**METHODS**

**Estimation of influenza- and RSV-associated mortality**

Different modeling approaches have been used to estimate influenza associated mortality, including (i) peri- and summer-season rate-difference models [[[1]](#endnote-1),[[2]](#endnote-2)], (ii) Serfling cyclical regression models, which do not incorporate influenza viral surveillance data [[[3]](#endnote-3),[[4]](#endnote-4)], (iii) autoregressive integrated moving average (ARIMA) models, which do not incorporate influenza viral surveillance data [[[5]](#endnote-5),[[6]](#endnote-6)] and (iv) regression models (Poisson, Negative-Binomial or linear), which do incorporate influenza surveillance data [[[7]](#endnote-7),[[8]](#endnote-8),[[9]](#endnote-9)]. A study comparing the four methods found comparable estimates of influenza associated mortality over 31 influenza seasons in the United States except for estimates from the summer-season rate-difference model, which were consistently higher [[[10]](#endnote-10)]. Regression models that incorporate viral covariates have been suggested as the preferred method when at least 5 years of mortality and viral surveillance data are available and the mortality associated with multiple pathogens is estimated [10].

In our study, we fitted age-specific Poisson regression models (with an identity link) to monthly deaths. The identity link was selected because it is considered the most biologically plausible link to model the impact of pathogen circulation on mortality [[[11]](#endnote-11),[[12]](#endnote-12),[[13]](#endnote-13),[[14]](#endnote-14)]. Indeed, an identity link assumes additive (rather than multiplicative) effects of different pathogens on mortality. The full model (model 1) included covariates for time trends and seasonal variation as well as viral circulation as follows:



 (1)

*E(Yi)* represents the age-specific number of deaths during a particular month *i*, *β0* is the model constant, *β1* to *β4* are coefficients associated with time trends (linear to quartic polynomial terms) included to account for annual variation of number of deaths, *β5* and *β6* are coefficients associated with harmonic terms included to account for seasonal variations, *β7* to *β9* are coefficients associated with the proportion of specimens testing positive for respiratory viruses (seasonal influenza: A(H1N1), A(H3N2) and B; pandemic influenza: A(H1N1)pdm09; and RSV) and *εi* is the error term. Model selection procedures included the assessment of model fit considering the inclusion of polynomial (1st to 6th degree) and harmonic terms. The final model (model 1) was that for which the Akaike value was minimized, that is, the model that provided best fit to the data whilst maintaining parsimony. We also considered b-spline instead of polynomial terms but polynomial terms provided the best fit to the South African data.

In South Africa, the diagnosis of AIDS is rarely coded on the death certificate [[[15]](#endnote-15)]. To assess changes in annual seasonal influenza excess mortality rates (as obtained from model 1) in relation to the HIV prevalence in the population and the HAART coverage among HIV-infected individuals over the years, we fitted separate multivariable Poisson regression models (model 2) for annual all-respiratory and P&I seasonal influenza-associated mortality rates by age group. The following model was used:

 (2)

*E(Yi/Ni)* represents the age-specific influenza-associated mortality rate during a particular year *i*, *β0* is the model constant, *β1* and *β2* are coefficients associated with time trends (linear and quadratic) included to account for potential variations of health indicators not associated with HIV or HAART, *β3* is the coefficient associated with dominant seasonal influenza type/subtype each year (A(H3N2), A(H1N1) and B; treated as categorical variable with A(H3N2)-dominant years as reference group), *β4* is the coefficient associated with age- and year-specific HIV prevalence in the population, *β5* is the coefficients associated with age- and year-specific HAART coverage among HIV-infected individuals and *εi* is the error term. Similar models, with the exclusion of the dominant influenza types/subtypes covariate, were used for RSV-associated mortality rates.

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