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4Flu - an individual based simulation tool to study the effects of vaccination on seasonal influenza in Germany

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Background

Influenza vaccines contain Influenza A and B antigens and are adjusted annually to match the antigenic characteristics of circulating viruses. Before 1985, Influenza B viruses only belonged to the B/Yamagata (B/yam) lineage, but since then, viruses of the antigenically distinct B/Victoria (B/vic) lineage have emerged. Since 2001, both B lineages have co-circulated with the Influenza A subtypes A(H3N2) and A(H1N1). Current trivalent influenza vaccines (TIV) contain antigens of both A subtypes, yet only one B lineage, resulting in frequent vaccine mismatches. Since 2012, the WHO has recommended vaccine strains from both B lineages, paving the way for quadrivalent influenza vaccines (QIV) containing both B lineages. The aim of this study is to model the concomitant transmission of four influenza strains in Germany and to compare the effects of vaccination with TIV and QIV on infection incidence.

Materials and method

We have developed an individual-based stochastic simulation model for the simultaneous transmission of four influenza strains (A(H1N1), A(H3N2), B/vic, B/yam) in a population which corresponds to one thousandth of the German population, structured by age and risk status. The age distribution matches the German demography throughout the 50 years of simulation time. Individuals are connected in a dynamically evolving contact network based on the German POLYMOD age mixing matrix. The transmission probability per contact is calculated by relating the largest eigenvalue of the contact network to the basic reproduction number R_0 and then multiplying a seasonal forcing factor. Furthermore, infections are introduced at a low rate from outside. Special care has been taken to incorporate a realistic immunity model allowing for maternal protection, boosting of existing immunity, gradual loss of immunity, and cross-immunizing events between the B lineages and between drift variants. New drift variants are introduced on average after 3.5 (A(H3N2)) or 7 years (other variants). Only part of the existing immunity is active against newly introduced variants (simulated by a sudden loss of immunity for part of the population). Vaccinations are performed annually in autumn; coverage depends on the age of vaccinees, their risk status and previous vaccination status. Vaccine efficacy depends on age; appearance of new drift variants may lead to a vaccine mismatch (i.e. reduced vaccine efficacy). The first 10 years of simulation time are used to initialize the contact network, the next 20 years to initialize the immunologic and epidemiologic state of the population (applying the reported TIV coverage), and during the final 20 years, individuals either receive TIV or QIV, using a mirrored simulation approach which allows for matched comparisons.

Results

After calibration to observed incidence data, our simulations lead to a median annual infection incidence of 10.6% in young adults. Compared to no vaccination, TIV reduces the annual incidence from 15,049,000 to 8,943,000 infections; QIV further reduces it by 4.3% or 11.2% of Influenza B infections. As in any simulation study, our results strongly depend on the parameter values used. If the average duration of naturally acquired immunity is varied from 4 to 12 years (baseline: 6 years), the annual incidence decreases from 11,267,000 to 6,735,000 (TIV scenario), yet the percentage of infections additionally prevented by QIV remains constant at about 4.3%. If we selectively double the assumed duration of naturally acquired Influenza B immunity to 12 years, Influenza B infection incidence decreases, yet QIV still annually prevents 284,000 more infections than TIV. If R_0 is varied from 1.2 to 2.0 (baseline: 1.575), the annual incidence grows from 3,354,000 to 12,973,000 (TIV scenario), yet the annual number of infections additionally prevented by QIV remains nearly constant at 395,000 infections for $R_0 \geq 1.5$.

Conclusions

4Flu describes the spread of influenza viruses under different vaccinations strategies in a dynamically evolving contact network, reflecting German demography. Our simulation results indicate that vaccination with TIV substantially reduces the number of influenza infections compared to no vaccination. Based on our model, QIV would further reduce influenza infection incidence by 4.3%.