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

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Background

Influenza vaccines contain Influenza A and B antigens and are adjusted annually trying to match the antigenic characteristics of circulating viruses. Before 1985, Influenza B viruses in Germany only belonged to the B/Yamagata (B/Yam) lineage, but since then, viruses of the antigenically distinct B/Victoria (B/Vic) lineage have emerged (1, 2). Since 2001, both B lineages co-circulate to varying degrees with the seasonal Influenza A subtypes A(H3N2) and A(H1N1) [1-3]. Current trivalent influenza vaccines (TIV) contain antigens of the two seasonal influenza A subtypes, but of only one of the two B lineages, resulting in frequent vaccine mismatches [4]. Since 2012, the WHO has annually supplied the names of vaccine strains for both B lineages [5], paving the way for quadrivalent influenza vaccines (QIV) which contain both B lineages. The aim of this study is to model the concomitant transmission of four influenza strains in Germany, using an individual-based simulation tool, and to compare the vaccination effects of trivalent (TIV) and quadrivalent influenza vaccines (QIV) on the infection incidence.

Material and methods

- 4Flu is 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 of about 80,000 inhabitants, corresponding 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 [6] age mixing matrix (Fig. 2a).
- Simulations run for 50 years: 10 years are used to initialize the contact network, 20 years to initialize infection and immunity, 20 years to compare the infection incidence using different vaccination strategies (Fig. 2e).
- The complex dynamics of immunity (cf. Fig. 2d) is addressed by considering maternal protection, boosting of existing immunity, gradual loss of immunity, cross-immunizing events between the B lineages (Fig. 1); newly emerging drift variants only share part of the immunity with previous ones.
- Vaccinations are performed annually in autumn; coverage corresponds to the current vaccine uptake in Germany and depends on the age of vaccinees, their risk status and their previous vaccination status (Table 1).
- Vaccine efficacy depends on age; emerging new drift variants can lead to a vaccine mismatch (i.e. reduced vaccine efficacy; Table 1).
- The model is calibrated such that the observed incidence of 10.6% of infections among young adults in Germany [7] is obtained for the transmission season 2006/07, yielding a basic reproduction number of R_0 = 1.575.

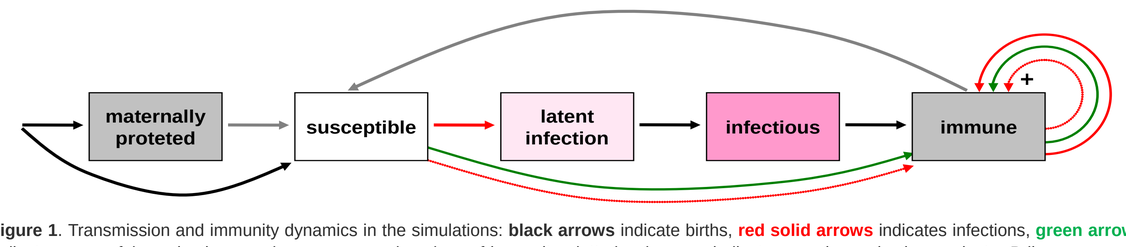

Figure 1. Transmission and immunity dynamics in the simulations: **black arrows** indicate births, **red solid arrows** indicates infections, **green arrows** indicate successful vaccinations, and **grey arrows** show loss of immunity; dotted red arrows indicate cross-immunization against a B lineage caused by an infection with the other B lineage; vaccinations and infections can also booster existing immunity (indicated by a "+").

Parameter	Baseline (default settings)
Basic reproduction number R_0 (resulting from model calibration to the epidemiology in Germany)	1.575
Maximum seasonal transmission factor	1.43
Day of maximum seasonal transmission	Dec. 21st
Duration of the latent period	2 days
External infection probability	0.0003/year
Duration of the infectious period - children (age 0-15 years) - adults (age 16 years and above)	 4 days 2 days
Duration of maternal protection	2 - 4 months
Average duration of naturally acquired immunity - A(H1N1), B/Vic, B/Yam - A(H3N2) (reduced average duration due to more frequent drift variants; see below)	 6.0 years 4.5 years
Average circulation time per drift variant - A(H1N1), B/Vic, B/Yam - A(H3N2)	 7.0 years 3.5 years
Probability of mismatched vaccine design when a new drift variant occurs	40%
Vaccination coverage - “no risk” group, 0.5-2 years of age - “no risk” group, 3-6 years of age - “no risk” group, 7-10 years of age - “no risk” group, 11-15 years of age - “no risk” group, 16-59 years of age - “no risk” group, 60 years of age or older - “elevated risk” group, 0.5-59 years of age - “elevated risk” group, 60 years of age or older	 19.2% 22.4% 23.6% 11.0% 16.9% 48.8% 33.0% 64.9%
Preference factor for individuals who were vaccinated in the year before	2
Vaccine efficacy (VE, well-matched vaccine) - 0-1 year of age - 2-5 years of age - 6-15 years of age - 16-64 years of age - 65 years of age or older	 45% 39% 69% 73% 58%
Cross protection after vaccination - VE multiplication factor for B lineage not contained in TIV - VE multiplication factor for vaccinations with drift mismatch	 0.6 0.6
Cross protection after infection - percentage of individuals who are immunized against a B lineage when they are infected (or booster-infected) with the other B lineage - percentage of individuals who were immune against the previous drift variant, who are still protected against the new one	 60% 60%
Immunity loss rate after vaccination	1/(1.8 years)
Percentage of individuals with elevated risk - newborn individuals - age 0 to 15 years - age 16 to 59 years - age 60 years and above	 3.0% 6.0% 14.2% 47.1%

Table 1. List of parameters and baseline values (default settings values). For references please contact the authors (see e-mail addresses below)

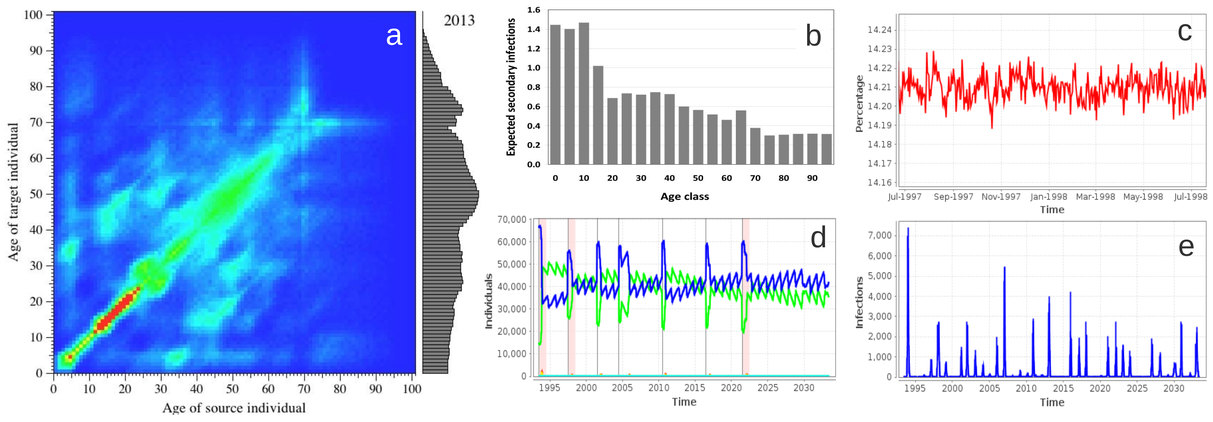

Figure 2. **(a)** Contact network at the beginning of the evaluation period (number of contacts increases from blue to light blue, green, yellow, red), and German age distribution (right). **(b)** Expected number of secondary infections by age of an infectious individual. **(c)** Random fluctuation of demographic features (exemplified by the risk fraction of young adults). **(d)** Dynamics of A(H1N1) immune (green) and susceptible (blue) individuals in a simulation; vertical lines show the introduction of new drift variants, pink areas show years with vaccine mismatch. **(e)** Simulated seasonal waves (TIV scenario).

Results

***(1)** Baseline results (parameters see Table 1). Each simulation reports the cumulative incidence of influenza infections for the final 20 simulation years (cf. Fig. 2e); because of the stochastic nature of the simulations, means of at least 1,000 simulations are calculated.*

- Current vaccination with TIV in Germany reduces the mean annual number of influenza infections from 15.0 million to 8.9 million, i.e. by 6.1 million infections (95% CI: 6.0 to 6.2).
- Using QIV instead of TIV, the mean annual infection incidence is further reduced by 395,000 Influenza B infections. This means that an average of 11.2% of all Influenza B infections which occur under TIV vaccination (95% CI: 10.7 to 11.8%) are prevented by QIV without increasing the vaccination coverage.
- QIV additionally prevents annually 79,000 Influenza B infections in children, 223,000 in young adults (16 to 59 years of age) and 93,000 in elderly.

***(2)** Sensitivity analysis on the basic reproduction number R_0 which summarizes the contagiousness of the infection:*

- The average annual number of infections grows with increasing R_0 (Figs. 3 a+b)
- The average number of infections annually prevented by QIV rises from 325,000 infections for R_0 = 1.2 to about 386,000 infections for R_0 = 1.5, and, thereafter, reaches a constant level of about 395,000 infections (Fig. 3 c)

***(3)** Sensitivity analyses on the Influenza B cross protection (i.e. the percentage of individuals who are immunized against an Influenza B lineage after successful vaccination or infection with the other B lineage):*

- Using the baseline value 0.6 of B lineage cross protection, the mean annual incidence of Influenza B infections is 3.35 million with TIV and 2.95 million with QIV; the difference are 395,000 infections (95% CI: 376,000 to 414,000).
- If a lower cross protection is used in the simulations, the number of Influenza B infections increases (Figs. 4a+b).
- Without any B lineage cross protection, the mean annual number of Influenza B infections is 6.55 million with TIV and 4.37 million with QIV; the difference are 2,180,000 infections (95% CI: 2,142,000 to 2,217,000), which is 5.5 times as high as that of the baseline result (Fig. 4c).
- If the B lineage cross protection is gradually reduced during the simulation time, the additional benefit of QIV increases: if cross protection declines from 0.6 (baseline value) at the start of the evaluation period to 0.3 at the end, the average number of prevented infections increases from 395,000 (baseline result) to 853.000 per year.

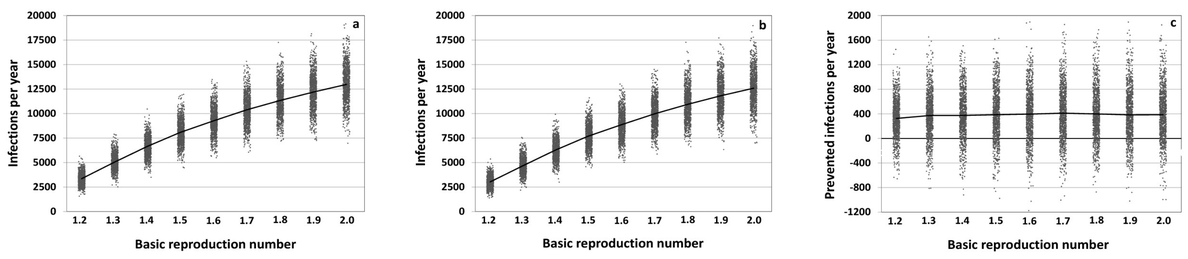

Figure 3. Results of a sensitivity analysis in which the basic reproduction number is varied from 1.2 to 2.0; for each value, 1,000 simulations with about 80,000 individuals were evaluated. Average annual number of infections for **(a)** the TIV scenario and **(b)** the QIV scenario. **(c)** Average number of infections prevented per year by QIV. Mean values are connected.

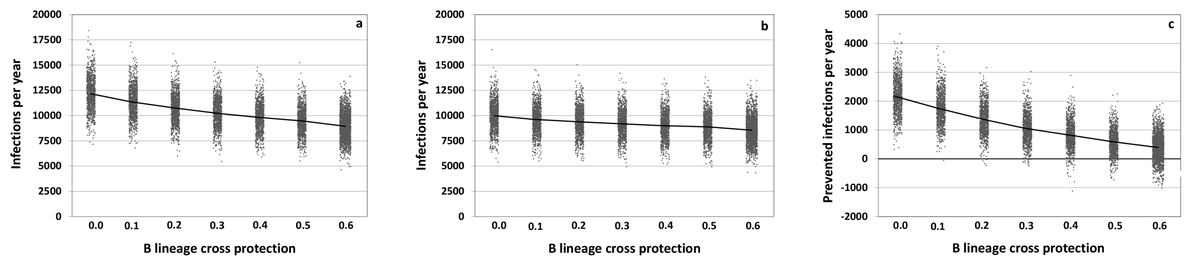

Figure 4. Results of a sensitivity analysis in which the lineage cross protection is varied (1,000 simulations with about 80,000 individuals each; 2,000 simulations for the baseline value 0.6). Average annual number of infections for **(a)** the TIV scenario and **(b)** the QIV scenario. **(c)** Average number of infections prevented per year by QIV. Mean values are connected

Conclusions

- **4Flu is a sophisticated individual-based simulation tool for the study of the spread of Influenza viruses. It uses a dynamically evolving contact network, it mirrors the predicted changes of the German age distribution, and it is highly flexible to implement and compare vaccination strategies.**
- **Current vaccination with TIV in Germany, although covering less than 30% of the population, substantially reduces the number of influenza infections compared to no vaccination.**
- **Depending on the assumed level of B lineage cross protection, QIV can further reduce Influenza B infections by 11-33% and overall influenza infection by 4.3 –17.9%.**

References

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Conflicts of Interests

ME is shareholder of Epimos GmbH & Co. KG, which has received research support from GlaxoSmithKline and Astra Zeneca. MS is shareholder of ExploSYS GmbH, which has received payments from Epimos GmbH & Co. KG for developing the simulation tool 4Flu. JH, AA and RSO are employees of GlaxoSmithKline. BS has received consultancy fees and honoraria for presentations from GlaxoSmithKline and Novartis. MK has received consultancy fees and honoraria for advisory activities and presentations from Novartis, GlaxoSmithKline and AstraZeneca.

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