for medically attended, influenza-associated, acute-respiratory, severe illness (rates: P&I-ecological, 53.7, vs SARI case-based, 48.8 per 100 000 individuals in the population) and 15.0% for medically attended, influenza-associated, all-respiratory, severe illness (rates: all-respiratory-ecological, 88.6, vs SRI case-based, 75.3 per 100 000 individuals in the population; Table 6 and Supplementary Tables S1 and S2). A similar percentage difference was observed for influenza-associated, acute-respiratory deaths (rates: P&I-ecological, 2.2, vs SARI case-based, 2.1 per 100 000 individuals in the population; difference, 6.4%) and influenza-associated, all-respiratory deaths (rates: all-respiratory-ecological, 3.8, vs SRI case-based, 3.5 per 100 000 individuals in the population; difference, 8.4%; Table 6). The estimated proportion of cases within a comparable syndrome attributable to influenza virus infection was also similar among ecological and case-based studies for mild respiratory illness (P&I-ecological, 13.4%, vs ILI case-based, 12.3%),

acute-respiratory, severe illness (P&I-ecological, 5.1%, vs SARI case-based, 4.3%), and all-respiratory, severe illness (all-respiratory-ecological, 4.3%, vs SRI case-based, 3.9%; Supplementary Tables S4 and S5).

DISCUSSION

During 2013–2015, we estimate that, on average, 19.8% (10 737 847) of the South African population was affected by influenza-associated illness annually, of which 97.8% cases were mild and 74.1% were nonmedically attended. Nonetheless, a substantial number of influenza-associated, severe-illness episodes (128 173) and deaths (11 536) occurred annually in the country. Influenza-associated respiratory illness accounted for the majority of influenza-associated mild illnesses (99.2%), but for a lower proportion of influenza-associated severe illnesses (65.5%) and deaths (33.7%). Overall, the rates of influenza-associated mild illness were highest among individuals aged 5–24 years; the rates of influenza-associated, severe, nonfatal illnesses and deaths were higher among infants aged <1 year and persons aged ≥65 years. The case-based estimates of medically attended, influenza-associated, mild and severe respiratory illnesses and deaths were similar to those from independently conducted ecological studies.

The estimated symptomatic CAR associated with influenza virus infection found in this study (19.8%) is lower than those observed in a community burden study (30.9%) implemented in South Africa in 2016 using polymerase chain reaction–confirmed influenza virus infection [24]. However, it should be noted that asymptomatic individuals were included in the above-mentioned study, but not accounted for in our estimates of illness episodes. Using pre- and postinfluenza season serology, influenza attack rates of 43.6% pertains to HIV-infected and 35.0% pertains to HIV-uninfected pregnant women were found among human immunodeficiency virus (HIV)-infected and HIV-uninfected pregnant women in South Africa [25]. Also using serology, influenza virus CARs of 18% and 35% have been reported in England and New Zealand, respectively [26, 27]. These studies also included asymptomatic individuals. A recent meta-analysis estimated that 19.1% (range, 1.6–62.5%) of influenza virus infections are asymptomatic [28]; this proportion was 20.0% in a South African household transmission study [29]. The exclusion of the asymptomatic fraction in our estimates may explain the lower CAR found in this study (19.8%), as compared to CAR estimates from South African studies that included asymptomatic individuals, as described above [24, 25].

In our study, we found that the proportion of influenza-associated illnesses with respiratory presentations was highest for mild illnesses, but proportionately lower for severe, nonfatal illnesses and deaths; influenza-associated, nonrespiratory illnesses accounted only for 0.8% of all influenza-associated, mild illnesses, but 66.3% of all influenza-associated deaths. Underlying medical conditions, such as chronic circulatory, renal, or liver diseases and diabetes, are known risk factors for influenza-associated, severe illnesses and death [30, 31]. Influenza virus infections in some individuals with such underlying medical conditions may manifest as acute exacerbations of those conditions, resulting in higher hospitalization and death rates than in healthy individuals and, with sufficiently severe exacerbations, a higher likelihood of being diagnosed by the attending physician as a nonrespiratory illness [32].

This high level of severity among influenza-associated, nonrespiratory illnesses was also reflected in the higher case fatality rates observed among individuals with influenza-associated circulatory illnesses (18.6%) or nonrespiratory/noncirculatory illnesses (12.9%), as compared to respiratory illnesses (4.4%), in our study. This increased severity among influenza-associated, nonrespiratory illness may be responsible for the higher contribution of these syndromes to influenza-associated severe illness and death, as compared to mild illness.

We found a high proportion of nonmedically attended illnesses, even among severe cases, across the syndromes evaluated in this study (56.1%). An elevated proportion of nonmedically attended, influenza-associated, SARI hospitalizations (79.2%) was found also in a recent study conducted in Kenya [33], suggesting that limited access to health care in such settings may prevent care seeking, even among individuals that develop severe illness. This was corroborated also by the high proportion of influenza-associated deaths taking place out of a hospital (57.2%), as found in this study and previously described in South Africa [4, 31].

The WHO recommends influenza surveillance among outpatients with ILI and inpatients with SARI [20]. In our study, medically and nonmedically attended, influenza-associated ILI, nonfatal SARI illnesses, and SARI deaths accounted only for 33.9% of all influenza-associated, mild illnesses, 40.3% of severe, nonfatal illnesses, and 19.8% of deaths, respectively. In this study, the proportion of the symptomatic fraction of influenza-associated mild illnesses that met the ILI case definition (33.9%) is similar to those reported in other studies. In a household transmission study conducted in Hong Kong, the proportion of influenza-positive household members that had symptoms consistent with the ILI case definition was 37.1% among any symptomatic individuals (defined as having at least 1 of 7 investigated symptoms) [34]. A recent meta-analysis estimated that 43.4% (range, 4.6–92.8%) of symptomatic individuals infected with influenza virus did not meet the ILI or acute respiratory infection case definition [28]. To our knowledge, there are no estimates of the proportional contribution of influenza-associated, nonfatal SARI illnesses and SARI deaths to all influenza-associated, severe illnesses or deaths. In our study, medically attended, influenza-associated ILI, nonfatal SARI illnesses, and SARI deaths accounted only for 8.7% of all influenza-associated mild illnesses, 19.7% of severe, nonfatal illnesses, and 9.7% of deaths, respectively. This suggests that using influenza surveillance data among medically-attended patients with ILI or SARI (as recommended by the WHO for global influenza surveillance [20]) can substantially underestimate the burden of influenza-associated illnesses in all levels of severity. This is due to 3 main factors: (1) the ILI and SARI case definitions do not capture all influenza-associated respiratory illnesses [10, 26, 28, 29, 34]; (2) influenza-associated, nonrespiratory illness contributes to a substantial proportion of all influenza-associated illnesses, especially among severe cases and deaths [2–4]; and (3) a high proportion of influenza-associated illness is nonmedically attended across levels of severity in our settings [4, 21, 22, 33].

Similar to other studies [35], we found higher rates of influenza-associated ILI among school-aged children and young adults compared to other age groups, highlighting the importance of these individuals in influenza virus transmission [36]. We found higher rates

of influenza-associated, severe illnesses and deaths among individuals aged <1 and 65 years; this has also been reported in other studies and settings [2–4, 8, 10, 11, 13–16], highlighting the increased risk of these individuals for influenza-associated severe illness.

We found similar ecological and case-based rate estimates for medically attended, influenza-associated, respiratory mild or severe illnesses and deaths (ie, P&I or all-respiratory ecological vs ILI, SARI, or SRI case-based). This similarity was also found among influenza-associated SARI deaths in another study conducted in South Africa [31].

Our study has limitations that warrant discussion. First, we could not compare ecological and case-based estimates for influenza-associated circulatory and nonrespiratory/noncirculatory illnesses, as we did not implement virological influenza surveillance in this group of patients. Case-based studies on the burden of influenza-associated illness among patients with nonrespiratory presentation are lacking, hampering the ability to validate ecological estimates for nonrespiratory syndromes. Second, whereas estimates for nonmedically attended, influenza-associated, mild and severe respiratory illnesses were obtained from HUS data, for nonmedically attended, influenza-associated, mild and severe circulatory and nonrespiratory/noncirculatory illnesses, we assumed the same proportion as among those medically attended cases calculated from estimated deaths occurring outside hospitals. If the case fatality rate was higher among non-medically attended than medically attended cases, this could have resulted in an overestimation of the nonmedically attended, influenza-associated, mild and severe, nonfatal, circulatory and nonrespiratory/noncirculatory illnesses.

In conclusion, we estimated that a substantial number of influenza-associated illness episodes, including a sizable number of medically and nonmedically attended, influenza-associated, severe, nonfatal illnesses and deaths, occur annually in South Africa. The combination of case-based and ecological studies, as well as HUS data, provided more comprehensive estimates of influenza-associated illness than the use of medically attended, case-based surveillance alone would have allowed. This suggests an important underestimation of influenza-associated illness across levels of severity when medically attended ILI and SARI surveillance data are used for disease burden estimation. The similar ecological and case-based estimates obtained for medically attended, influenza-associated, mild, fatal, and severe, nonfatal respiratory illnesses provide an important validation of ecological estimates for these categories. Nonetheless, these findings should be validated in other countries and settings. In addition, a better understanding of the validity of ecological estimates of influenza-associated circulatory and nonrespiratory/noncirculatory illnesses across levels of severity is needed. Influenza virus circulation patterns, crowding, population density/interaction and age structure, the prevalence of underlying medical conditions in the community, and access to health care are factors that, among others, may affect the size and proportional contribution of the different compartments of the burden pyramid, as estimated in this study, and this should be investigated in other countries and settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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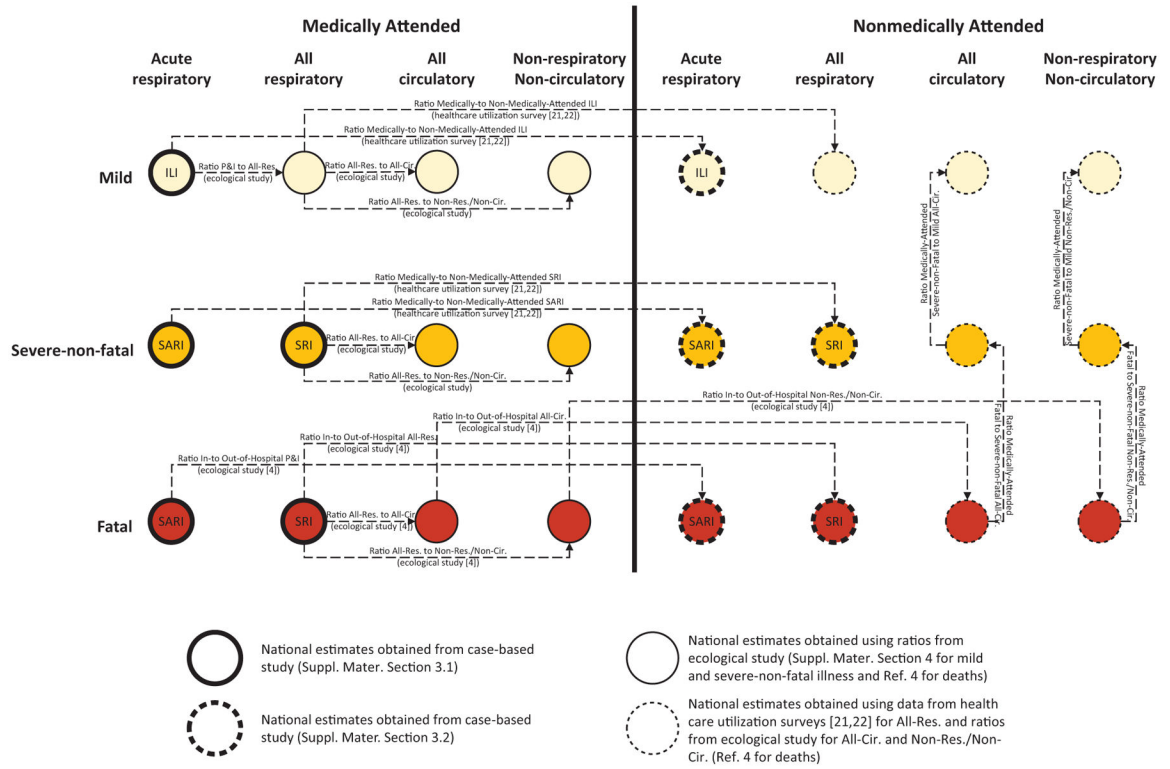


Figure 1. Schematic of the method used to estimate influenza-associated illness in South Africa, 2013–2015. Each circle represents a compartment (24) in the estimation approach. Abbreviations: All-Cir, all-circulatory; All-Res, all-respiratory; ILI, influenza-like illness; Non-Res/Non-Cir, nonrespiratory/noncirculatory; P&I, pneumonia and influenza; SARI, severe, acute respiratory infection; SRI, severe respiratory illness.

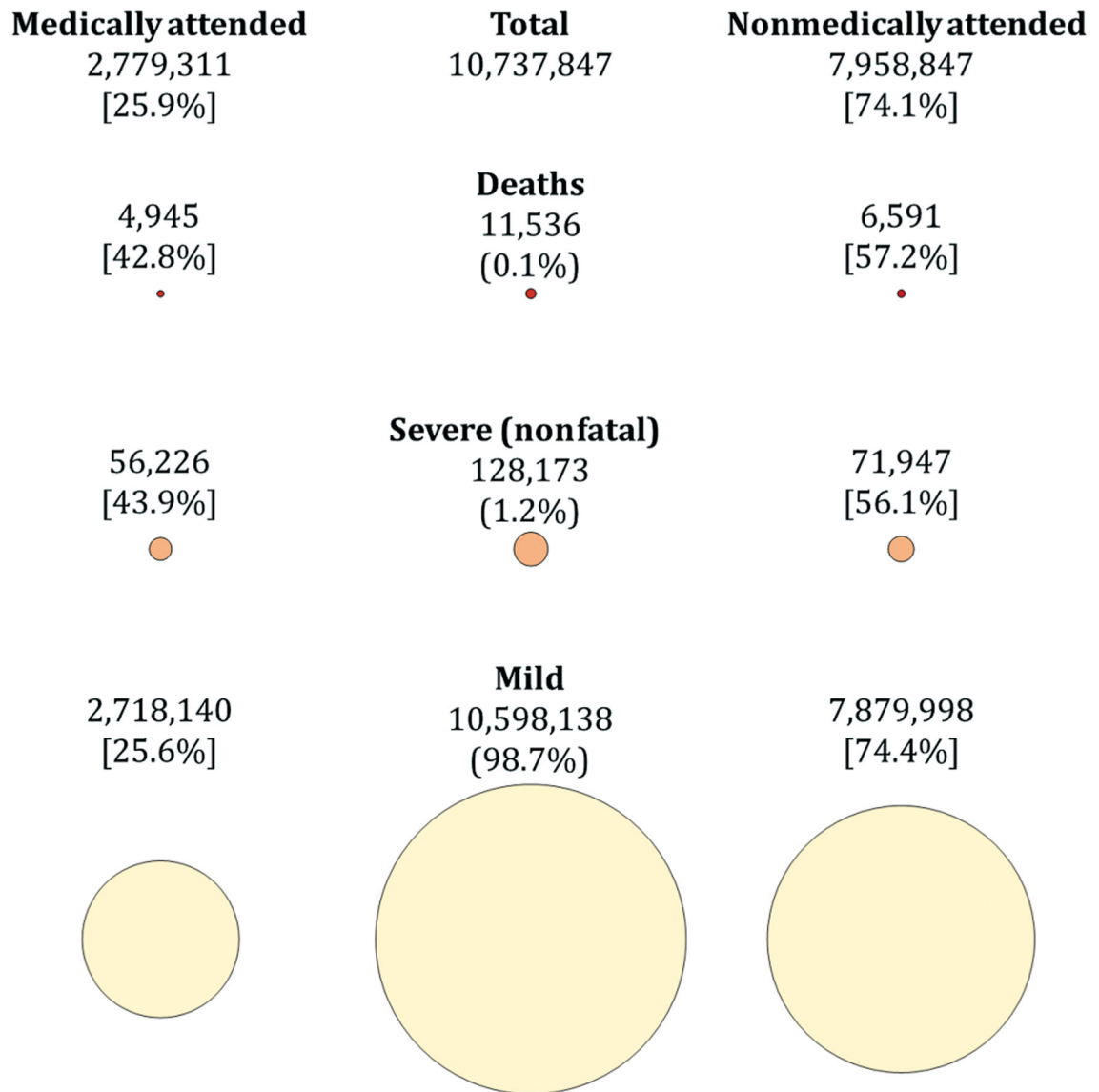


Figure 2.

Estimated mean annual number of total, medically, and nonmedically attended influenza-associated illness in South Africa, 2013–2015. The () indicate column percentages and [] indicate row percentages. The circles' size is proportional to the number of influenza-associated illness episodes.

Table 1. Data Sources and Definitions Used for the Estimation of Influenza-associated Illness in South Africa, 2013–2015**Data sources**

- (1) Laboratory-confirmed (using real-time reverse transcription polymerase chain reaction assays) influenza surveillance among inpatients (including deaths) with SARI (duration of illness < 10 days) or SRI (any respiratory illness, irrespective of symptoms duration), implemented at 3 hospitals and among outpatients with ILI, at 2 affiliated clinics, situated in the North West and KwaZulu-Natal provinces, during 2013–2015 [10].
- (2) Any hospitalization and outpatient consultation diagnosis data, coded according to the *International Classification of Diseases, 10th Revision*, without laboratory confirmation of influenza, from a large network of private hospitals (NetCare) active in 7/9 provinces during 2013–2015 [19].
- (3) Healthcare-seeking behavior data among individuals with reported ILI, SARI, and SRI from healthcare-utilization surveys [21, 22].
- (4) Population denominators from census data.

Definitions**Study type**

1. **Case-based:** estimates obtained from data source 1.
2. **Ecological:** estimates obtained from data source 2 (for mild and severe, nonfatal illnesses). Ecological estimates for deaths were obtained from published literature from South Africa [4].

Healthcare attendance

1. **Medically attended illness:** attended by a registered medical care provider/institution, excluding pharmacies.
2. **Nonmedically attended illness:** not attended by a registered medical care provider/institution, including pharmacies.

Illness severity

1. **Mild:** medically or nonmedically attended illness not warranting hospitalization.
2. **Severe, nonfatal:** medically or nonmedically attended illness warranting hospitalization (excluding deaths).
3. **Fatal:** in- and out-of-hospital deaths.

Abbreviations: ILI, influenza-like illness; SARI, severe, acute respiratory infection; SRI, severe respiratory illness.

Table 2. Case Definitions Used to Estimate Influenza-associated Illness Using Case-based and Ecological Studies in South Africa, 2013–2015

Illness Category	Case Definitions	
	Case-based Study	Ecological Study ^a
Mild illness		
Acute respiratory	<ul style="list-style-type: none"> • ILI: an outpatient of any age, presenting with either temperature $\geq 38^{\circ}\text{C}$ or history of fever and cough of duration of ≥ 10 days. 	<ul style="list-style-type: none"> • J09-J18 (P&I) among outpatients.
All-respiratory	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • J00-J99 among outpatients.
All-circulatory	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • I00-I99 among outpatients.
Nonrespiratory/ noncirculatory	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • All medical outpatient consultations, excluding J00-J99 and I00-I99.
Severe illness		
Acute respiratory	<ul style="list-style-type: none"> • SARI (a subset of SRI): a hospitalized person who had illness onset ≥ 10 days of admission and who met age-specific clinical inclusion criteria. <ul style="list-style-type: none"> – Children aged 2 days to <3 months: any hospitalized patient with diagnosis of suspected sepsis or physician-diagnosed acute lower respiratory tract infection irrespective of signs and symptoms. – Children aged 3 months to <5 years: any hospitalized patient with physician-diagnosed acute lower respiratory tract infection, including bronchitis, bronchiolitis, pneumonia, and pleural effusion. – Individuals aged ≥ 5 years, including any hospitalized patient presenting with manifestation of acute lower respiratory tract infection with temperature $\geq 38^{\circ}\text{C}$ or history of fever and cough. 	<ul style="list-style-type: none"> • J09-J18 (P&I) among inpatients.
All-respiratory	<ul style="list-style-type: none"> • SRI: same as SARI, but with any duration of illness. 	<ul style="list-style-type: none"> • J00-J99 among inpatients.
All-circulatory	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • I00-I99 among inpatients.
Nonrespiratory/ noncirculatory	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • All-medical hospitalization, excluding J00-J99 and I00-I99.
Deaths		
Acute respiratory	<ul style="list-style-type: none"> • SARI (as described above) deaths 	<ul style="list-style-type: none"> • J09-J18 (P&I) deaths.
All-respiratory	<ul style="list-style-type: none"> • SRI (as described above) deaths 	<ul style="list-style-type: none"> • J00-J99 deaths.

Illness Category	Case Definitions	
	Case-based Study	Ecological Study ^a
All-circulatory	• N/A	• 100-199 deaths.
Nonrespiratory/ noncirculatory	• N/A	• All medical deaths, excluding J00-J99 and 100-199.

Abbreviations: ILI, influenza-like illness; N/A, not applicable; P&I, pneumonia and influenza; SARI, severe, acute respiratory infection; SRI, severe respiratory illness.

^a Outpatient consultations or admissions diagnoses, coded according to the *International Classification of Diseases, 10th revision 23*.

Table 3. Estimated Mean Annual Number and Rates of Influenza-associated Mild Illness in South Africa, 2013–2015

Age Group	Total			Influenza-associated Mild Illness ^a			Nonmedically Attended		
	Number (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^b (95% CI)	
All-respiratory^c									
<1	303 503 (209 662–455 521)	25 605.2 (17 688.2–38 430.2)	69 331 (47 894–104 057)	5849.1 (4040.6–8778.8)	234 172 (161 768–351 464)	19 756 (13 647.6–29 651.4)			
1–4	1 090 378 (515 506–1 303 363)	23 655.8 (11 183.9–28 276.6)	252 053 (119 165–301 287)	5468.3 (2585.3–6536.4)	838 325 (396 341–1 002 076)	18 1875 (8598.6–21 740.1)			
5–24	5 743 071 (3 511 241–6 576 115)	28 922.7 (17 683.0–33 118.0)	1 368 290 (836 555–1 566 763)	6890.9 (4213–7890.4)	4 374 781 (2 674 686–5 009 352)	22 031.9 (13 470.0–25 227.6)			
25–44	2 604 278 (515 857–3 154 125)	15 491.8 (3068.6–18 762.6)	785 019 (155 497–950 762)	4669.8 (925–5655.7)	1 819 259 (360 360–2 203 363)	10 822 (2143.6–13 106.9)			
45–64	755 288 (268 068–981 283)	8764.2 (3110.6–11 386.6)	215 636 (76 534–280 158)	2502.2 (888.1–3250.9)	539 652 (191 534–701 125)	6262 (2222.5–8135.7)			
65	79 628 (32 066–125 885)	2639.4 (1062.9–4172.7)	18 903 (7612–29 884)	626.6 (252.3–990.6)	60 725 (24 454–96 001)	2012.9 (810.6–3182.2)			
<5	1 393 881 (717 416–1 745 549)	24 054.6 (12 380.6–30 123.4)	321 384 (165 413–402 467)	5546.2 (2854.6–6945.5)	1 072 497 (552 003–1 343 082)	18 508.4 (9526.1–23 177.9)			
5	9 182 265 (3 342 869–11 073 068)	19 010.1 (6920.8–22 924.6)	2 387 848 (869 313–2 879 551)	4943.6 (1799.7–5961.6)	6 794 417 (2 473 556–8 193 517)	14 066.5 (5121.0–16 963.1)			
All	10 576 146 (3 983 349–12 795 931)	19 550.4 (7363.4–23 653.8)	2 709 232 (1 020 392–3 277 862)	5008.1 (1886.2–6059.3)	7 866 914 (2 962 957–9 518 069)	14 542.3 (5477.1–17 594.5)			
All-circulatory^d									
<1	48 (29–115)	4 (2.4–9.7)	32 (19–77)	2.7 (1.6–6.5)	16 (10–38)	1.3 (0.8–3.2)			
1–4	154 (123–247)	3.3 (2.7–5.4)	103 (82–165)	2.2 (1.8–3.6)	51 (41–82)	1.1 (0.9–1.8)			
5–24	540 (450–900)	2.7 (2.3–4.5)	232 (193–387)	1.2 (1–1.9)	308 (257–513)	1.6 (1.3–2.6)			
25–44	842 (702–2245)	5 (4.2–13.4)	362 (302–965)	2.2 (1.8–5.7)	480 (400–1280)	2.9 (2.4–7.6)			
45–64	1561 (1086–1968)	18.1 (12.6–22.8)	671 (467–846)	78 (5.4–9.8)	890 (619–1122)	10.3 (7.2–13)			
65	900 (666–1476)	29.8 (22.1–48.9)	387 (286–635)	12.8 (9.5–21)	513 (380–841)	17 (12.6–27.9)			
<5	202 (162–364)	3.5 (2.8–6.3)	135 (1.08–2.43)	2.3 (1.9–4.2)	67 (54–121)	1.2 (0.9–2.1)			
5	3843 (2882–6725)	8 (6–13.9)	1652 (1239–2891)	3.4 (2.6–6)	2191 (1643–3834)	4.5 (3.4–7.9)			
All	4045 (3034–6741)	75 (5.6–12.5)	1787 (1340–2978)	3.3 (2.5–5.5)	2258 (1694–3763)	4.2 (3.1–7)			
Nonrespiratory and noncirculatory^d									

Age Group	Total			Influenza-associated Mild Illness ^d			Nonmedically Attended		
	Number (95% CI)	Rate ^b (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^b (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^b (95% CI)	Rate ^b (95% CI)
<1	7418 (3753–9444)	625.8 (316.6–796.7)	3190 (614–4061)	269.1 (136.2–342.6)	4228 (2139–5383)	356.7 (180.5–454.1)			
1–4	2010 (718–2680)	43.6 (15.6–58.1)	864 (309–1152)	18.7 (6.7–25)	1146 (409–1528)	24.9 (8.9–33.2)			
5–24	1933 (1074–2792)	9.7 (5.4–14.1)	696 (387–1005)	3.5 (1.9–5.1)	1237 (687–1787)	6.2 (3.5–9)			
25–44	3181 (2009–5190)	18.9 (12–30.9)	1145 (723–1868)	6.8 (4.3–11.1)	2036 (1286–3322)	12.1 (7.6–19.8)			
45–64	2266 (1295–4613)	26.3 (15–53.5)	816 (466–1661)	9.5 (5.4–19.3)	1450 (829–2952)	16.8 (9.6–34.3)			
65	1139 (666–2020)	378 (22.1–67)	410 (240–727)	13.6 (8–24.1)	729 (426–1293)	24.2 (14.1–42.9)			
<5	9428 (4428–12 142)	162.7 (76.4–209.5)	4054 (1904–5221)	70 (32.9–90.1)	5374 (2524–6921)	92.7 (43.6–119.4)			
5	8519 (5274–15 010)	176 (10.9–31.1)	3067 (1899–5404)	6.3 (3.9–11.2)	5452 (3375–9606)	11.3 (7–19.9)			
All	17 947 (9842–28 368)	33.2 (18.2–52.4)	7121 (3905–11 256)	13.2 (7.2–20.8)	10 826 (5937–17 112)	20 (11–31.6)			
All									
<1	310 969 (213 444–465 080)	26 235 (18 0073–39 236.7)	72 553 (49 527–108 195)	6121 (4178.4–91279)	23 8416 (163 917–356 885)	20 114.1 (13 828.9–30 108.7)			
1–4	1 092 542 (516 347–1 306 290)	23 702.8 (11 202.2–28 340.1)	253 020 (119 556–302 604)	5489.3 (2593.8–6565.0)	839 522 (396 791–1 003 686)	18 213.5 (8608.4–21 775.0)			
5–24	5 745 544 (3 512 765–6 579 807)	28 935.2 (17 690.7–33 136.6)	1 369 218 (837 135–1 568 155)	6895.5 (4215.9–7897.4)	4 376 326 (2 675 630–5 011 652)	22 039.6 (13 474.8–25 239.2)			
25–44	2 608 301 (518 568–3 161 560)	15 515.7 (30 84.7–18 806.8)	786 526 (156 522–953 595)	4678.7 (931.1–5672.5)	1 821 775 (362 046–2 207 965)	10 837 (2153.7–13 134.3)			
45–64	759 115 (270 449–987 864)	8808.6 (3138.2–11 463)	217 123 (77 467–282 665)	2519.5 (898.9–3280.0)	541 992 (192 982–705 199)	6289.2 (2239.3–8183.0)			
65	81 667 (33 398–129 381)	2707.0 (11070–4288.6)	19 700 (8138–31 246)	653.0 (269.8–1035.7)	61 967 (25 260–98 135)	2054 (8373–3252.9)			
<5	1 403 511 (722 006–1 758 055)	24 220.8 (12 459.9–30 339.2)	325 573 (167 425–407 931)	5618.5 (2889.3–7039.8)	1 077 938 (554 581–1 350 124)	18 602.3 (9570.6–23 299.5)			
5	9 194 627 (3 351 025–11 094 803)	19 035.7 (69376–22 969.6)	2 392 567 (872 451–2 887 846)	4953.3 (1806.2–5978.7)	6 802 060 (2 478 574–8 206 957)	14 082.3 (5131.4–16 990.9)			
All	10 598 138 (3 996 225–12 831 040)	19 591.1 (73872–23 718.7)	2 718, 140 (1 025 637–3 292 096)	5024.6 (1895.9–6085.6)	7 879 998 (2 970 588–9 538 944)	14 566.5 (5491.3–17 633.1)			

Abbreviation: CI, confidence interval.

^aMild illness is defined as not requiring hospitalization.^bRates expressed are per 100 000 individuals in the population.^cObtained from case-based surveillance at 5 facilities and extrapolated nationally.

ρ Obtained using ratios of respiratory to nonrespiratory (ie, circulatory or nonrespiratory/noncirculatory), from ecological studies.

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Table 4.

Estimated Mean Annual Number and Rates of Influenza-associated Severe Illness (Excluding Deaths) in South Africa, 2013–2015

Age Group	Total	Influenza-associated Severe Illness ^a				
		Medically Attended		Nonmedically Attended		
	Number (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^b (95% CI)
All-respiratory^c						
<1	13 829 (9469–18 951)	1166.7 (798.9–1598.8)	6373 (4610–8169)	537.7 (388.9–689.2)	7456 (4857–10 782)	629.0 (409.8–909.6)
1–4	13 049 (8669–18 427)	283.1 (188.1–399.8)	6030 (4185–7942)	130.8 (90.8–172.3)	7019 (4483–10 486)	152.3 (97.3–227.5)
5–24	8737 (4025–14 941)	44 (20.3–75.2)	4054 (1978–6522)	20.4 (10.0–32.8)	4683 (2046–8441)	23.6 (10.3–42.5)
25–44	20 147 (14 043–28 167)	119.8 (83.5–167.6)	9390 (6850–12 365)	55.9 (40.7–73.6)	10 757 (7177–15 805)	64.0 (42.7–94)
45–64	15 329 (9709–22 215)	177.9 (112.7–257.8)	7073 (4640–9610)	82.1 (53.8–111.5)	8256 (5059–12 611)	95.8 (58.7–146.3)
65	12 850 (5811–21 710)	425.9 (192.6–719.6)	5861 (2752–9538)	194.3 (91.2–316.2)	6989 (3055–12 177)	231.7 (101.3–403.6)
<5	26 878 (18 140–37 371)	463.8 (313.0–644.9)	12 403 (8797–16 110)	214.0 (151.8–278.0)	14 475 (9336–21 265)	249.8 (161.1–367.0)
5	57 063 (33 499–87 053)	118.1 (69.4–180.2)	26 378 (16 208–38 046)	54.6 (33.6–78.8)	30 685 (17 332–49 023)	63.5 (35.9–101.5)
All	83 941 (51 604–124 594)	155.2 (95.4–230.3)	38 781 (24 978–54 283)	71.7 (46.2–100.3)	45 160 (26 620–70 329)	83.5 (49.2–130.0)
All-circulatory^d						
<1	282 (224–671)	23.8 (18.9–56.6)	189 (150–449)	15.9 (12.7–37.9)	93 (74–221)	7.8 (6.2–18.6)
1–4	339 (297–415)	7.4 (6.4–9)	227 (199–278)	4.9 (4.3–6.0)	112 (98–137)	2.4 (2.1–3.0)
5–24	326 (186–745)	1.6 (0.9–3.8)	140 (80–320)	0.7 (0.4–1.6)	186 (106–425)	0.9 (0.5–2.1)
25–44	3202 (1774–5063)	19.0 (10.6–30.1)	1377 (763–2177)	8.2 (4.5–13.0)	1825 (1011–2885)	10.9 (6–17.2)
45–64	3570 (2273–9116)	41.4 (26.4–105.8)	1535 (977–3920)	17.8 (11.3–45.5)	2035 (1296–5197)	23.6 (15.0–60.3)
65	5974 (2324–10 481)	198.0 (77.0–347.4)	2569 (1000–4507)	85.2 (33.1–149.4)	3405 (1325–5974)	112.9 (43.9–198.0)
<5	621 (522–1080)	10.7 (9.0–18.6)	416 (350–723)	7.2 (6.0–12.5)	205 (172–357)	3.5 (3.0–6.2)
5	13 072 (6446–25 722)	27.1 (13.3–53.3)	5621 (2772–11 061)	11.6 (5.7–22.9)	7451 (3674–14 662)	15.4 (7.6–30.4)
All	13 693 (6813–26 785)	25.3 (12.6–49.5)	6037 (3004–11 809)	11.2 (5.6–21.8)	7656 (3809–14 976)	14.2 (7.0–27.7)
Nonrespiratory and noncirculatory^d						
<1	4272 (2285–5625)	360.4 (192.8–474.6)	1837 (982–2419)	155 (82.8–204.1)	2435 (1302–3206)	205.4 (109.8–270.5)
1–4	1644 (600–1888)	35.7 (13.0–41.0)	707 (258–812)	15.3 (5.6–17.6)	937 (342–1076)	20.3 (7.4–23.3)
5–24	2542 (2217–4381)	12.8 (11.2–22.1)	915 (798–1577)	4.6 (4.0–7.9)	1627 (1419–2804)	8.2 (7.1–14.1)
25–44	12 764 (8299–23 732)	75.9 (49.4–141.2)	4595 (2988–8544)	27.3 (17.8–50.8)	8169 (5311–15 189)	48.6 (31.6–90.4)

Age Group	Influenza-associated Severe Illness ^a					
	Total			Medically Attended		Nonmedically Attended
	Number (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^b (95% CI)
45–64	5175 (2500–9891)	60.0 (29–114.8)	1863 (900–3561)	21.6 (10.4–41.3)	3312 (1600–6330)	38.4 (18.6–73.5)
65	4142 (1638–8696)	137.3 (54.3–288.2)	1491 (590–3130)	49.4 (19.6–103.8)	2651 (1048–5566)	87.9 (34.7–184.5)
<5	5916 (2882–7579)	102.1 (49.7–130.8)	2544 (1239–3259)	43.9 (21.4–56.2)	3372 (1643–4320)	58.2 (28.4–74.6)
5	24 623 (13 447–47 792)	51.0 (27.8–98.9)	8864 (4841–17 205)	18.4 (10.0–35.6)	15 759 (8606–30 588)	32.6 (17.8–63.3)
All	30 539 (16 395–56 578)	56.5 (30.3–104.6)	11 408 (6124–21 135)	21.1 (11.3–39.1)	19 131 (10 270–35 443)	35.4 (19.0–65.5)
All						
<1	18 383 (11 976–25 245)	1550.9 (1010.4–2129.8)	8399 (5742–11 035)	708.6 (484.4–931.0)	9984 (6232–14 208)	842.3 (525.8–1198.7)
1–4	15 032 (9569–20 735)	326.1 (207.6–449.8)	6964 (4644–9035)	151.1 (100.8–196.0)	8068 (4925–11 702)	175.0 (106.8–253.9)
5–24	11 605 (6430–20 074)	58.4 (32.4–101.1)	51.09 (2857–8422)	25.7 (14.4–42.4)	6496 (3572–11 674)	32.7 (18.0–58.8)
25–44	36 113 (24 132–56 993)	214.8 (143.6–339.0)	15 362 (10 609–23 100)	91.4 (63.1–137.4)	20 751 (13 506–33 895)	123.4 (80.3–201.6)
45–64	24 074 (14 499–41 263)	279.3 (168.2–478.8)	10 471 (6527–17 110)	121.5 (75.7–198.5)	13 603 (7963–24 159)	157.8 (92.4–280.3)
65	22 966 (9789–40 946)	761.3 (324.5–1357.2)	9921 (4350–17 203)	328.9 (144.2–570.2)	13 045 (54.35–23 748)	432.4 (180.2–787.2)
<5	33 415 (21 545–46 033)	576.7 (371.8–794.4)	15 363 (10 386–20 094)	265.1 (179.2–346.8)	18 052 (11 152–25 943)	311.5 (192.5–447.7)
5	94 758 (53 445–160 703)	196.2 (110.6–332.7)	40 863 (23 848–66 376)	84.6 (49.4–137.4)	53 895 (29 637–94 345)	111.6 (61.4–195.3)
All	128 173 (74 868–208 092)	236.9 (138.4–384.7)	56 226 (34 135–87 290)	103.9 (63.1–161.4)	71 947 (40 726–120 820)	133.0 (75.3–223.3)

Abbreviation: CI, confidence interval.

^aSevere illness is defined as requiring hospitalization, excluding deaths.

^bRates expressed are per 100 000 individuals in the population.

^cObtained from case-based surveillance at 5 facilities and extrapolated nationally.

^dObtained using ratios of respiratory to nonrespiratory (ie, circulatory or nonrespiratory/noncirculatory), from ecological studies.

Table 5. Estimated Mean Annual Number and Rates of Influenza-associated Deaths in South Africa, 2013–2015

Age Group	Influenza-associated Deaths					
	Total		Medically Attended ^d		Nonmedically Attended ^b	
	Number (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^c (95% CI)	Number (95% CI)	Rate ^c (95% CI)
All-respiratory^d						
<1	356 (244–488)	30.0 (20.6–41.2)	178 (129–228)	15.0 (10.9–19.2)	178 (116–257)	15.0 (9.8–21.7)
1–4	140 (93–198)	3.0 (2.0–4.3)	70 (49–92)	1.5 (1.1–2)	70 (45–105)	1.5 (1.0–2.3)
5–24	114 (53–195)	0.6 (0.3–1)	56 (27–90)	0.3 (0.1–0.5)	58 (25–105)	0.3 (0.1–0.5)
25–44	873 (609–1221)	5.2 (3.6–7.3)	428 (312–564)	2.5 (1.9–3.4)	445 (297–654)	2.6 (1.8–3.9)
45–64	1057 (669–1532)	12.3 (7.8–17.8)	518 (340–704)	6.0 (3.9–8.2)	539 (330–823)	6.3 (3.8–9.5)
65	1353 (612–2286)	44.8 (20.3–75.8)	663 (311–1079)	22.0 (10.3–35.8)	690 (302–1202)	22.9 (10.0–39.8)
<5	496 (335–690)	8.6 (5.8–11.9)	248 (176–322)	4.3 (3.0–5.6)	248 (160–364)	4.3 (2.8–6.3)
5	3397 (1994–5182)	7.0 (4.1–10.7)	1665 (1023–2401)	3.4 (2.1–5.0)	1732 (978–2767)	3.6 (2–5.7)
All	3893 (2393–5778)	7.2 (4.4–10.7)	1913 (1232–2678)	3.5 (2.3–5.0)	1980 (1167–3084)	3.7 (2.2–5.7)
All-circulatory^e						
<1	24 (19–57)	2.0 (1.6–4.8)	16 (13–38)	1.3 (1.1–3.2)	8 (6–19)	0.7 (0.5–1.6)
1–4	33 (29–40)	0.7 (0.6–0.9)	22 (19–27)	0.5 (0.4–0.6)	11 (10–13)	0.2 (0.2–0.3)
5–24	26 (15–59)	0.1 (0.1–0.3)	11 (6–25)	0.1 (0–0.1)	15 (9–34)	0.1 (0.0–0.2)
25–44	267 (148–422)	1.6 (0.9–2.5)	115 (64–182)	0.7 (0.4–1.1)	152 (84–240)	0.9 (0.5–1.4)
45–64	821 (523–2097)	9.5 (6.1–24.3)	353 (225–901)	4.1 (2.6–10.5)	468 (298–1195)	5.4 (3.5–13.9)
65	1967 (765–3451)	65.2 (25.4–114.4)	846 (329–1484)	28.0 (10.9–49.2)	1121 (436–1967)	37.2 (14.5–65.2)
<5	57 (48–99)	1.0 (0.8–1.7)	38 (32–66)	0.7 (0.6–1.1)	19 (16–33)	0.3 (0.3–0.6)
5	3081 (1519–6063)	6.4 (3.1–12.6)	1325 (653–2607)	2.7 (1.4–5.4)	1756 (866–3455)	3.6 (1.8–7.2)
All	3138 (1561–6138)	5.8 (2.9–11.3)	1363 (678–2666)	2.5 (1.3–4.9)	1775 (883–3472)	3.3 (1.6–6.4)
Nonrespiratory and noncirculatory^e						
<1	572 (306–753)	48.3 (25.8–63.5)	246 (132–324)	20.8 (11.1–27.3)	326 (174–429)	27.5 (14.7–36.2)
1–4	105 (38–121)	2.3 (0.8–2.6)	45 (16–52)	1.0 (0.3–1.1)	60 (22–69)	1.3 (0.5–1.5)
5–24	267 (233–460)	1.3 (1.2–2.3)	96 (84–165)	0.5 (0.4–0.8)	171 (149–295)	0.9 (0.8–1.5)
25–44	1964 (1277–3652)	11.7 (7.6–21.7)	707 (460–1315)	4.2 (2.7–7.8)	1257 (817–2337)	7.5 (4.9–13.9)

Age Group	Total			Influenza-associated Deaths			Nonmedically Attended ^b		
	Number (95% CI)	Rate ^b (95% CI)	Number (95% CI)	Rate ^c (95% CI)	Number (95% CI)	Rate ^c (95% CI)	Number (95% CI)	Rate ^c (95% CI)	
45–64	758 (366–1449)	8.8 (4.2–16.8)	273 (132–522)	3.2 (1.5–6.1)	485 (234–927)	5.6 (2.7–10.8)			
65	839 (332–1761)	27.8 (11–58.4)	302 (119–634)	10.0 (3.9–21)	537 (212–1127)	17.8 (7–37.4)			
<5	677 (330–867)	11.7 (5.7–15)	291 (142–373)	5.0 (2.5–6.4)	386 (188–494)	6.7 (3.2–8.5)			
5	3828 (2091–7430)	7.9 (4.3–15.4)	1378 (753–2675)	2.9 (1.6–5.5)	2450 (1338–4755)	5.1 (2.8–9.8)			
All	4505 (2418–8346)	8.3 (4.5–15.4)	1669 (896–3092)	3.1 (1.7–5.7)	2836 (1522–5254)	5.2 (2.8–9.7)			
All									
<1	952 (570–1301)	80.3 (48.1–109.8)	440 (274–591)	37.1 (23.1–49.9)	512 (297–707)	43.2 (25.1–59.6)			
1–4	278 (161–362)	6.0 (3.5–7.9)	137 (84–173)	3.0 (1.8–3.8)	141 (77–188)	3.1 (1.7–4.1)			
5–24	407 (301–714)	2.0 (1.5–3.6)	163 (117–280)	0.8 (0.6–1.4)	244 (183–434)	1.2 (0.9–2.2)			
25–44	3104 (2038–5304)	18.5 (12.1–31.6)	1250 (838–2065)	7.4 (5–12.3)	1854 (1201–3237)	11 (7.1–19.3)			
45–64	2636 (1564–5089)	30.6 (18.1–59.1)	1144 (699–2132)	13.3 (8.1–24.7)	1492 (865–2951)	17.3 (10.0–34.2)			
65	4159 (1713–7515)	137.9 (56.8–249.1)	1811 (762–3205)	60.0 (25.3–106.2)	2348 (952–4305)	77.8 (31.6–142.7)			
<5	1230 (715–1661)	21.2 (12.3–28.7)	577 (351–764)	10.0 (6.1–13.2)	653 (365–894)	11.3 (6.3–15.4)			
5	10 306 (5619–18 713)	21.3 (11.6–38.7)	4368 (2436–7701)	9.0 (5.0–15.9)	5938 (3190–10 998)	12.3 (6.6–22.8)			
All	11 536 (6390–20 305)	21.3 (11.8–37.5)	4945 (2815–8455)	9.1 (5.2–15.6)	6591 (3581–11 833)	12.2 (6.6–21.9)			

Abbreviation: CI, confidence interval.

^aMedically attended deaths are defined as occurring in a hospital.

^bNonmedically attended deaths are defined as occurring out of a hospital.

^cRates expressed are per 100 000 individuals in the population.

^dObtained from case-based surveillance at 5 facilities and extrapolated nationally.

^eObtained using ratios of respiratory to nonrespiratory (ie, circulatory or nonrespiratory/noncirculatory), from ecological studies.

Table 6.

Estimated Mean Annual Rates of Influenza-associated, Medically Attended Respiratory Illness From Case-based and Ecological Studies, South Africa, 2013–2015

Age Group (In Years)	Medically Attended, Influenza-associated Respiratory Illness ^a					% Difference (Ecological vs Case Based) ^e
	Case-based ^b Rate (95% CI)	Ecological ^c Rate (95% CI)	% Difference (Ecological vs Case Based) ^e	Case-based ^b Rate (95% CI)	Ecological ^c Rate (95% CI)	
Mild illness						
<5	(ILI) 1743.2 (1406.7–2109.1)	(P&LJ09–J18) ^b 1609.1 (1044.2–2176.6)	-7.7	(N/A)	(All-respiratory, J00–J99) ^b 5142.4 (2646.7–6439.8)	N/A
5	1698.5 (1404.5–2027.7)	1794.4 (651.5–1967.1)	5.6	N/A	5236.8 (1906.5–6315.2)	N/A
All	1703.3 (1404.7–2036.4)	1778.8 (684.8–1984.8)	4.4	N/A	5228.6 (1969.3–6326.0)	N/A
Severe illness^f						
<5	(SARI) 196.8 (138.1–260.0)	(P&LJ09–J18) 181.3 (85.5–237.1)	-7.9	(SRI)	(All-respiratory, J00–J99) 196.4 (112.7–307.7)	-11.1
5	31.2 (14.6–50.7)	41.8 (19.6–47.8)	34.0	220.8 (156.6–286.8)	76.4 (37.7–92.9)	31.5
All	48.8 (27.7–72.9)	53.7 (25.2–63.9)	10.0	75.3 (48.5–105.4)	86.6 (44.1–111.2)	15.0
Deaths^g						
<5	(SARI) 3.2 (2.3–4.2)	(P&LJ09–J18) ^d 3.6 (2.5–4.8)	11.1	(SRI)	(All-respiratory, J00–J99) ^d 4.7 (3.2–5.9)	10.3
5	1.9 (0.9–3.2)	2.1 (1.0–3.4)	9.5	4.3 (3.0–5.6)	3.7 (2.3–5.2)	8.4
All	2.1 (1.2–3.1)	2.2 (1.3–3.3)	6.4	3.5 (2.3–5.0)	3.8 (2.5–5.4)	8.4

Abbreviations: CI, confidence interval; ILI, influenza-like illness; N/A, not applicable; P&L, pneumonia and influenza; SARI, severe, acute respiratory infection; SRI, severe respiratory illness.

^aRates expressed are per 100 000 individuals in the population.

^bRates from case-based studies are extrapolated nationally, 2013–2015.

^cRates from ecological studies are from the NetCare private hospital network, 2013–2015.

^dRates from published ecological studies are from South Africa, 2009–2013 [4].

^ePercentage difference is calculated as: (rate from ecological studies – rate from case-based study) / rate from case-based study × 100.

^fSevere illness, including deaths.

^gMedically attended deaths are defined as occurring in a hospital.

Adjusted by the proportion of individuals with ILI that sought health care in private hospital clinics, among those that sought health care with any private healthcare provider, including private general practitioners.

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