To date, even the most sophisticated mathematical approaches for influenza pandemic planning do not consider basic features of antiviral pharmacology. Indeed, the best strategy typically considered drug effect as either "on" or "off" in terms of viral transmission, with little consideration of variability in PK/PD. Accordingly, we sought to incorporate antiviral pharmacology into influenza epidemiology models in a semi-mechanistic manner, thus gaining a greater understanding of the potential impact that PK and PD variability has on disease resolution. This approach may provide an improved understanding of the potential impact which differing antiviral strategies (such as dose and deployment) may have on the population burden of influenza infection.

METHODS

Epidemiological Model

We used a stochastic susceptible-exposed-infected-recovered [SERR] epidemiologic model, adapted to incorporate the impact of antiviral therapy. (see Figure 2)

\[
\frac{dS}{dt} = -\beta SI
\]

\[
\frac{dE}{dt} = \beta SI - \gamma EI - \delta E
\]

\[
\frac{dI}{dt} = \gamma EI - \delta I - \alpha I
\]

\[
\frac{dR}{dt} = \delta (E + I + R)
\]

Where \(S\) = number in the population susceptible to infection, \(E\) = number in latent stage of infection, \(I\) = infected, and \(R\) = recovered from infection and are immune to reinfection, \(S\), governs the transmission from susceptible to infected pools, \(E\), is composed of both frequency of individual interactions (population density and social behavior), and the probability that an interaction will result in a successful infection in a susceptible individual. \(I\) = is total time from \(S\) to \(E\), \(F\), and \(R\), and \(F\) represents the fraction of the infected population not receiving therapy, or an antiviral with an effectiveness less than or greater than 14.18 mg/h, respectively.

Monte Carlo Simulations

PK and PD/PK distributions described above were inputs for the SERR model simulation scenarios. The scenarios evaluated included the % of the infected population treated with 150 mg or 75 mg twice daily oseltamivir (0.25%, 1%, 5%, 10%, and 25%) and also two possible relapsing or model attack rates of 370/1000 infected (1%) or 750/1000 infected (1.5%), and a higher attack rate of 750/1000 infected (1.5%) (Collazo et al., 2010). Parameters of F were allowed to achieve the required attack rates as outlined in Table 3.

For each scenario, 1000 Monte Carlo simulations (80 seasons) were completed to provide results from the output of the models. The fraction of people who were more than 8000 infected cases in the 100,000 population occurred and the medium attack rate (np<0.05) or 1000 infected cases (0.05<np<0.5) for each season. All simulations were conducted in Berkeley Madonna. Parameter values are outlined in Table 3.

RESULTS

The SERR model has the capacity to provide results in general with prior data on the attack rate of specific strains. Nevertheless, following 1000 simulations (Figure 3b) there is extensive variability between simulated flu seasons and the likelihood of an epidemic occurring, supporting using the mean behavior of the simulation system and the percent of time that a threshold [15% infected population] was exceeded or not.

In Figure 4, when no treatment was provided, 625 of the 1000 simulations resulted in more than 5% of the population being infected with influenza. The overall average number of infected individuals (attack rate) was 750 per 1000. For a virus with higher transmissibility [E=0.25], 970 of 1000 season results had >5% of a population infected, and an overall average attack rate of 675 cases per 1000.

CONCLUSIONS

These results demonstrated that antiviral pharmacology [PK/PD] should be considered as an important component to inform influenza epidemiology models, as oseltamivir dose and variant influenza transmissibility play a key role.

The linkages of PK/PD to influenza epidemiology also suggests that antiviral PK/PD can be used to optimize treatment not only at an individual patient level, but may also now be used to help inform epidemic planning (such as optimal influenza vaccination strategies) to inform containment strategies, and may offer utility for evaluating the potential impact other antivirals.

This work has been extended to health economics in Abstract 1715, linking Pharmacology to the Payor.