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Vaccinating children against influenza increases variability in epidemic size

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ABSTRACT

Seasonal influenza causes a high disease burden. Many influenza vaccination programmes target the elderly and persons at high risk of complications. Some countries have recommended or even implemented a paediatric vaccination programme. Such a programme is expected to reduce influenza transmission in the population, offering direct protection to the vaccinated children and indirect protection to the elderly.

We study the impact of a child vaccination programme with an age- and risk-structured transmission model, calibrated to data of 11 influenza seasons in the Netherlands. The model tracks the build-up of immunes and susceptibles in each age cohort over time, and it allows for seasonal variation in vaccine match and antigenic drift. Different vaccination strategies are evaluated for three target age groups (2–3, 2–12 and 2–16 year olds) over the full range of vaccination coverages (0–100%).

The results show that the paediatric vaccination programme has only a limited impact on the elderly age groups, which account for most influenza morbidity and mortality. This is due to two notable changes in infection dynamics. First, an age shift is observed: influenza infections are reduced in vaccinated children, but are increased in young adults with limited natural immunity after years of vaccination. These young adults assume the role of driving the epidemic. Second, a year with low influenza activity can be followed by a large epidemic due to build-up of susceptibles. This variation of the infection attack rate increases with increasing vaccination coverage.

The increased variability in the infection attack rate implies that health care facilities should be prepared for rare but larger peaks in influenza patients. Moreover, vaccinating the group with the highest transmission potential, results in a larger dependency on a secure vaccine supply. These arguments should be taken into account in the decision to introduce mass vaccination of school-aged children against influenza.

1. Introduction

Seasonal influenza epidemics cause substantial morbidity and mortality in high-risk groups (World Health Organization, 2016; Iuliano et al., 2018). In most developed countries, yearly vaccination offers direct protection to the elderly and persons with an increased risk of medical complications upon infection with the influenza virus. Such vaccination programmes have a small impact on the circulation of influenza virus (Backer et al., 2018). As school-aged children are considered to drive influenza transmission (Worby et al., 2015), they are the main target for an additional vaccination programme that aims to reduce transmission. Such a paediatric vaccination programme has first been explored in Japan (Reichert et al., 2001) and has recently been adopted in the United Kingdom (Government, 2012) and Finland (Heikkinen et al., 2013).

Modelling can contribute to the decision making by evaluating different strategies and scenarios. To what extent vaccination of children will reduce influenza incidence depends on the age group to be vaccinated, the vaccination coverage and the vaccine efficacy. Comparison of different modelling studies reveals large discrepancies in projected outcomes. For example, for a strategy that is targeted at all school-aged children, a coverage of 50%, and an efficacy of 80%, projected reductions in influenza incidence can range from 20% (Gibson et al., 2016) to 84% (Pitman et al., 2012) due to different modelling choices. Models used for evaluation of child vaccination fall roughly into two categories: models that capture the long-term infection dynamics due to immunity gains and losses over successive seasons (Weycker et al., 2005; Vynnycky et al., 2008; Pitman et al., 2012; Rose et al., 2014; Gerlier et al., 2017; Gibson et al., 2016), and models that capture the high variation in epidemic size between seasons (Baguelin et al., 2013; Meeyai et al., 2015; Weidemann et al., 2017). Both aspects are expected to affect the impact of a vaccination programme for

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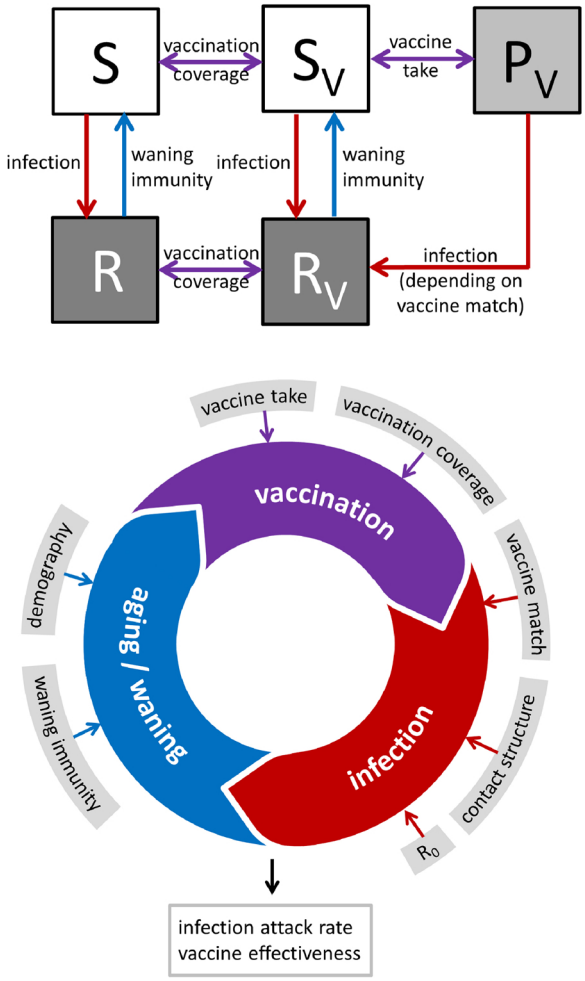

Fig. 1. Overview of the influenza model. A: Compartmental model for discrete time steps of one year, with classification according to vaccination and infection status: fully susceptible (S and S_V), immune through natural infection (R and R_V), and partially protected by vaccination (P_V), where subscript V denotes a vaccinated compartment. The model lacks an explicit infectious compartment because of the use of final size calculations. Each compartment is subdivided in 100 age classes (from 0 to 99 years of age), 3 risk groups (low, medium and high) and 2 sexes. B: Simulation cycle for each season consists of three stages: vaccination before the start of the season (purple), infection during the season (red), and age increase and immunity waning at the end of the season (blue). Outcome measures are the infection attack rate and vaccine effectiveness of that season. The outer ring shows the model parameters (structured by age, risk group and/or sex): demographic composition (age, risk, sex), vaccination coverage (age, risk), vaccine take (age), and contact matrix (age, sex), as well as the estimated model parameters: basic reproduction number R_0 (1.8 (1.3–2.7), median with 95% credible interval), waning immunity rate (average of 0.19 (0.12–0.35) yr^{-1} and standard deviation of 0.031 (0.011–0.067) yr^{-1}), and vaccine match (average of 0.56 (0.49–0.66) and standard deviation of 0.11 (0.078–0.14)). See Backer et al. (2018) for model details and parameter estimation.

children (Woolthuis et al., 2017), but no study has evaluated such programmes with a model that accounts for both aspects.

We evaluate influenza vaccination programmes for children, using a transmission model that captures the build-up and loss of naturally acquired and vaccine-induced immunity over seasons, and that allows for seasonal variation in vaccine match and antigenic drift (Backer et al., 2018). We vary the age groups to include in the programme and the vaccination coverage, and we explore the impact of the influenza vaccination programme on the infection dynamics. Furthermore, we evaluate the effect of an unexpected interruption of vaccine supply, and perform a sensitivity analysis on the vaccine efficacy. We will discuss how our results compare with previous studies that assess the impact of child vaccination programmes.

2. Methods

The dynamic transmission model was developed previously and fitted to influenza attack rates from the Netherlands and vaccine effectiveness values from literature (Backer et al., 2018). In short, a structured compartmental model is used to calculate the seasonal infection attack rate in each age- and risk-group. The influenza epidemics end due to depletion of susceptibles rather than seasonal forcing (te Beest et al., 2013), which allows for the use of final size equations to approximate the epidemic size. Each time step of one influenza season consists of three stages of a cycle (Fig. 1). Before the start of the season, people are vaccinated according to the vaccination coverage of their risk and age class, but whether they develop an antibody response depends on their age, captured by the vaccine take. During the season, the number of infections and distribution over the various groups is determined by the virus transmissibility and the contact structure between age and sex classes (Van de Kassteele et al., 2017). Persons that respond to vaccination can still be infected, depending on the how well the vaccine strain matches the circulating virus strain. The vaccine match can vary per season. At the end of the season, the population ages by one year and newborns enter the population. A part of the infected population becomes susceptible to infection again due to antigenic drift, as the circulating strain less and less resembles the virus strain that caused the initial infection. This is modelled as immunity waning where individuals go from an immune state to a susceptible state. The waning immunity rate can also vary per season. Finally, vaccinated individuals return to an unvaccinated status as vaccine protection is assumed to last one season.

We do not make a distinction between the currently used vaccine and the vaccine for children. Currently, trivalent influenza vaccines (TIV) are used containing two influenza A subtypes (H1N1 and H3N2) and one influenza B lineage (Yamagata or Victoria). For the paediatric vaccination programme a quadrivalent live-attenuated influenza vaccine (QLAIV) is envisaged, administered by a nasal spray. Because of the inclusion of both influenza B subtypes, QLAIV mismatches are less likely, and because of the live vaccine, QLAIV is expected to provide broader and longer protection. Both effects should translate to a higher vaccine effectiveness, which was indeed observed in randomised controlled trials (Belshe et al., 2007; Rhorer et al., 2009; Ambrose et al., 2012). In practice however, lower (Chung et al., 2016; Poehling et al., 2018), similar (Caspard et al., 2016; Nohynek et al., 2016), and higher (Helmeke et al., 2015) vaccine effectiveness estimates are reported for QLAIV compared to TIV. For this reason, we do not make a distinction between the two vaccines as a conservative choice.

The current vaccination programme in the Netherlands targets persons of 60 years and older (24% of the population) and other high-risk individuals (11% of the population). In the targeted population, 46% of the at-risk individuals younger than 60 years and 66% of the individuals of 60 years and older choose to be vaccinated, resulting in an overall vaccination coverage of 21%. We study the additional vaccination programme for children, in increasingly inclusive age groups of 2–3, 2–12, and 2–16 year olds. These age groups coincide with the age limits for day-care, primary school and secondary school. Vaccination coverage ranges from 0% to 100% in steps of 5%. In the most extensive strategy (targeting 2–16 year olds, at a 100% coverage) 38% of the total population would be vaccinated. We assume that the coverage in high-risk children is either the current coverage or the coverage in low-risk children, whichever is highest. In all strategies, roll-out of the new vaccination programme starts in 2020. In the first year all 2- and 3-year olds are targeted for vaccination and each subsequent year the age limit is increased by one year until the age maximum is reached, i.e. the introduction method as implemented in

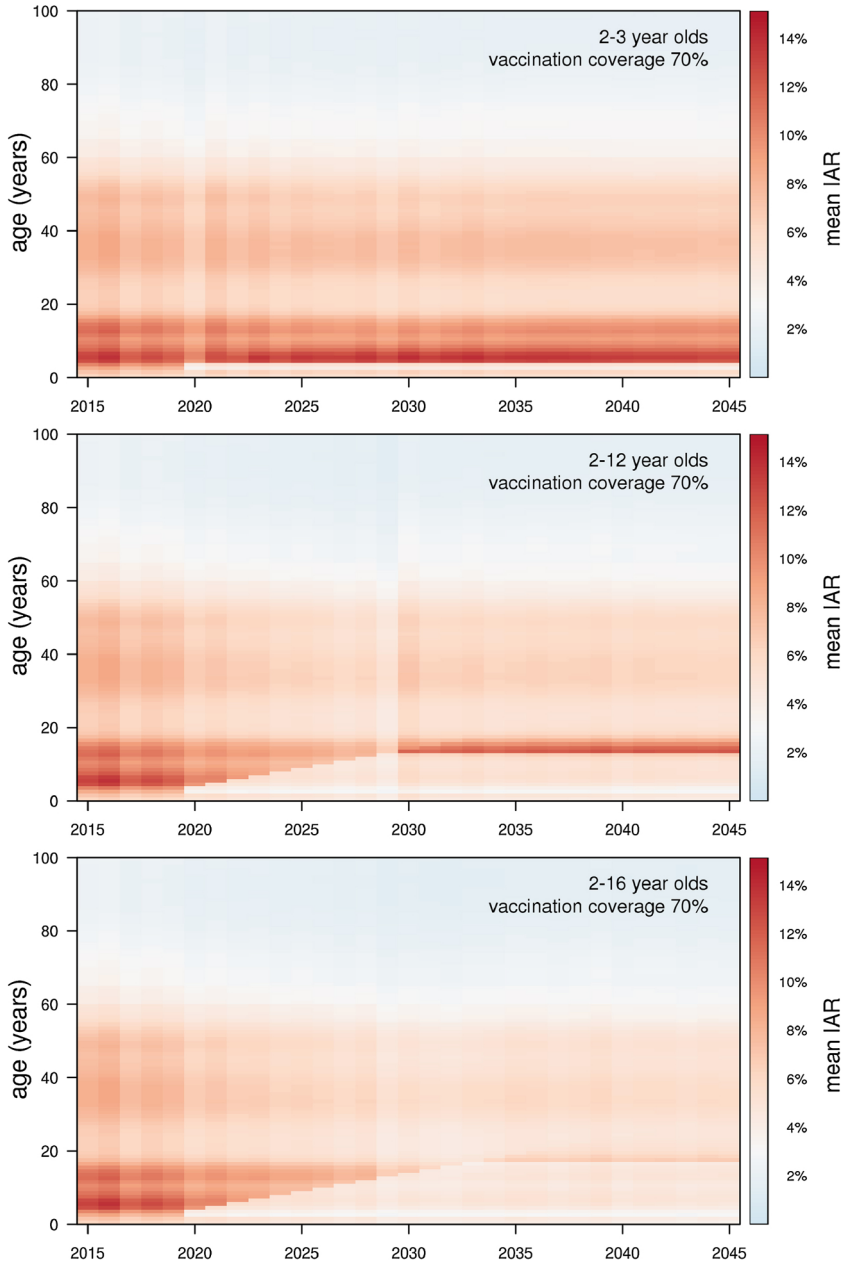

Fig. 2. Mean infection attack rate (IAR) per age class before, during and after roll-out of the paediatric vaccination programme for 2–3 (top), 2–12 (middle) and 2–16 year olds (bottom) at an 80% vaccination coverage. In all cases roll-out starts in 2020 with 2–3 year olds, and increases the age limit annually by one year until the age maximum is reached. Vertical bands with higher or lower infection attack rates are caused by expected changes in demography.

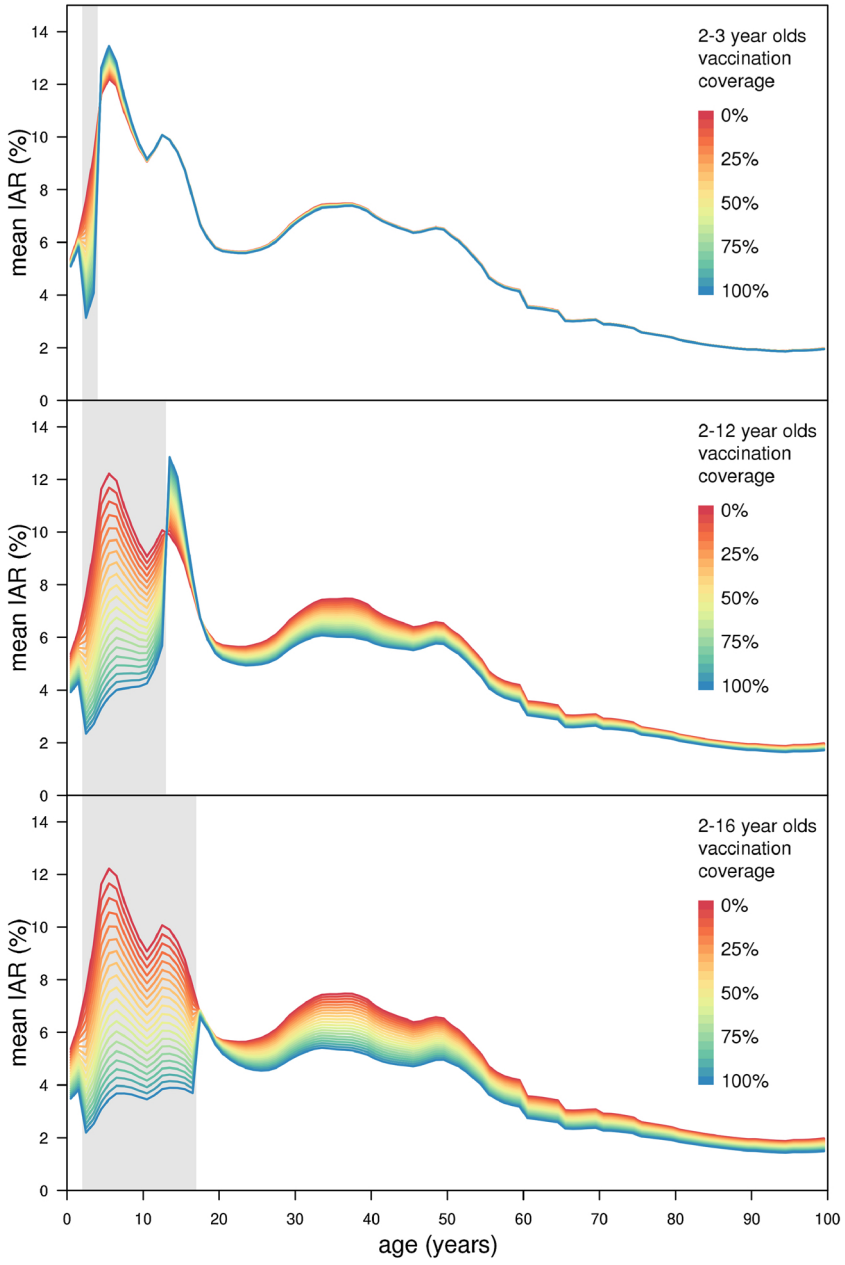

Fig. 3. Mean infection attack rate (IAR) per age class after roll-out of the paediatric vaccination programme (averaged over the period 2040–2045) for 2–3 (top), 2–12 (middle) and 2–16 year olds (bottom) at various vaccination coverages between 0% and 100%. The grey area shows the age groups targeted in the vaccination programme.

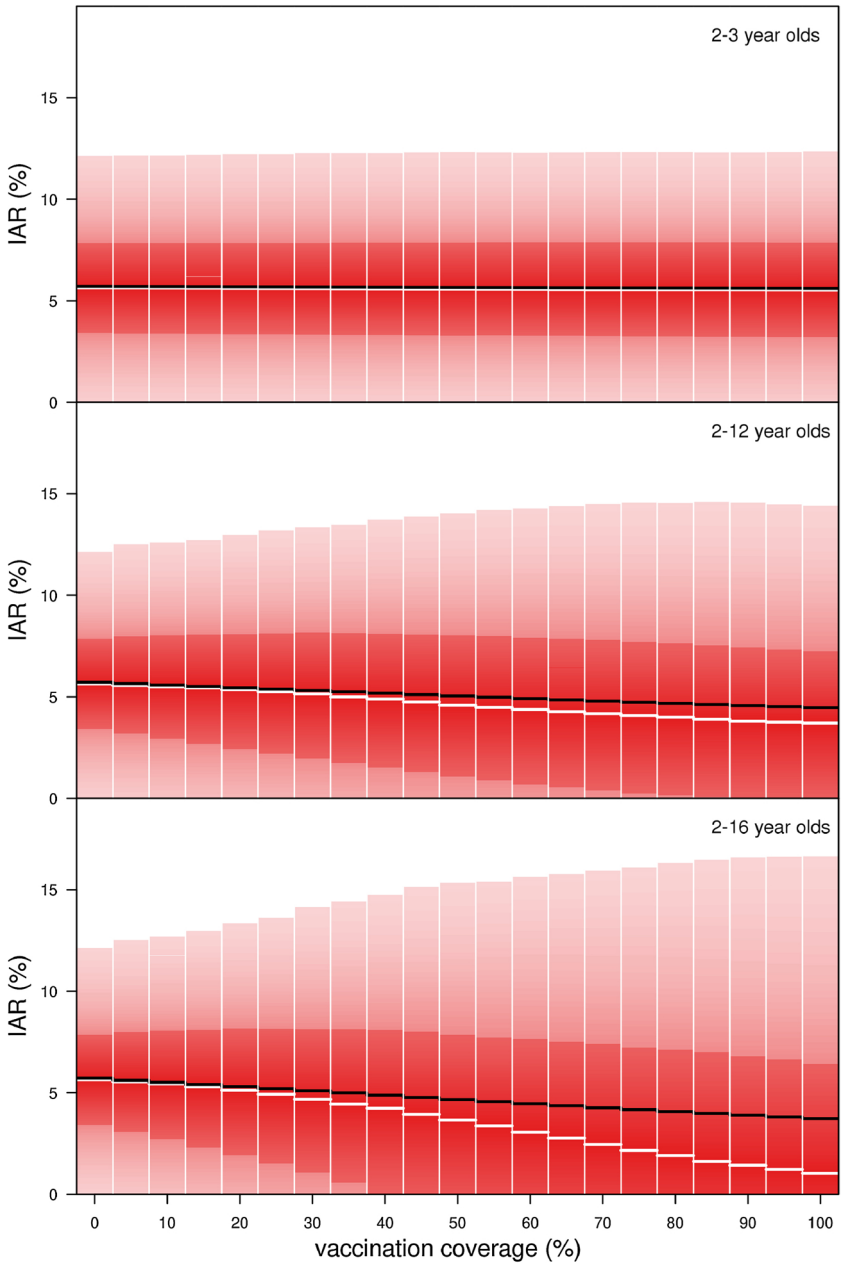

Fig. 4. Infection attack rate (IAR) distribution after roll-out of the paediatric vaccination programme (averaged over the period 2040–2045) for 2–3 (top), 2–12 (middle) and 2–16 year olds (bottom) as a function of vaccination coverage; mean (black line), median (white line), interquartile range (dark red area) and 95% range (light red area).

Table 1
Infection attack rate (IAR) for the current vaccination programme, and changes in IAR when vaccinating 40% or 80% of the targeted age groups, either 2–3, 2–12 or 2–16 year olds (averaged over the period 2040–2045). Given are the mean (change in) IAR and the 95% interval between brackets.

	Vaccination coverage in low-risk children of					
	0% IAR (%)		40% Change in IAR (%)		80% Change in IAR (%)	
2–3 year olds						
Overall	5.7	(0–12)	−0.76	(−49 to +0.58)	−1.5	(−75 to +0.83)
Target group	8.5	(0–19)	−24	(−64 to −22)	−47	(−89 to −42)
Non-target group	5.7	(0–12)	−0.021	(−48 to +1.3)	−0.022	(−74 to +2.2)
2–12 year olds						
Overall	5.7	(0–12)	−9.4	(−100 to +12)	−18	(−100 to +18)
Target group	10	(0–21)	−27	(−100 to −3.1)	−51	(−100 to −12)
Non-target group	5.1	(0–11)	−4.6	(−100 to +16)	−9.4	(−100 to +26)
2–16 year olds						
Overall	5.7	(0–12)	−15	(−100 to +20)	−29	(−100 to +34)
Target group	9.9	(0–20)	−29	(−100 to +6.3)	−54	(−100 to +2.8)
Non-target group	4.9	(0–11)	−8.9	(−100 to +25)	−19	(−100 to +45)

England. Using different parameter sets from the posterior distributions, 1000 simulations are run from 2015 to 2045 for each strategy. The outcome measures of interest are the reduction of the infection attack rate overall, and the infection attack rate in different age groups.

Furthermore, we explore the consequences when the vaccine is unexpectedly not available. This is tested by simulating a vaccine supply stop for the additional programme for one season, while the original target groups of high-risk persons and elderly are vaccinated as before. Finally, a sensitivity analysis assesses the effect of a higher vaccine efficacy of the paediatric vaccine compared to the current vaccine.

3. Results

3.1. Effect on influenza infection dynamics

Fig. 2 shows the mean influenza infection attack rate by age over time while the vaccination programme for children is implemented at an 80% coverage. During roll-out, the vaccinated cohort will grow each year as the age limit increases, reflected by the stair-like transition to a lower infection attack rate. Once roll-out is complete, the age classes that were first vaccinated enter the non-vaccination regime with little natural immunity, resulting in a higher infection attack rate in these age classes. The specific roll-out strategy does not alleviate this transition (Fig. S1). The effect is most apparent when vaccinating 2–12 year olds, but also present when vaccinating 2–3 year olds or 2–16 year olds. The age distribution of infection thus shifts to higher age classes, that partly take on the role of epidemic driver. This effect is clearly shown in the mean infection attack rate as a function of age (Fig. 3). For vaccination of 2–3 year olds the direct effects are offset by the increased infection attack rate in 4–6 year olds, leaving the infection attack rate in older age groups unchanged. Only for larger target groups the vaccination starts having indirect effects on older age groups.

The limited effect of vaccinating children on the mean infection attack rate is further explained by considering the distribution of overall infection attack rates (Fig. 4). When vaccinating larger age groups at a higher coverage, the distribution mean and median start to diverge and the variation increases. This means that influenza epidemics would become smaller or even absent in some years, but such seasons could be followed by a very large epidemic due to the build-up of susceptibility (illustrated in Fig. S2). The overall effect, expressed by the mean infection attack rate, is therefore limited.

The average infection attack rate decreases with increasing vaccination coverage (Fig. 4 and Table 1). Direct effects of vaccination in the targeted groups are always larger than the indirect effects in the non-targeted groups where most influenza morbidity and mortality are expected. For instance, the overall mean infection attack rate reduction is 29% when vaccinating 80% of the 2–16 year olds, but the average reduction in the non-targeted groups is only 19%. Although this is the best result obtained for the non-targeted group, the variation is also the largest, ranging from a 100% reduction to a 45% increase of the infection attack rate.

3.2. Effect of influenza vaccine supply stop

The introduction of a child vaccination programme leaves the target group with little natural immunity, leading to a large potential for an epidemic. If the yearly vaccination can not take place due to unavailability of the vaccine, or due to an extreme mismatch with the circulating virus, the infection attack rates will be much higher than without vaccinating children (Fig. 5). This attack rate increases with vaccination coverage in the years before, and is largest for the target group. If, for instance, 80% of the 2–16 year olds were vaccinated yearly, on average 4.5 (0–21)% of them would be infected when vaccination is in place. In a subsequent season without vaccination the attack rate increases to 37 (15–52)%, which is significantly larger than 9.9 (0–20)% if the childhood programme were not implemented (Table 1). Note that in these scenarios only the vaccine supply for the child vaccination programme is affected, and the vaccination of high-risk groups and elderly persons continues as before.

3.3. Sensitivity analysis on vaccine efficacy

We have assumed that the vaccine used to vaccinate low-risk children is as efficacious as the vaccine used in the current programme. As the first vaccine has a possibly higher efficacy and presumed longer protection, we study the effect of a higher vaccine match in a sensitivity analysis. The vaccine match has little effect on the infection attack rate at low vaccination coverages (Fig. 6). At higher vaccination coverages, the mean infection attack rate decreases, and a higher vaccine match reduces it even further. Conversely, an increase in vaccination coverage leads to an increased 95th percentile of the infection attack rate, as seen before (Fig. 4). Only at a vaccination coverage over 70%, a higher vaccine match is able to counter this effect.

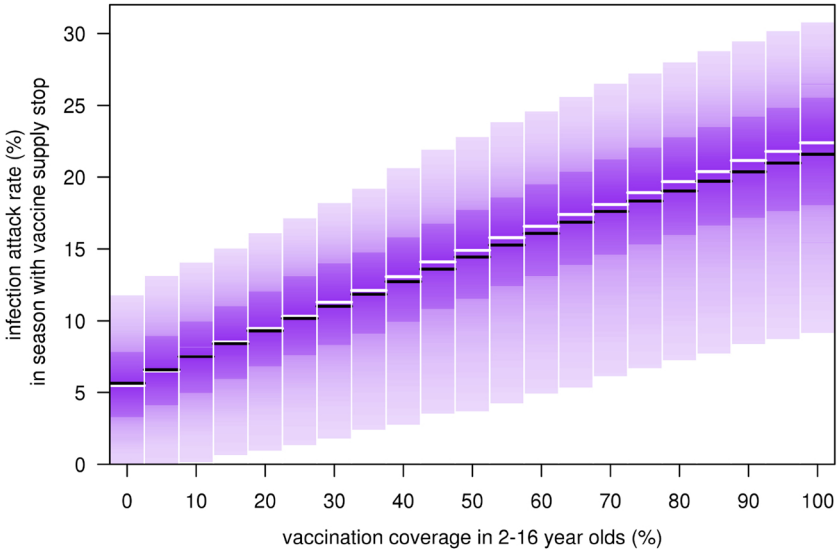

Fig. 5. Effect of a supply stop of the vaccine for 2–16 year olds. Infection attack rate distribution during a season without vaccination, as a function of vaccination coverage in the years before; mean (black line), median (white line), interquartile range (dark purple area) and 95% range (light purple area). The infection attack rate distribution when vaccination is in place is shown in the bottom panel of Fig. 4.

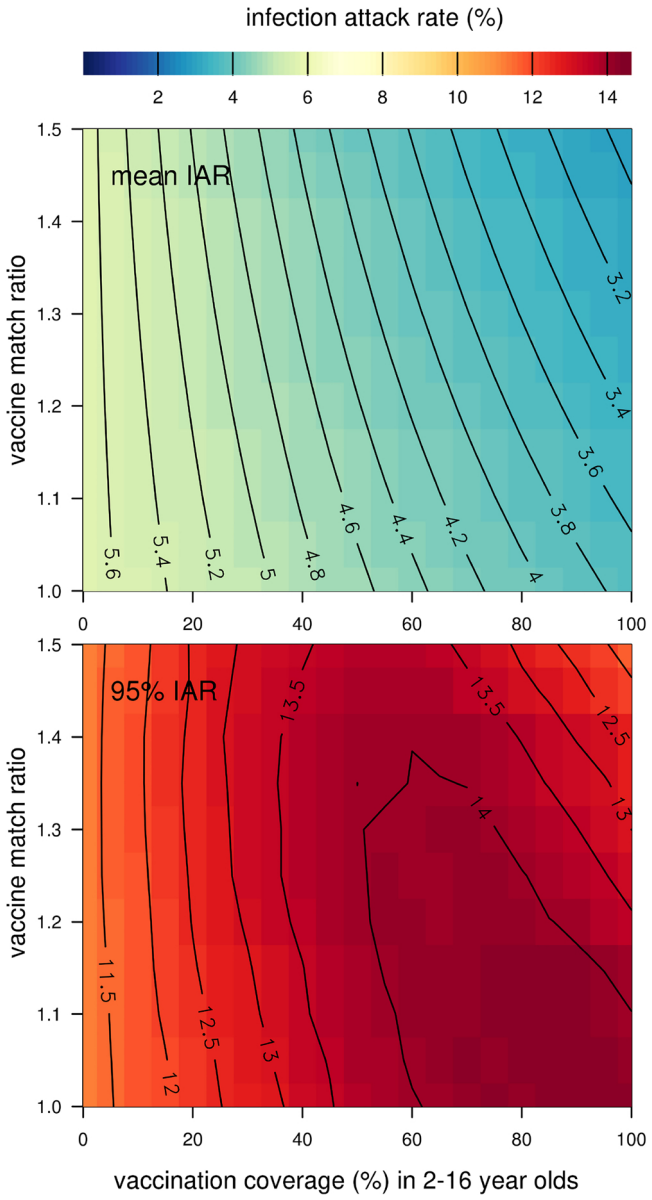

Fig. 6. Sensitivity analysis on vaccine efficacy. Effect on the infection attack rate (IAR) of the vaccine match ratio between the vaccines used in the child vaccination programme and the current programme, for different vaccination coverages in 2–16 year olds. A vaccine match ratio of 1.3 means that in each season the vaccine for children is 30% more efficacious than the current vaccine (with a maximum of 100%). Contour plots are shown for the mean infection attack rate (top) and the 95th percentile of the infection attack rate (bottom).

4. Discussion

In comparison with other modelling studies, our analyses predict a smaller impact of vaccinating children on the infection attack rate (Fig. 7). Four notable differences in model structure may explain these discrepancies. First, the inclusion of variable waning immunity and vaccine match leads to increased variation in epidemic size which reduces the overall impact. Second, studies without multiseason dynamics (Baguelin et al., 2013; Meeyai et al., 2015; Weidemann et al., 2017) do not incorporate the effect of decreasing natural immunity levels in the long term, which may lead to an overly optimistic assessment of the impact of vaccinating children. Third, the incidence of infection in the vaccinated age groups decreases but increases in the age groups that just left the child vaccination programme. This age shift is observed in our results because the model carries age cohorts from one season to the next. Studies with a similar model structure have not mentioned the age shift in their results (Rose et al., 2014; Gerlier et al., 2017; Gibson et al., 2016). Finally, the assumed vaccine induced protection affects the impact of the child vaccination programme. The assumption that the protection by natural infection and vaccination last equally long results in very high impacts (Vynnycky et al., 2008; Pitman et al., 2012), but is deemed unrealistic in more recent studies (Rose et al., 2014; Gerlier et al., 2017; Gibson et al., 2016). We have assumed the vaccine protection lasts one year, although there is some evidence that live-attenuated influenza vaccines may provide protection for longer (Tam et al., 2007). Such a longer vaccine protection would lead to a larger decrease in the average infection attack rate, and mitigate the effect of the age shift.

We have assumed one generic influenza strain instead of modelling specific strains and subtypes. Although a strong assumption, the more parsimonious model does not require assumptions on the interaction between the different strains and subtypes. We expect that in an analysis that does include multiple strains and subtypes, the impact on the results will be small. First, because the shift in the age of the epidemic drivers to older unvaccinated children will not be affected, and second, because the increased variability in infection attack rate for one generic strain can be considered a conservative estimate. If anything, the variability is expected to increase even further when multiple strains and subtypes show more erratic behaviour.

Paediatric vaccination programmes against influenza have recently been implemented in the UK (Government, 2012) and Finland (Heikkinen et al., 2013). Early pilot studies in the UK have shown positive effects of vaccinating children on several influenza indicators (Pebody et al., 2014, 2015). Roll-out of the new vaccination programme started in 2013/2014, but due to the variation in seasonal epidemics, it is probably too early to assess its impact on influenza activity (Public Health England, 2017). Our study shows that adverse effects, like the age shift and increased variation of the infection attack rate, are only expected after the roll-out has been completed.

We use a model that tracks the build-up of immunes and susceptibles in each age cohort over time. This allows us to detect the increased infection attack rate in older age groups with little natural immunity after years of vaccination. New in our model is the combination of multiseason dynamics with variation between seasons. This allows us to detect the increased variation in epidemic size. This finding implies that with the child vaccination programme in place, there may be years without any influenza activity followed by an aggravated epidemic year due to the build-up of susceptibility. Health care facilities should be prepared for rare but larger peaks in influenza-related health care demand as compared to the current situation without a child vaccination programme against influenza.

Our results demonstrate the paradox of paediatric influenza vaccination. The more effectively children are vaccinated, the larger the average reduction of influenza-induced morbidity and mortality is expected. The drawback is the lower level of naturally acquired immunity in the target age group with the highest transmission potential. This manifests itself as an increased variability of the epidemic sizes, and a larger dependency on a secure annual supply of vaccines. This study shows that when deciding to implement a child vaccination programme, one should look beyond the expected average impact.

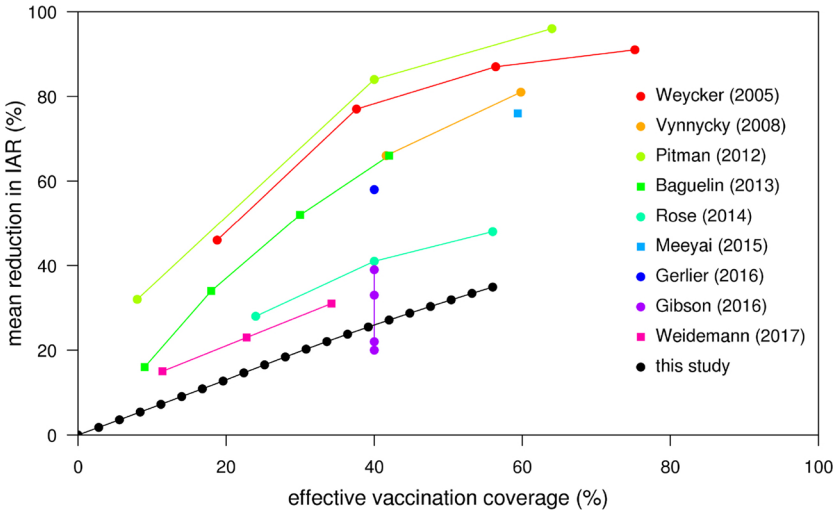

Fig. 7. Mean reduction in infection attack rate (IAR) as a function of effective vaccination coverage, for previously published results. The effective vaccination coverage is the multiplication of the vaccination coverage and the assumed vaccine efficacy for the target age group. Results are shown for the largest target groups in each study from minimally 0.5–2 year old to maximally 16–18 year old. Considered studies are subdivided in studies with multiseason dynamics (circles) and isolated variable seasons (squares): Weycker et al. (2005), Vynnycky et al. (2008), Pitman et al. (2012), Baguelin et al. (2013) (vaccine efficacy of 60% is weighted average between matched and mismatched seasons), Rose et al. (2014), Meeyai et al. (2015), Gerlier et al. (2017), Gibson et al. (2016) (different countries), and Weidemann et al. (2017) (reduction in medically attended acute respiratory illness; vaccine efficacy of 57% is average of estimates against influenza A(H3N2) and A(H1N1) over seasons 2004-2014).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.epidem.2018.10.003.

References

Ambrose, C.S., Wu, X., Knuf, M., Wutzler, P., 2012. The efficacy of intranasal live attenuated influenza vaccine in children 2 through 17 years of age: a meta-analysis of 8 randomized controlled studies. Vaccine 30 (5), 886–892.

Backer, J.A., Wallinga, J., Meijer, A., Donker, G.A., Van der Hoek, W., Van Boven, M., 2018. The impact of influenza vaccination on infection, hospitalisation and mortality in the Netherlands between 2003 and 2015. Epidemics. https://doi.org/10.1016/j.epidem.2018.10.001. (in press).

Baguelin, M., Flasche, S., Camacho, A., Demiris, N., Miller, E., Edmunds, W.J., 2013. Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study. PLoS Med. 10 (10) e1001527.

Belshe, R.B., Edwards, K.M., Vesikari, T., Black, S.V., Walker, R.E., Hultquist, M., Kemble, G., Connor, E.M., 2007. Live attenuated versus inactivated influenza vaccine in infants and young children. N. Engl. J. Med. 356 (7), 685–696.

Caspard, H., Gaglani, M., Clipper, L., Belongia, E.A., McLean, H.Q., Griffin, M.R., Talbot, H.K., Poehling, K.A., Peters, T.R., Veney, N., Ambrose, C.S., 2016. Effectiveness of live attenuated influenza vaccine and inactivated influenza vaccine in children 2–17 years of age in 2013–2014 in the United States. Vaccine 34 (1), 77–82.

Chung, J.R., Flannery, B., Thompson, M.G., Gaglani, M., Jackson, M.L., Monto, A.S., Nowalk, M.P., Talbot, H.K., Treanor, J.J., Belongia, E.A., Murthy, K., Jackson, L.A., Petrie, J.G., Zimmerman, R.K., Griffin, M.R., McLean, H.Q., Fry, A.M., 2016. Seasonal effectiveness of live attenuated and inactivated influenza vaccine. Pediatrics 137 (2), e20153279.

Gerlier, L., Lamotte, M., Greneche, S., Lenne, X., Carrat, F., Weil-Olivier, C., Damm, O., Schwehm, M., Eichner, M., 2017. Assessment of public health and economic impact of intranasal live-attenuated influenza vaccination of children in France using a dynamic transmission model. Appl. Health Econ. Health Policy 15 (2), 261–276.

Gibson, E., Begum, N., Martinon-Torres, F., Safadi, M.A., Sackeyfio, A., Hackett, J., Rajaram, S., 2016. Cost-effectiveness analysis of the direct and indirect impact of intranasal live attenuated influenza vaccination strategies in children: alternative country profiles. J. Mark. Access Health Policy 4.

Government, U.K., 2012. JCVI Statement on the Annual Influenza Vaccination Programme – Extension of the Programme to Children. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224775/JCVI-statement-on-the-annual-influenza-vaccination-programme-25-July-2012.pdf.

Heikkinen, T., Tsolia, M., Finn, A., 2013. Vaccination of healthy children against seasonal influenza: a European perspective. Pediatr. Infect. Dis. J. 32 (8), 881–888.

Helmeke, C., Grafe, L., Irmscher, H.M., Gottschalk, C., Karagiannis, I., Oppermann, H., 2015. Effectiveness of the 2012/13 trivalent live and inactivated influenza vaccines in children and adolescents in Saxony-Anhalt, Germany: a test-negative case-control study. PLoS ONE 10 (4), e0122910.

Iuliano, A.D., Roguski, K.M., Chang, H.H., Muscatello, D.J., Palekar, R., Tempia, S., Cohen, C., Gran, J.M., Schanzer, D., Cowling, B.J., Wu, P., Kyncl, J., Ang, L.W., Park, M., Redlberger-Fritz, M., Yu, H., Espenhain, L., Krishnan, A., Emukule, G., van Asten, L., Pereira da Silva, S., Aungkulanon, S., Buchholz, U., Widdowson, M.A., Bresee, J.S., Azziz-Baumgartner, E., Cheng, P.Y., Dawood, F., Foppa, I., Olsen, S., Haber, M., Jeffers, C., 2018. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 391 (10127), 1285–1300.

Meeyai, A., Praditsitthikorn, N., Kotirum, S., Kulpeng, W., Putthasri, W., Cooper, B.S., Teerawattananon, Y., 2015. Seasonal influenza vaccination for children in Thailand: a cost-effectiveness analysis. PLoS Med. 12 (5), e1001829 discussion e1001829.

Nohynek, H., Baum, U., Syrjanen, R., Ikonen, N., Sundman, J., Jokinen, J., 2016. Effectiveness of the live attenuated and the inactivated influenza vaccine in two-year-olds – a nationwide cohort study Finland, influenza season 2015/16. Euro Surveill. 21 (38).

Pebody, R.G., Green, H.K., Andrews, N., Zhao, H., Boddington, N., Bawa, Z., Durnall, H., Singh, N., Sunderland, A., Letley, L., Ellis, J., Elliot, A.J., Donati, M., Smith, G.E., de Lusignan, S., Zambon, M., 2014. Uptake and impact of a new live attenuated influenza vaccine programme in England: early results of a pilot in primary school-age children, 2013/14 influenza season. Euro Surveill. 19 (22).

Pebody, R.G., Green, H.K., Andrews, N., Boddington, N.L., Zhao, H., Yonova, I., Ellis, J., Steinberger, S., Donati, M., Elliot, A.J., Hughes, H.E., Pathirannehelage, S., Mullett, D., Smith, G.E., de Lusignan, S., Zambon, M., 2015. Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza A and B strains, England, 2014/15. Euro Surveill. 20 (39).

Pitman, R.J., White, L.J., Sculpher, M., 2012. Estimating the clinical impact of introducing paediatric influenza vaccination in England and Wales. Vaccine 30 (6), 1208–1224.

Poehling, K.A., Caspard, H., Peters, T.R., Belongia, E.A., Congeni, B., Gaglani, M., Griffin, M.R., Irving, S.A., Kavathekar, P.K., McLean, H.Q., Naleway, A.L., Ryan, K., Talbot, H.K., Ambrose, C.S., 2018. 2015–2016 vaccine effectiveness of live attenuated and inactivated influenza vaccines in children in the United States. Clin. Infect. Dis. 66 (5), 665–672.

Public Health England, 2017. Surveillance of Influenza and Other Respiratory Viruses in the UK: Winter 2016 to 2017. , PHE publications gateway number: 2017044. https://www.gov.uk/government/statistics/annual-flu-reports.

Reichert, T.A., Sugaya, N., Fedson, D.S., Glezen, W.P., Simonsen, L., Tashiro, M., 2001. The Japanese experience with vaccinating schoolchildren against influenza. N. Engl. J. Med. 344 (12), 889–896.

Rhorer, J., Ambrose, C.S., Dickinson, S., Hamilton, H., Oleka, N.A., Malinoski, F.J., Wittes, J., 2009. Efficacy of live attenuated influenza vaccine in children: a meta-analysis of nine randomized clinical trials. Vaccine 27 (7), 1101–1110.

Rose, M.A., Damm, O., Greiner, W., Knuf, M., Wutzler, P., Liese, J.G., Kruger, H., Wahn, U., Schaberg, T., Schwehm, M., Kochmann, T.F., Eichner, M., 2014. The epidemiological impact of childhood influenza vaccination using live-attenuated influenza vaccine (LAIV) in Germany: predictions of a simulation study. BMC Infect. Dis. 14, 40.

Tam, J.S., Capeding, M.R., Lum, L.C., Chotpitayasunondh, T., Jiang, Z., Huang, L.M., Lee, B.W., Qian, Y., Samakoses, R., Lolekha, S., Rajamohanan, K.P., Narayanan, S.N., Kirubakaran, C., Rappaport, R., Razmpour, A., Gruber, W.C., Forrest, B.D., 2007. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. Pediatr. Infect. Dis. J. 26 (7), 619–628.

te Beest, D.E., van Boven, M., Hooiveld, M., van den Dool, C., Wallinga, J., 2013. Driving factors of influenza transmission in the Netherlands. Am. J. Epidemiol. 178 (9), 1469–1477.

Van de Kassteele, J., Van Eijkeren, J., Wallinga, J., 2017. Efficient estimation of age-specific contact rates between men and women. Ann. Appl. Stat. 11 (1), 320–339.

Vynnycky, E., Pitman, R., Siddiqui, R., Gay, N., Edmunds, W.J., 2008. Estimating the impact of childhood influenza vaccination programmes in England and Wales.

Vaccine 26 (41), 5321–5330.
Weidemann, F., Remschmidt, C., Buda, S., Buchholz, U., Ultsch, B., Wichmann, O., 2017. Is the impact of childhood influenza vaccination less than expected: a transmission modelling study. BMC Infect. Dis. 17 (1), 258.
Weycker, D., Edelsberg, J., Halloran, M.E., Longini, I.M., Nizam, A., Ciuryla, V., Oster, G., 2005. Population-wide benefits of routine vaccination of children against influenza. Vaccine 23 (10), 1284–1293.
Woolthuis, R.G., Wallinga, J., Van Boven, M., 2017. Variation in loss of immunity shapes influenza epidemics and the impact of vaccination. BMC Infect. Dis. 17 (1), 632.
Worby, C.J., Chaves, S.S., Wallinga, J., Lipsitch, M., Finelli, L., Goldstein, E., 2015. On the relative role of different age groups in influenza epidemics. Epidemics 13, 10–16.
World Health Organization, 2016. Influenza Fact Sheet. Seasonal Epidemics and Disease Burden. (accessed September 2018). http://www.who.int/mediacentre/factsheets/fs211/en.