Published in final edited form as:

Clin Infect Dis. 2015 October 01; 61(7): 1063–1070. doi:10.1093/cid/civ448.

Mortality Associated With Seasonal and Pandemic Influenza Among Pregnant and Nonpregnant Women of Childbearing Age in a High-HIV-Prevalence Setting—South Africa, 1999–2009

Stefano Tempia[1,2,3], **Sibongile Walaza**[3,4], **Adam L. Cohen**[1,2], **Claire von Mollendorf**[3,4], **Jocelyn Moyes**[3,4], **Johanna M. McAnerney**[3], and **Cheryl Cohen**[3,4]

[1]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia

[2]Influenza Program, Centers for Disease Control and Prevention, Pretoria

[3]Center for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases of the National Health Laboratory Service, University of the Witwatersrand, Johannesburg, South Africa

[4]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Abstract

Background—Information on the mortality burden associated with seasonal and pandemic influenza virus infection among pregnant women is scarce in most settings, particularly in sub-Saharan Africa where pregnancy and maternal mortality rates as well as human immunodeficiency virus (HIV) prevalence are elevated.

Methods—We used an ecological study design to estimate the seasonal and A(H1N1)pdm09 influenza-associated mortality among pregnant and nonpregnant women of childbearing age (15–49 years) by HIV serostatus during 1999–2009 in South Africa. Mortality rates were expressed per 100 000 person-years.

Correspondence: Stefano Tempia, DVM, MSc, PhD, Center for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, Private Bag X4, Sandringham 2131, Gauteng, South Africa (stefanot@nicd.ac.za).

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Author contributions. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: S. T., C. C., A. L. C. Acquisition, analysis, or interpretation of data: S. T., C. C., A. L. C., S. W., C. v. M., J. M., J. M. M. Drafting of the manuscript. S. T. Critical revision of the manuscript for important intellectual content: S. T., C. C., A. L. C., S.W., C. v. M., J. M., J. M. M. Statistical analysis: S. T.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the affiliated institutions.

Potential conflicts of interest. All authors: No potential conflicts of interest.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Results—During 1999–2009, the estimated mean annual seasonal influenza–associated mortality rates were 12.6 (123 deaths) and 7.3 (914 deaths) among pregnant and nonpregnant women, respectively. Among pregnant women, the estimated mean annual seasonal influenza–associated mortality rates were 74.9 (109 deaths) among HIV-infected and 1.5 (14 deaths) among HIV–uninfected individuals. Among nonpregnant women, the estimated mean annual seasonal influenza–associated mortality rate was 41.2 (824 deaths) among HIV-infected and 0.9 (90 deaths) among HIV-uninfected individuals. Pregnant women experienced an increased risk of seasonal influenza–associated mortality compared with nonpregnant women (relative risk [RR], 2.8; 95% confidence interval [CI], 1.7–3.9). In 2009, the estimated influenza A(H1N1)pdm09–associated mortality rates were 19.3 (181 deaths) and 9.4 (1189 deaths) among pregnant and nonpregnant women, respectively (RR, 3.2; 95% CI, 2.3–4.1).

Conclusions—Among women of childbearing age, the majority of estimated seasonal influenza–associated deaths occurred in HIV-infected individuals. Pregnant women experienced an increased risk of death associated with seasonal and A(H1N1)pdm09 influenza infection compared with nonpregnant women.

Keywords

influenza; HIV; pregnancy; mortality; South Africa

"Those most vulnerable of all to influenza, those most likely of the most likely to die, were pregnant women. And these women were the most likely group to already have other children, so an unknown but enormous number of children lost their mothers", observed John Barry, writing about the 1918 influenza pandemic in *The Great Influenza* (p. 239) [1].

The elevated burden of influenza-associated mortality among pregnant women during influenza pandemics is well documented [2–9]. Although less well described, increased risk of seasonal influenza–associated mortality among pregnant women has been suggested [10], and several studies have described an increased risk of seasonal influenza–associated hospitalization in this group [11–13].

The World Health Organization considers pregnant women to be the top priority group for influenza vaccination because of their increased risk of severe disease and death in addition to complications such as stillbirth, neonatal death, preterm delivery, and decreased birth weight subsequent to influenza infection. In addition, children aged <6 months are not eligible to receive currently licensed influenza vaccines and should be protected against influenza through vaccination of their mothers during pregnancy [14].

The reduction of maternal and child mortality is a key part of the Millennium Development Goals [15, 16], and influenza immunization in pregnancy has been recommended as routine component of antenatal care [17]. However, influenza immunization during pregnancy remains underutilized, especially in low- and middle-income countries.

In 2014, the Board of the Global Alliance for Vaccine and Immunization advocated for more evidence to fund influenza vaccines for pregnant women [18]. However, data on the mortality burden associated with seasonal influenza virus infection among pregnant women remain severely limited in sub-Saharan Africa, where pregnancy and maternal mortality rates as well as human immunodeficiency virus (HIV) prevalence are elevated.

In 2009 in South Africa, there were approximately 1 million pregnant women, accounting for 7.3% of women of childbearing age (15–49 years) [19]. In the same year, the HIV prevalence among pregnant and nonpregnant women of childbearing age was 25.3% and 23.7%, respectively [20].HIV-infected individuals are at increased risk for influenza-associated severe disease and death [21–24] and are also considered an important target group for influenza vaccination [14]. Since 2009, a limited number of doses of influenza vaccine (approximately 1 million doses per year for a population of approximately 53 million people) have been made available in the public sector for high-risk groups, which include young children, the elderly, pregnant or postpartum women, and persons of any age with underlying medical conditions such as heart and lung diseases and HIV infection [25]. Approximately the same number of doses is available annually in the private sector. A better understanding of the burden of influenza-associated mortality among pregnant women in low- and middle-income countries could assist with the prioritization of interventions.

We aimed to estimate the burden and relative risk (RR) of seasonal and A(H1N1)pdm09 influenza-associated mortality among South African pregnant women from 1999 through 2009 using nonpregnant women of childbearing age as a comparison group.

METHODS

Study Population and Definitions

Our study population was South African women of childbearing age (15–49 years). We defined pregnant women as either pregnant or puerperal (within 42 days after childbirth).

Mortality Data and Population Denominators

We obtained data on underlying causes of death among pregnant and nonpregnant women of childbearing age from Statistics South Africa from 1999 through 2009 [26]. For each individual, we evaluated multiple underlying and contributing causes of death. Maternal deaths were obtained using *International Classification of Diseases, Tenth Revision* (*ICD-10*) O codes. Thereafter, we used the *ICD-10* codes to compile monthly mortality time series for all-cause (*ICD-10*: any), all-respiratory (J00–J99), all-circulatory (I00–I99), and pneumonia and influenza (J10–J18; a subset of all-respiratory deaths) deaths among pregnant women and women of childbearing age (pregnant and nonpregnant). We adjusted for annual maternal death underreporting using the estimates provided by the Health Data Advisory and Co-ordination Committee of South Africa [27]. According to these estimates, completeness of reporting ranged between 47% and 71% over the study period [28]. To obtain the number of deaths among nonpregnant women, we subtracted the monthly adjusted number of deaths among pregnant women from the monthly number of deaths among all women of childbearing age (pregnant and nonpregnant).

Because of the important differences in the age distribution of pregnant and nonpregnant women, we obtained number of deaths and population denominators by pregnancy status in 5 equal age groups (15–21, 22–28, 29–35, 36–42, and 43–49 years) to allow us to compare age-standardized mortality rates between pregnant and nonpregnant women. Midyear population denominators were obtained from Statistics South Africa [19], and estimates of HIV prevalence and highly active antiretroviral therapy (HAART) coverage among HIV-infected pregnant and nonpregnant women by year and age group were obtained from the Actuarial Society of South Africa AIDS and Demographic Model [20].

Influenza Surveillance Data

Prior to 2002, we obtained influenza virus data from influenza-like illness surveillance implemented by the National Institute for Communicable Diseases, a division of the National Health Laboratory Services (NHLS), South Africa [29]. From 2002 to 2009, we acquired influenza virologic data from a national database (the NHLS corporate data warehouse) that includes all patients tested by the NHLS laboratory network.

Estimation of Influenza-Associated Mortality

We conducted a 2-stage analysis; in the first stage we estimated the national mortality burden of influenza among pregnant and nonpregnant women of childbearing age in South Africa, and in the second stage we inferred the proportionate burden experienced by HIV-infected and HIV-uninfected individuals using a previously developed methodology [21, 30].

In the first stage, to estimate seasonal and pandemic influenza-associated mortality, we fitted regression models using a Poisson distribution and an identity link [21, 30] to the number of monthly deaths among pregnant and nonpregnant women. The small number of deaths among pregnant women did not allow us to obtain age group–specific estimates of influenza-associated mortality. Hence, an overall estimate of influenza-associated mortality among pregnant women aged 15–49 years was obtained. Conversely, for nonpregnant women, available data allowed us to obtain estimates of influenza-associated mortality within the age groups previously reported. The full model (model 1) included covariates for time trends and seasonal variation as well as viral circulation. Model specification and selection procedures are reported in the Supplementary Material.

In South Africa, the diagnosis of AIDS is rarely coded on the death certificate [26], hindering direct estimation of influenza-associated mortality by HIV status. To assess the proportionate mortality burden of influenza among HIV-infected and HIV-uninfected individuals, we used a previously developed methodology [21, 30] that leverages the increasing trend in HIV prevalence in South Africa. The rationale is that if HIV is a risk factor for influenza-associated mortality, then influenza-related mortality rates should increase over time proportionally to the observed increase in HIV prevalence. Our approach also controls for increasing HAART coverage, which may decrease the severity of influenza in HIV-infected patients [31]. In this second-stage analysis, we fit regression models (model 2) to annual estimates of influenza-associated excess mortality rates obtained from model 1, including terms for HIV prevalence and HAART coverage, time trends, and dominant influenza subtypes [21, 30]. Model specification, selection procedures, and full model results are provided in Supplementary Table 1.

Standardization of Influenza-Associated Mortality Rates

We used indirect standardization (using nonpregnant women as the standard population) to compare the rates of influenza-associated mortality between pregnant and nonpregnant women. The method used for annual standardization of rates is provided in the Supplementary Material.

Rates were expressed per 100 000 person-years. The statistical analysis was implemented using Stata software, version 12.1 (StataCorp, College Station, Texas).

Ethical Considerations

Because this analysis used only publicly available mortality data and de-identified and aggregated laboratory data, the analysis was considered to be exempt from human subjects ethics review.

RESULTS

Population and Mortality Data

In South Africa in 2009, there were approximately 13.7 million women of childbearing age, of whom approximately 1 million were pregnant. Over the study period, the pregnancy rates among women of childbearing age slowly declined from 9.6% in 1999 to 7.3% in 2009. Pregnancy rates were highest among women aged 25–29 years (12.5%) and lowest among women aged 45–49 years (0.6%). The median age was 26 and 37 years among pregnant and nonpregnant women, respectively.

Among women of childbearing age, the HIV prevalence increased from 10.5% in 1999 to 22.8% in 2004, plateauing thereafter. In the same group, the HAART coverage among HIV-infected individuals progressively increased from 0.9% in 2004 to 14.3% in 2009. Over the study period, the HIV prevalence and HAART coverage were similar among pregnant and nonpregnant women.

During 1999–2009, a mean of 3431 (range, 2434–3945) deaths were reported annually among pregnant women, of which 1168 (34.0%) were attributable to respiratory and 432 (12.6%) to circulatory causes of death. Among nonpregnant women, the mean annual number of deaths was 61 942 (range, 31 349–76 651), of which 20 183 (32.6%) were attributable to respiratory and 8605 (13.9%) to circulatory causes of death.

Respiratory deaths among pregnant and nonpregnant women were seasonal, with peaks observed during the winter months (May–August). In 2009 a second peak of mortality was observed following the introduction of influenza A(H1N1)pdm09 (Figure 1*A* and 1*B*). Overall, mortality rates increased from 1999 to 2004 following the increasing HIV prevalence in the population and decreased thereafter concomitantly with the progressive rollout of HAART. A similar pattern was observed among the other underlying causes of death evaluated in this study (data not shown).

Influenza Laboratory Surveillance

A mean of 3337 (range, 227–15 321) samples were tested for influenza annually. The mean annual number of specimens testing positive for influenza was 988 (30%). Over the study period, the influenza season peaked between June and August, with 10 of the 11 years experiencing peak activity (highest detection rate) in June–July (Figure 1*C*). In 2009, a first wave of influenza A(H3N2) peaked in June, followed by a second wave of influenza A(H1N1)pdm09 that peaked in August.

Influenza-Associated Mortality

During 1999–2009, the estimated mean annual all-cause seasonal influenza–associated mortality rates obtained from model 1 were 12.6 (123 deaths) and 7.3 (914 deaths) among pregnant and nonpregnant women, respectively (Table 1). Among pregnant women, the estimated mean annual seasonal influenza–associated mortality rates obtained from model 2 were 74.9 (109 deaths) and 1.5 (14 deaths) among HIV-infected and HIV-uninfected individuals, respectively. Also using model 2, among nonpregnant women the estimated mean annual seasonal influenza–associated mortality rate was 41.2 (824 deaths) among HIV-infected and 0.9 (90 deaths) among HIV-uninfected individuals. Overall, pregnant women experienced an increased risk of seasonal influenza–associated mortality compared with nonpregnant women (all-cause HIV-adjusted and age-standardized RR, 2.8; 95% confidence interval [CI], 1.7–3.9). The estimated risk of influenza-associated mortality related to pregnancy was similar among HIV-uninfected (all-cause age-standardized RR, 2.4; 95% CI, 2.1–2.7) and HIV-infected individuals (all-cause age-standardized RR, 2.9; 95% CI, 2.1–3.7). A similar pattern was observed for the other underlying causes of death evaluated in this study (Table 1).

In 2009 we estimated 113 all-cause seasonal influenza–associated deaths among pregnant women, among whom 84 (74%) were HIV-infected. In the same year, we estimated 792 all-cause seasonal influenza–associated deaths among nonpregnant women, of whom 617 (78%) were HIV-infected. In 2009 the estimated all-cause influenza A(H1N1)pdm09–associated mortality rates obtained from model 1 were 19.3 (181 deaths) and 9.4 (1189 deaths) among pregnant and nonpregnant women, respectively (Table 2). Pregnant women had an estimated increased risk of influenza A(H1N1)pdm09–associated mortality compared with nonpregnant women (all cause age-standardized RR, 3.2; 95% CI, 2.3–4.1). This risk was similar to that observed for seasonal influenza over the study period. A similar pattern was observed for the other underlying cause of death evaluated in this study (Table 2).

The estimated risk of seasonal and A(H1N1)pdm09 influenza–associated mortality during pregnancy increased after age standardization and was highest, but not statistically different, among circulatory deaths compared to the other causes of death evaluated in this study (Tables 1 and 2).

DISCUSSION

We provide estimates of seasonal and A(H1N1)pdm09 influenza–associated mortality among pregnant and nonpregnant women of childbearing age in a high-HIV-prevalence setting in Africa. Among women of childbearing age, the majority of estimated seasonal influenza–associated deaths occurred among HIV-infected individuals. Pregnant women experienced an approximately 3-fold increased risk of death associated with seasonal and A(H1N1)pdm09 influenza infection compared with nonpregnant women.

We estimated that approximately 90% of seasonal influenza–associated deaths occurred among HIV-infected women irrespective of the pregnancy status. HIV infection is a known risk factor for severe outcome due to influenza virus infection [21–24, 30]. Modeling and case-based studies conducted in South Africa reported a similar proportion of HIV-infected individuals (80%–90%) among seasonal influenza–associated deaths and hospitalizations in individuals 19–44 years of age [24, 30]. In 2009 in South Africa, 25 laboratory-confirmed influenza A(H1N1)pdm09 deaths were reported among pregnant or puerperal women. Among those tested, 10 of 14 (71%) were HIV infected [8]. Although in our study we could not estimate influenza A(H1N1)pdm09–associated mortality by HIV status, in 2009 we estimated that 74% of seasonal influenza–associated deaths among pregnant women were HIV infected. A meta-analysis conducted in 2013 reported nonsignificant association between HIV infection and increased risk of seasonal and pandemic influenza-associated mortality [32]; however, for seasonal influenza only 1 study was included in the review, and recent data on increased risk of influenza-associated mortality among HIV-infected individuals in South Africa [24] were not included.

Overall, pregnant women experienced an estimated increased risk of seasonal influenza–associated mortality compared to nonpregnant women. Whereas HIV-infected pregnant and nonpregnant women experienced an increased risk of influenza-associated mortality compared with HIV-uninfected individuals, the increased risk associated with pregnancy was similar among HIV-infected and HIV-uninfected women. To our knowledge, there are no studies that quantify the risk of seasonal influenza–associated mortality during pregnancy. In a systematic review conducted in 2013, no conclusions could be made about the risk of seasonal influenza–associated mortality during pregnancy as no data were available, highlighting the lack of knowledge in this domain and the need for further studies [32]. Nonetheless, assessing the risk of influenza-associated mortality during pregnancy using a case-based cohort study design may not be feasible given the large sample size needed to investigate such a rare event.

Pregnant women also experienced an estimated increased risk of influenza A(H1N1)pdm09–associated mortality compared with nonpregnant women. Our estimated crude risk of influenza A(H1N1)pdm09–associated mortality (all-cause RR, 1.7) during pregnancy was similar to the crude risk (RR, 1.9) reported in a global pooled analysis of risk factors for severe outcomes following influenza A(H1N1)pdm09 infection [9].

Although the estimated number of influenza A(H1N1) pdm09–associated deaths was higher compared to seasonal influenza, the estimated RR of influenza-associated mortality during pregnancy was similar for seasonal and A(H1N1)pdm09 influenza (all-cause, age-standardized RR, 2.8 vs 3.2, respectively; with overlapping CIs). This suggests that the estimated higher number of influenza A(H1N1)pdm09–associated deaths compared to seasonal influenza deaths among pregnant women in 2009 may be due to the observed heavy burden of the pandemic virus among adolescents and young adults (the age group in which the majority of pregnancies occur) rather than an increased lethality of the pandemic virus during pregnancy. An age shift of the burden of influenza A(H1N1)pdm09 toward younger individuals has been reported in several countries [33], including South Africa [30, 34]. Similarly, a heavy burden of the pandemic influenza viruses of the 20th century among adolescents and young adults has been documented [35]. Nonetheless, it cannot be excluded that highly virulent influenza viruses could disproportionately affect pregnant women. Although appropriate nonpregnant control groups were generally not available, mortality rates among pregnant women during the severe 1918 and 1957 pandemics were reported to be “abnormally” high [2, 4]. Conversely, the severity of influenza A(H1N1)pdm09 in 2009 has been reported to be similar overall to those of seasonal influenza [24, 34, 36].

Our study has limitations that warrant discussion. First, accurate estimates of maternal mortality remain difficult to obtain. Although we adjusted for underreporting of maternal deaths, the uncertainty associated with this adjustment could not be estimated. Nonetheless, our estimates are similar to global independent estimates of maternal mortality for South Africa [37–39]. Second, due to the ecological nature of our study, we could not assess the effect of comorbidities or behavioral factors on the estimated risk of influenza-associated mortality during pregnancy. Third, because of poor recording of HIV infection in the death register in the early years of our study, we utilized indirect methods to assess the mortality burden among HIV-infected and HIV-uninfected individuals. The HIV epidemic in South Africa is considered to be a major factor responsible for the increased mortality rates observed over the years [40]; however, the lack of time-series data for other potential comorbidities/risk factors may have resulted in overestimating the increased risk of death associated with HIV infection. Last, whereas increased risk of hospitalization and death has been reported during the second and third trimester of pregnancy and among women who were <4 weeks postpartum [12, 13, 32], we could not estimate such differential risk in our study as this information was not available.

In conclusion, we estimated that HIV-infected and pregnant women were at increased risk of influenza-associated mortality. The trivalent inactivated influenza vaccine has been shown to confer protection from influenza infection in pregnant women and their newborns [41, 42] and has also been demonstrated to be effective in HIV-infected adults [43], including pregnant women [44]. The increased risk of influenza-associated mortality among pregnant women and HIV-infected individuals found in this study indicates that influenza immunization may be most beneficial in these groups. Targeting influenza vaccination specifically in these high-risk groups may be particularly relevant in low- and middle-income countries where pregnancy and maternal mortality rates as well as HIV prevalence are elevated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Barry, JM. The great influenza: the story of the deadliest pandemic in history. Penguin Books Ltd; 2005. p. 239
2. Harris JW. Influenza occurring in pregnant women: a statistical study of thirteen hundred and fifty cases. JAMA. 1919; 72:978–80.
3. Woolston JM, Conley DO. Epidemic pneumonia (Spanish influenza) in pregnancy: effect in one hundred and one cases. JAMA. 1918; 71:1898–9.
4. Freeman DW, Barno A. Deaths from Asian influenza associated with pregnancy. Am J Obstet Gynecol. 1959; 78:1172–5. [PubMed: 13824729]
5. Greenberg M, Jacobziner H, Pakter J, et al. Maternal mortality in the epidemic of Asian influenza, New York City, 1957. Am J Obstet Gynecol. 1958; 76:897–902. [PubMed: 13583035]
6. Martin CM, Kunin CM, Gottlieb LS, et al. Asian influenza A in Boston, 1957–1958. I. Observations in thirty-two influenza associated fatal cases. AMA Arch Intern Med. 1959; 103:515–31. [PubMed: 13636470]
7. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009; 374:451–8. [PubMed: 19643469]
8. Archer BN, Cohen C, Naidoo D, et al. Interim report on pandemic H1N1 influenza virus infections in South Africa, April to October 2009: epidemiology and factors associated with fatal cases. Euro Surveill. 2009; 14:pii:19369.
9. Van Kerkhove MD, Vandemaele KAH, Shinde V, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med. 2011; 8:e1001053. [PubMed: 21750667]
10. Mak TK, Mangtani P, Leese J, et al. Influenza vaccination in pregnancy: current evidence and selected national policies. Lancet Infect Dis. 2008; 8:44–52. [PubMed: 18156088]
11. Neuzil KM, Reed GW, Mitchel EF, et al. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol. 1998; 148:1094–102. [PubMed: 9850132]
12. Neuzil KM, Reed GW, Mitchel EF, et al. Influenza-associated morbidity and mortality in young and middle-aged women. JAMA. 1999; 281:901–7. [PubMed: 10078486]
13. Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of person hospitalized with acute respiratory diseases during influenza epidemics in Houston, 1978–1981. Am Rev Respir Dis. 1987; 136:550–5. [PubMed: 3631727]
14. World Health Organization. Vaccines against influenza. WHO position paper—November 2012. Wkly Epidemiol Rec. 2012; 47:461–76.
15. United Nations. [Accessed 17 June 2015] Millennium Development Goals and beyond 2015—Goal 5: improve maternal health. Available at: http://www.un.org/millenniumgoals/pdf/Goal_5_fs.pdf
16. United Nations. [Accessed 17 June 2015] Millennium Development Goals and beyond 2015—Goal 4: reduce child mortality. Available at: http://www.un.org/millenniumgoals/pdf/Goal_4_fs.pdf
17. Steinhoff MC, MacDonald N, Pfeifer D, et al. Influenza vaccine in pregnancy: policy and research strategies. Lancet. 2014; 383:1611–13. [PubMed: 24814446]
18. World Health Organization. Meeting of the strategic advisory group of experts on immunization, April 2014—conclusion and recommendations. Wkly Epidemiol Rec. 2014; 21:221–36.
19. Statistics South Africa. [Accessed 17 June 2015] Population statistics. Available at: http://www.statssa.gov.za/?s=census&sitem=publications
20. Actuarial Society of South Africa (ASSA). [Accessed 17 June 2015] AIDS and demographic model. Available at: http://www.actuarialsociety.org.za/Societyactivities/CommitteeActivities/AidsCommittee/Models.aspx
21. Tempia S, Walaza S, Viboud C, et al. Mortality associated with seasonal and pandemic influenza and respiratory syncytial virus among children <5 years of age in a high HIV prevalence setting—South Africa, 1998–2009. Clin Infect Dis. 2014; 58:1241–9. [PubMed: 24567249]
22. Sheth AN, Althoff KN, Brooks JT. Influenza susceptibility, severity, and shedding in HIV-infected adults: a review of the literature. Clin Infect Dis. 2011; 52:219–27. [PubMed: 21288848]

23. Ope MO, Katz MA, Aura B, et al. Risk factors for hospitalized seasonal influenza in rural western Kenya. PLoS One. 2011; 6:e20111. [PubMed: 21637856]

24. Cohen C, Moyes J, Tempia S, et al. Severe influenza-associated lower respiratory tract infection in a high HIV-prevalence setting—South Africa, 2009–2011. Emerg Infect Dis. 2013; 19:1766–74. [PubMed: 24209781]

25. Schoub B. Recommendations pertaining to the use of viral vaccines: influenza 2013. S Afr Med J. 2013; 103:80.

26. Statistics South Africa. Mortality and cause of death in South Africa, 1999 through 2009. Pretoria: Statistics South Africa; 2009.

27. Medical Research Council. [Accessed 17 June 2015] Health Data Advisory and Co-Ordination Committee (HDACC) Report, November 2011. Available at: http://www.poa.gov.za/Outcome2/Supporting%20Documentation/Doc%201%20HDACC%20Final%20Report%20Submitted%2002%20November%202011%20(2).pdf

28. Bradshaw, D., Dorrington, R., Laubscher, R. Rapid mortality surveillance report 2011. Burden of Disease Research Unit, Medical Research Council; Available at: http://www.mrc.ac.za/bod/RapidMortality2011.pdf [Accessed 17 June 2015]

29. McAnerney JM, Cohen C, Moyes J, et al. Twenty-five years of outpatient influenza surveillance in South Africa (1984–2008). J Infect Dis. 2012; 206(suppl 1):S153–8. [PubMed: 23169963]

30. Tempia S, Walaza S, Viboud C, et al. Deaths associated with respiratory syncytial and influenza viruses among persons ≥5 years of age in HIV-prevalent area, South Africa, 1998–2009. Emerg Infect Dis. 2015; 21:600–8. [PubMed: 25811455]

31. Cohen C, Simonsen L, Sample J, et al. Influenza-related mortality among adults aged 25–54 years with AIDS in South Africa and the United States of America. Clin Infect Dis. 2012; 55:996–1003. [PubMed: 22715173]

32. Mertz D, Kim TH, Johnstone J, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ. 2013; 347:f5061. [PubMed: 23974637]

33. Simonsen L, Spreeuwenberg P, Lustig R, et al. Global mortality estimates for the 2009 influenza influenza pandemic from the GLaMOR project: a modeling study. PLoS Med. 2013; 10:e1001558. [PubMed: 24302890]

34. Cohen AL, Hellferscee O, Pretorius M, et al. Epidemiology of influenza virus types and subtypes in South Africa, 2009–2012. Emerg Infect Dis. 2014; 20:1162–9. [PubMed: 24960314]

35. Simonsen L, Clarke MJ, Schonberger LB, et al. Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. J Infect Dis. 1998; 178:53–60. [PubMed: 9652423]

36. Hayward AC, Fragaszy EB, Bermingham A, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. Lancet Respir Med. 2014; 2:445–54. [PubMed: 24717637]

37. United Nations Population Fund. Trends in maternal mortality: 1990 to 2010. WHO, UNICEF, UNFPA and The World Bank estimates; Available at: https://www.unfpa.org/webdav/site/global/shared/documents/publications/2012/Trends_in_maternal_mortality_A4-1.pdf [Accessed 17 June 2015]

38. World Health Organization. [Accessed 17 June 2015] WHO maternal mortality estimates 1990–2010, country profile: South Africa. Available at: http://www.who.int/gho/maternal_health/countries/zaf.xls

39. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, et al. Global, regional and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014; 384:980–1004. [PubMed: 24797575]

40. Bradshaw, D., Pillay-Van Wyk, V., Laubscher, R., et al. [Accessed 17 June 2015] Causes of death for South Africa: challenges and possibilities for improvement. Available at: http://www.mrc.ac.za/bod/cause_death_statsSA.pdf

41. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med. 2008; 359:1555–64. [PubMed: 18799552]

42. Eick AA, Uyeki TM, Klimov A, et al. Maternal influenza vaccination and effect on influenza virus in young infants. Arch Pediatr Adolesc Med. 2011; 165:104–11. [PubMed: 20921345]

43. Madhi SA, Maskew M, Koen A, et al. Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus: double blind, randomized clinical trial of efficacy, immunogenicity, and safety. Clin Infect Dis. 2011; 52:128–37. [PubMed: 21148531]

44. Madhi SA, Cutland CL, Kuwanda L, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med. 2014; 371:918–31. [PubMed: 25184864]

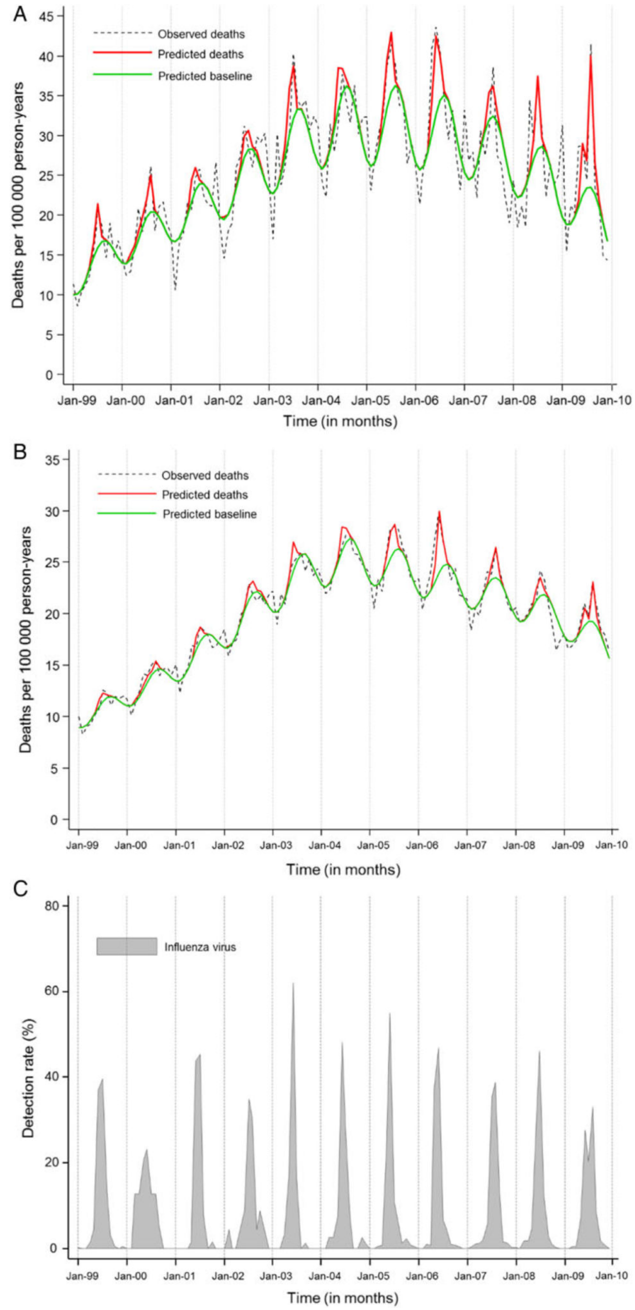

Figure 1.

Monthly mortality and influenza virus detection rates in South Africa, 1999–2009. A, Observed all-respiratory deaths, predicted deaths, and predicted baseline (Model 1) among pregnant women of childbearing age (15–49 years of age). B, Observed all-respiratory deaths, predicted deaths, and predicted baseline (Model 1) among nonpregnant women of childbearing age (15–49 years of age). C, Influenza detection rate (ie, monthly number of positive specimens divided by total specimens). Observed deaths are adjusted for maternal death underreporting.

Table 1

Estimated Mean Annual Seasonal Influenza–Associated Mortality Among Pregnant and Nonpregnant Women of Childbearing Age (15–49 Years) by Human Immunodeficiency Virus Status and Relative Risk for Mortality Associated With Pregnancy in South Africa, 1999–2009[a]

	Estimated Mean Annual Seasonal Influenza–Associated Deaths (1999–2009)					
	Pregnant		Nonpregnant		Crude Relative Risk (Pregnant vs Nonpregnant) (95% CI)	Age-Standardized Relative Risk (Pregnant vs Nonpregnant) (95% CI)
Cause of Death	No. (95% CI)	Rate[b] (95% CI)	No. (95% CI)	Rate[b] (95% CI)		
All-cause						
HIV$^-$	14 (8–20)	1.5 (.9–2.1)	90 (57–123)	0.9 (.6–1.2)	1.6 (1.2–2.0)	2.4 (2.1–2.7)
HIV$^+$	109 (62–156)	74.9 (42.7–107.1)	824 (519–1129)	41.2 (26.0–56.4)	1.8 (1.3–2.3)	2.9 (2.1–3.7)
Total	123 (70–176)	12.6 (7.2–18.0)	914 (576–1252)	7.3 (4.6–10.0)	1.7 (1.2–2.2)[c]	2.8 (1.7–3.9)[c]
All-respiratory						
HIV$^-$	7 (3–11)	0.9 (.4–1.4)	45 (25–65)	0.5 (.3–.7)	1.8 (1.3–2.3)	2.3 (1.8–2.8)
HIV$^+$	60 (27–93)	41.3 (18.6–64.0)	410 (226–595)	20.5 (11.3–29.7)	2.0 (1.4–2.6)	2.9 (1.9–3.9)
Total	67 (30–104)	6.8 (3.1–10.5)	455 (250–660)	3.8 (2.1–5.5)	1.9 (1.2–2.6)[c]	2.8 (1.6–4.0)[c]
All-circulatory						
HIV$^-$	3 (1–5)	0.4 (.2–.6)	16 (8–14)	0.2 (.1–.3)	2.1 (1.2–3.0)	3.9 (2.9–5.2)
HIV$^+$	28 (12–44)	19.3 (8.1–30.5)	142 (67–217)	7.4 (3.5–11.3)	2.6 (1.6–3.6)	4.1 (3.6–4.5)
Total	31 (13–49)	3.1 (1.3–4.9)	158 (74–242)	1.3 (.6–2.0)	2.4 (1.5–3.3)[c]	4.0 (3.7–4.4)[c]
Pneumonia and influenza						
HIV$^-$	6 (3–9)	0.8 (.4–1.2)	35 (20–50)	0.4 (.2–.6)	1.9 (1.1–2.7)	2.7 (1.9–3.5)
HIV$^+$	53 (25–81)	36.8 (17.3–56.3)	320 (182–458)	16.9 (9.6–24.2)	2.2 (1.3–3.1)	3.1 (2.2–4.0)

Cause of Death	Estimated Mean Annual Seasonal Influenza–Associated Deaths (1999–2009)				Crude Relative Risk (Pregnant vs Nonpregnant) (95% CI)	Age-Standardized Relative Risk (Pregnant vs Nonpregnant) (95% CI)
	Pregnant		Nonpregnant			
	No. (95% CI)	Rate[b] (95% CI)	No. (95% CI)	Rate[b] (95% CI)		
Total	59 (28–90)	6.1 (2.9–9.3)	355 (202–508)	2.9 (1.7–4.1)	2.1 (1.3–2.9)[c]	2.9 (1.8–4.0)[c]

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

[a]Estimated from model 1 (overall deaths) and model 2 (deaths by HIV status).

[b]Crude death rates per 100 000 person-years.

[c]Relative risk adjusted for HIV status.

Table 2

Estimated Influenza A(H1N1)pdm09–Associated Mortality Among Pregnant and Nonpregnant Women of Childbearing Age (15–49 Years) and Relative Risk for Mortality Associated With Pregnancy in South Africa, 2009[a]

	Estimated Influenza A(H1N1)pdm09–Associated Deaths in 2009					
	Pregnant		Nonpregnant			
Cause of Death	**No. (95% CI)**	**Rate[b] (95% CI)**	**No. (95% CI)**	**Rate[b] (95% CI)**	**Crude Relative Risk (Pregnant vs Nonpregnant) (95% CI)**	**Age-Standardized Relative Risk (Pregnant vs Nonpregnant) (95% CI)**
All-cause	181 (103–259)	19.3 (11.0–27.6)	1189 (773–1605)	9.4 (6.1–12.7)	2.1 (1.3–2.9)	3.2 (2.3–4.1)
All-respiratory	104 (51–157)	11.0 (5.4–16.6)	634 (368–900)	5.0 (2.9–7.1)	2.2 (1.3–3.1)	3.3 (2.1–4.5)
All-circulatory	41 (17–65)	4.4 (1.8–7.0)	237 (116–358)	1.9 (.9–2.9)	2.3 (1.3–3.3)	4.2 (3.3–5.1)
Pneumonia and influenza	82 (39–125)	8.8 (4.2–13.4)	457 (260–654)	3.6 (2.1–5.1)	2.4 (1.4–3.4)	3.3 (2.2–4.4)

Abbreviation: CI, confidence interval.

[a]Estimated from model 1 (overall deaths).

[b]Crude death rates per 100 000 person-years.