Assessment of Public Health and Economic Impact of Intranasal Live-Attenuated Influenza Vaccination of Children in France Using a Dynamic Transmission Model

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Running title: Economic, public health impact of paediatric influenza vaccination in France.

Abstract

OBJECTIVES: We estimated the epidemiological and economic impact of extending the French influenza vaccination programme from at-risk/elderly (≥ 65 years) only to healthy children (2-17 years). **METHODS**: A deterministic, age-structured, dynamic transmission model was used to simulate the transmission of influenza in the French population, using the current vaccination coverage with trivalent inactivated vaccine (TIV) in at-risk/elderly individuals (=current strategy) or gradually extending the vaccination to healthy children (aged 2-17 years) with intranasal, quadrivalent live-attenuated influenza vaccine (QLAIV) from current uptake up to 50% (=evaluated strategy). Epidemiological, medical resource use and cost data were taken from international literature and country-specific information. The model was calibrated to the observed numbers of influenza-like illness visits/year. The 10-year number of symptomatic cases of confirmed influenza and direct medical costs ('all-payer') were calculated for the 0-17 (direct and indirect effects) and ≥18 year old (indirect effect). The incremental cost-effectiveness ratio (ICER) was calculated for the total population, using a 4% discount rate/year. **RESULTS**: Assuming 2.3 million visits/year and 1,960 deaths/year, the model calibration yielded an all-year average basic reproduction number R_0=1.27. In the population aged 0-17 years, QLAIV prevented 865,000 influenza cases/year (58.4%), preventing 10-year direct medical expenses of €374 million. In those aged ≥18 years with unchanged TIV coverage, 1.2 million cases/year were averted (27.6%) via indirect effects (additionally prevented expenses: €457 million). On average, 613 influenza-related deaths were avoided annually overall. The ICER was €18,001/life-year gained. The evaluated strategy had a 98% probability of being cost-effective at a €31,000/life-year gained threshold. **CONCLUSIONS**: The model demonstrated strong direct and indirect benefits of protecting healthy children against influenza with QLAIV on public health and economic outcomes in France.

Key Points for Decision Makers

- A simulation tool taking into account the transmission of the influenza virus among the population was used to estimate the impact of vaccinating children, on top of at-risk/elderly people, against influenza in France;
- When 50% of children aged 2-17 years are vaccinated with a quadrivalent live-attenuated influenza vaccine, the model highlights a direct protection effect in vaccinated children and an indirect protection of older, vaccinated or unvaccinated, individuals;
- The extra cost of the paediatric vaccination programme is compensated by the averted influenza burden to an acceptable extent according to commonly used cost-effectiveness thresholds.

1. Introduction

Since the 2009 H1N1 influenza pandemic, public awareness and surveillance measures have strongly increased worldwide (the number of articles which refer to "influenza" as referenced in PubMed almost doubled between 2008 and 2010). Stimulated by the media, the general population has realised the risks of possible severe complications due to influenza, whether pandemic or seasonal, even in young healthy individuals [1]. Governments were, therefore, expected to take actions that would adequately protect the population against influenza. Currently, there are two distinct influenza vaccination policies: in Belgium, France and Germany, it is recommended to target at-risk persons from 6 months of age including elderly people aged ≥60 or 65 years. This aims to directly protect people who most likely develop severe complications (90% of influenza deaths occur in the elderly [2]). On the other hand, a shift towards vaccinating children has recently occurred in UK, Baltic and Nordic countries, Israel and South America: targeting the most important transmitters of influenza aims at reducing the spread of the virus and, thus, at indirectly reducing the number of cases in adults and elderly as well as in children. Using appropriately designed modelling studies [3], the positive impact of paediatric vaccination on public health outcomes has been demonstrated. Such studies have also contributed to the decision making process in countries that extended their influenza vaccination recommendations [4-8]. Analyses of surveillance data confirmed the positive impact of such programmes [9]. This move towards generalised paediatric influenza vaccination has become an incentive for some European countries and stakeholders to develop their own simulation studies, e.g. in Germany [10, 11] and Belgium [12]. However, such evaluations are not yet available in the French setting. We have therefore conducted a cost-effectiveness assessment of paediatric influenza vaccination in France, using a previously published dynamic transmission model [10] which allows assessing direct and indirect vaccination effects.

2. Aims and Objectives

This study aimed to estimate the public health and economic impact, as well as the cost-effectiveness, of extending the French influenza vaccination recommendations from at-risk individuals and elderly ≥65 years only to additionally including all children aged 2 to 17 years without severe asthma.

3. Methods

3.1 Study design

A deterministic, age-structured, dynamic transmission model was used to simulate the transmission of influenza in the French population, and to compare the outcomes of different vaccination strategies on average over 10 seasons. Although our focus was on vaccinating children, the whole population had to be simulated in order to capture indirect effects in the non-targeted population. Demographic changes and transmission dynamics are described by a system of 23,648 interacting differential equations. Technical details on the two-strain version of the simulation tool, previously used for Germany, were published by Rose *et al.* [10] and Damm *et al.* [11]. A Scientific Committee composed of three French experts in influenza epidemiology, paediatric influenza and pharmacoeconomics contributed to adapt the simulation tool to France (referred to as 'expert opinion' in this article). The model input values and references are presented in Table 1 and described below. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) were used (see completed checklist in supplementary material S1).

3.2 Demographics and contact patterns

The French population was clustered into one-year age cohorts which were subdivided into risk classes with regards to influenza complications. Demographic data for mainland France, as well as population projections until 2060, were retrieved from the National Institute of Statistics and Economic Studies' (INSEE) website [13]. The proportion of individuals with a risk factor was estimated from the vaccination coverage statistics of Tuppin *et al.* 2009 [14]. It was estimated that 11% of children with asthma suffer from a severe form of asthma and, thus, are not eligible for vaccination with a live-attenuated vaccine [15]. Contact patterns (i.e. average age-dependent numbers of contacts per person per day) were derived from the Polymod study [16], using the contact matrix for Belgium which was believed to best capture French contact patterns because of the similarities regarding women employment and modes of child care.

3.3 Natural history of influenza

The simulation tool considers the concomitant and independent transmission of four influenza viruses (the two A strains A(H1N1) and A(H3N2) and the two B lineages B/Yamagata and B/Victoria). The average duration of latency in the model was 1 day, followed by an average 5-day period of contagiousness [17]. The transmissibility of infectious individuals was assumed to vary over the year: it was 43% higher than average around Christmas and 43% lower in summer [5]. The all-year average basic reproduction number R_0 was calibrated to the observed

numbers of influenza-like illness visits per year (see section on calibration). During the simulations, the whole population was assumed to be exposed to an external infection rate of 1 per 1,000 susceptible person-years which also fluctuated seasonally. Following infection, immunity was assumed to last for 6 years after influenza A and 12 years after influenza B [5]. The proportion of individuals developing symptoms in case of infection was assumed to be 66.9% [17]. The mean duration of illness per symptomatic influenza case was 6 days [18]. Two most frequent influenza complications were taken into account: acute otitis media (AOM) occurring frequently in children, and community-acquired pneumonia (CAP) [19]. Finally, patients who developed CAP as a complication of influenza had a specific probability to die; influenza-related CAP was the only cause of death considered in the model.

3.4 Compared vaccination strategies

Two strategies were compared in the base case analysis:

(1) The reference strategy was the current trivalent inactivated vaccination (TIV) coverage in at-risk and elderly (aged ≥65 years) individuals; coverage rates per age and risk status were taken from the sick fund statistics [14, 20, 21].

(2) The evaluated strategy was an extension of the current vaccination to all children aged 2-17 years without severe asthma, using an intranasal, quadrivalent live-attenuated influenza vaccine (QLAIV) and increasing the vaccine uptake from 0 to 50% in 3 annual steps. The comparison of both strategies over ten seasons (2014/15-2023/24) followed the creation of a realistic age-dependent immunity pattern, obtained after running a simulation for 20 years (1992-2013), based on the reported TIV vaccination coverage [22]. Vaccinations were performed annually from October 1st to November 30th in the model. As recommended, two doses of influenza vaccine (TIV or QLAIV) were assumed to be administered in children below 9 years who are receiving influenza vaccine for the first time. As the sick fund statistics indicated that individuals vaccinated in a given year had a higher probability of being vaccinated the following year (OR 30-60) [14], preferential re-vaccination was implemented in the simulations accordingly.

3.5 Vaccination properties

The average vaccine efficacy against influenza infection was determined using meta-analyses of controlled studies including both matched-strains and non-matched-strains seasons, in specific groups: in children aged 2-17 years, efficacy was assumed to be 59% with TIV and 80% with QLAIV [23, 24]; in adults, the average TIV efficacy assumed in the model was 68%

(low-risk [25]) and 58% (at-risk [26]). The duration of vaccination-acquired immunity is known to wane quickly after TIV; 100% immunity loss was therefore assumed at the end of the first season [27]. There is evidence that the immunity acquired after QLAIV vaccination lasts at least until the following season (according to an Asian study, 70% of the children who were protected in the first year were also protected in the second year [28]). Accordingly, we assumed that 30% of the QLAIV-acquired immunity was lost at the end of the first season, and 100% at the end of the second.

These vaccine properties are linked to the inactivated or live-attenuated type of influenza vaccine, and are not modified by the number of strains included in the vaccine: QLAIV can immunise against all four influenza strains, while TIV immunises against three. The composition of TIV was known until season 2014/15; for future years, a random choice was made annually to determine which B lineage is included in TIV. To account for the random TIV composition, model results were provided on average over 1,000 simulations.

3.6 Medical resource use and cost inputs

Direct medical resource use was distinguished between the treatment of symptomatic influenza, influenza-related AOM or CAP. The French literature, confirmed by experts' opinion, allowed quantifying the frequencies of physician visits, prescriptions, self-medication and hospitalisations, specifically in children and adults, per low/at-risk status (Table 2). The corresponding unit costs (year 2014) were obtained from the official tariffs available on the French sick fund's website [29] and from the French technical agency of information on hospitals (ATIH) [30]. An 'all-payer' perspective was adopted, including sick fund plus patient co-payments as recommended by the French National Authority for Health (HAS) [15]. A societal perspective, including productivity losses caused by sick leave, using the human capital method, was examined in sensitivity analysis.

3.7 Model calibration

The all-year average of the basic reproduction number (R_0) was calibrated on the estimated number of annual influenza visits, all other demographic and epidemiologic parameters being set. The calibration target was derived from the numbers of influenza-like illness (ILI) visits/year published annually by the French institute for public health surveillance (INVS): (1) From 2005/06 to 2012/13, an average of 2,545,714 ILI visits occurred annually in France [31]; (2) we assumed that 65% of these visits occurred during the 9-week influenza epidemic window lasting from December to February; (3) during that window, we further assumed that 75% of

ILI were caused by influenza, compared to 25% during the rest of the year, excluding July and August (no influenza) as per expert opinion. Combining these data led to an annual calibration target of 2.2 million influenza visits for the seasons 2005/06 to 2012/13 i.e. 3.5% of the French population annually. A secondary calibration target was the annual number of deaths. Based on time series analysis over 10 seasons (1980-1990) in France, the number of influenza-related pneumonia deaths ranged between 1,100 and 17,100 per season in the 75+ age group only [32]. Another, more general, source, indicated that 1,500-2,000 deaths were caused by influenza every season in France [2]. To ensure a conservative number of deaths predicted by the model, this latter range was used as our secondary calibration target, by adjusting the probabilities of CAP-related deaths, we ensured that this target was reached. The probabilities were set specifically in children (<18) and adults (18+), per risk status.

3.8 Model outcomes

The epidemiologic and public health outcomes of interest were the numbers of symptomatic cases of confirmed influenza, AOM, CAP, influenza-related hospitalisations, deaths caused by influenza-related CAP and life-years lost during an evaluation period of 10 years. Although incidence rates are available per season, using a deterministic model implies that stochastic transmission events are smoothed out (annual incidence fluctuates less than in reality) and, consequently, results should only be interpreted as averages over 10 seasons. The economic outcomes of interest were the total vaccination costs, influenza-related treatments costs and the total direct medical costs ('all-payer' perspective). The costs of productivity losses were considered in a sensitivity analysis. The outcomes were first estimated for children aged below 18 years, to assess the effect of the new versus the current vaccination recommendations in this targeted group. The indirect protection effect in the adult population was estimated separately. Finally, the total effect in the French population was assessed. The epidemiological and costs outcomes per strategy were first presented in a disaggregated, undiscounted way. The incremental cost-effectiveness ratio (ICER) was then calculated in Euros per life-year gained for the total population, using an annual 4% discount rate for life-years and costs [15].

3.9 Sensitivity and scenario analyses

A tornado diagram was produced to show the impact of univariate variations of key model parameters on the number of averted cases of confirmed symptomatic influenza. The included parameters were the basic reproduction number R_0, the vaccine efficacy of QLAIV, the immunity duration after infection or vaccination, respectively, the percentage of the population

with risk factors, the proportion of infected individuals developing symptoms, the duration of the evaluation period and discount rates.

A probabilistic sensitivity analysis (PSA) was performed whereby the cost-effectiveness plane represents the incremental cost as a function of the incremental life-years gained. Variations of +/-25% around the central estimate were generally used to determine the PSA distributions' parameters (see supplementary material S4).

Finally, the following scenario analyses were presented: (1) inclusion of indirect costs (societal perspective); (2) comparison QLAIV vs. trivalent live-attenuated influenza vaccine (TLAIV) to assess the added value of having both B strains (B/Victoria, B/Yamagata) in the live vaccine; (3) comparison QLAIV vs. quadrivalent inactivated vaccine (QIV) to assess the added value of the live over the inactivated influenza vaccine; (4) targeting the age group 2-6 years with coverage rates varying from 10 to 90%; (5) ICER re-estimation assuming that all influenza-related CAP deaths occurred in the 65+ age group.

4. Results

4.1 Calibration

Model calibration led to 2.3 million influenza visits/year and 1,960 influenza-related CAP deaths/year when using a mean R_0 of 1.27 (the deviation from the calibration target was less than 10%). Most deaths (88%) occurred in adults at higher risk of severe complications and elderly aged above 65, and other death cases occurred in at-risk children aged 0-17.

4.2 Epidemiologic and public health impact

QLAIV vaccination coverage of 50% among children aged 2 to 17 years prevented a total of 20.2 million symptomatic cases of confirmed influenza within the 10-year evaluation period as a result of direct and indirect protection (Table 3). The highest number of averted cases was found among adults (≥18 years) for which the vaccination coverage remained unchanged: 11.6 million cases (28% of the cases which occur under the current strategy) were avoided in this group via indirect protection effects obtained by vaccinating children. In the targeted paediatric population, 8.6 million cases (58%) of confirmed influenza were averted in the 10-year evaluation period. Overall, the attack rate for symptomatic influenza cases dropped from 8.6% annually with the current strategy to 5.6% with the evaluated strategy. In the total population, the relative reductions of influenza-related events ranged from 31% (613 averted CAP-related deaths/season, 77% thereof in at-risk adults) to 50% (108,000 AOM cases averted/season, 89% thereof in those aged 0-17 years). This range of percent reductions reflects the higher relative

reduction of influenza cases in children in which most of the AOM cases are found, while deaths occur mainly in the elderly/at-risk individuals.

Influenza infection dynamics over time with both current and evaluated strategies is shown in supplementary material S2.

4.3 Economic and cost-effectiveness analysis

Adopting the new vaccination strategy saved €831 million in influenza-related medical treatments within 10 years in total (Table 3). The highest savings occurred in the population not targeted by the new vaccination strategy (€457 million in adults aged ≥18 years vs. €374 million in children aged <18 years). The avoided costs of sick leave prescriptions in adults were more than three times as high as the avoided costs of "sick-children days-off" (€1,702 vs. €510 million). The evaluated vaccination strategy was cost-effective from both the 'all-payer' (ICER €18,001/life-year gained) and the societal perspective (€1,596/life-year gained).

4.4 Sensitivity analyses

The factor that had the largest impact on the number of averted influenza cases was the duration of immunity after influenza A infection (Figure 1). Decreasing the duration of natural immunity against influenza A to 2 years instead of 6 years yielded twice as many averted cases, both in adults and in children. The immunity duration after influenza B infection is also among the main influential factors, with approximately 20% more cases averted if the immunity duration is limited to 6 years (base case: 12 years). Comparatively, further increasing the natural immunity duration had a smaller impact on the averted cases (-15%).

The second most influential factor was the basic reproduction number R_0. Using an extreme value of R_0 =2.5 led to more averted cases in the targeted paediatric population (Figure 1a), but less averted cases in the adult group (Figure 1b). This non-linear pattern reflects the complexity of the relationships between the dynamic transmission parameters.

As expected, the total number of averted cases increased with the time horizon (+/- 50% averted paediatric cases and -30% to +21% averted adult cases with an evaluation period of 5 to 15 years; see influenza infection dynamics over 15 years in supplementary material S3). With variation of +/- 10% around the base case value (66.9%), the proportion of infected individuals developing symptoms led to variations of +/- 10% around the base case number of averted cases.

The above-described parameters were also driving the cost-effectiveness results: the ICER ranged from €7,202 to €22,889 per life-year gained for natural immunity durations after

influenza A infection from 2 to 12 years (base case 6 years) (Figure 1c). Smaller values of the discount rate improved the ICER.

Other tested factors (QLAIV vaccine efficacy, QLAIV immunity loss after 1 season, percentage of at-risk children) had a less than 10% impact on the results.

Based on a PSA with 5,000 simulations, and assuming a willingness-to-pay threshold of €31,000/life-year gained (French GDP/capita), a coverage of 50% in children aged 2-17 years with QLAIV was cost-effective in 98% of the simulations (Figure 2). The central 95% of ICER values ranged from €12,201 to €29,662/life-year gained (base case €18,001).

4.5 Scenario analyses

Assuming a maximum coverage of 50% in children aged 2-17 years, the 10-year number of symptomatic cases was 44.8 million when using QIV and 43.7 million when using TLAIV, while it was 36.5 million when using QLAIV (compared to 56.7 million cases in the reference scenario). The average number of prevented cases per year in the total population dropped from 2.0 million with QLAIV to 1.3 million when using TLAIV (-35%) and 1.2 million when using QIV (-42%).

In terms of prevented symptomatic cases, the benefit of using the live-attenuated instead of the inactivated influenza vaccine (QLAIV vs. QIV) seemed therefore slightly higher than the benefit of using the quadrivalent instead of the trivalent version of the live vaccine (QLAIV vs. TLAIV).

Restricting QLAIV vaccination to children aged 2-6 years (instead of those aged 2-17 years) would avert between 0.9 million (coverage rate 10%) and 7.2 million (coverage rate 90%) symptomatic cases over 10 years. The situation is less cost-effective than the strategy targeting all children aged 2-17 years (ICER between €29,000 and €40,000/life-year gained when varying the coverage rate from 10% to 90%), as the indirect protection does not reach the same magnitude.

According to the model developed, a programme vaccinating 90% of children aged 2-17 years with QLAIV achieves a 57% reduction of symptomatic cases overall (48% reduction of adult cases) compared to the reference scenario, while remaining cost-effective (ICER €22,885/life-year gained; Figure 3) according to the commonly used willingness-to-pay thresholds.

Our last scenario analysis concerned the age-distribution of CAP-related deaths in the model. In our base case, about half (48%) of the prevented deaths occurred in the 65+ age group. The corresponding life-years saved (from the averted deaths in the 65+ group only) were 43,831 (undiscounted) and 24,665 (discounted). If the other half of the prevented deaths would have occurred in the 65+ as well instead of occurring in the younger age group, a total of 87,662 undiscounted life-years (base case 246,087) or 49,331 discounted life-years (base case 82,117) would have been saved. The ICER re-calculated with the newly estimated number of life-years was €29,965 per life-year gained (base case €18,001), which is still smaller than the French GDP per capita.

5. Discussion

Our simulation studies demonstrated strong positive direct and indirect impact for public health and economic outcomes in France when routine vaccination with QLAIV is implemented in healthy children aged 2-17 years. A vaccination strategy targeting this population with QLAIV (accompanied by the current TIV vaccination for the rest of the population) is estimated to be a cost-effective strategy compared to the current coverage of the at-risk/elderly population. The magnitude of these results is in line with findings using the Belgian version of the model [33] and with a previously published German simulation study [10, 11], based on an older version of the same simulation tool which did not yet use four influenza strains, but only distinguished between influenza A and B. The effects of generalised paediatric vaccination was less promising in our simulation studies than in the UK studies [5, 6, 8] which reported up to 84% of averted cases in the total population when vaccinating 50% of children aged 2-17 years with LAIV as compared to the current policy. The positive effects in these studies may have mostly derived from assuming that a single vaccination (TIV or LAIV) prevented influenza A and B infections for 6 and 12 years, respectively. A Belgian model reported about 12-24% averted cases with 30-80% QLAIV uptake in children aged 2-17 years [12]. The latter transmission model had specific features regarding the key epidemiologic parameters (number of strains, seasonal fluctuations, immunity duration, basic reproduction number R_0), and was using a global search algorithm to estimate the best fitting set of input values. Distinct programming approaches of dynamic transmission models are expected to lead to a wide range of results; however, all models quoted above lead to compatible conclusions with regard to paediatric influenza vaccination, from very cost-effective with an ICER as low as £251 per QALY in the UK [7] to borderline cost-effective (€45,000 per QALY) in Belgium [12]. Our base case ICER expressed in cost per QALY gained falls in between the previous estimates: €8,522 per QALY

from the 'all-payer' perspective, and €755 per QALY from the societal perspective, assuming 0.007 QALY lost per influenza episode [34].

Our last scenario analysis assuming that all deaths occur in the 65+ age group highlighted the critical impact of the age-distribution of influenza-related deaths on the total life-years gained, and thus on the ICER (increasing from €18,001 to €29,965 per life-year gained in our scenario, and from €8,522 to €30,306 per QALY gained). The age distribution of mortality was earlier reported as an influential factor when evaluating new influenza vaccination strategies [12] [35]. Despite very conservative assumptions (1,500-2,000 deaths per year in the 65+ and no deaths in 0-64 year-old), our evaluated strategy remained cost-effective according to a generally accepted (informal) threshold (ICERs per life-year and QALY gained lower than €31,000, the French GDP per capita).

Our main reasons for reporting 'cost per life-year gained' rather than 'cost per QALY gained' ratios in the main analysis were the absence of French studies providing influenza-related utility data and the difficulty to estimate QALY losses during an acute event –such as influenza- generally with no sequelae. In addition, the number of deaths remains the main clinical outcome of influenza vaccination policy in France.

The model was calibrated to the average number of symptomatic confirmed cases registered by the French national influenza surveillance network. As per the deterministic nature of our simulation tool, it was outside the model scope to make predictions of how future individual influenza seasons will look like, or how seasons' variability would be modified by QLAIV vaccination. Similarly, the variability in the circulating respiratory viruses within and across seasons were not included in the model 10-year average results.

Further benchmarks were used to ensure model validity however: the population size and structure followed the French national statistics and predictions between 1992 and 2024, and the average number of hospitalisations (27,500/year) was in line with a recent analysis of French hospital records, reporting an average of 65,399 hospital admissions/year with a diagnosis of confirmed influenza or pneumonia (CAP) [36]. Finally, the average attack rate of symptomatic influenza over 10 years was 8.6% in the current strategy, which is within the range of national statistics [2], despite important uncertainty regarding the distribution of influenza cases and flu positivity rates during and outside the epidemic period.

Our choice of parameter values has been considered by experts to be highly conservative, especially regarding the rate of events in at-risk individuals. Furthermore, although influenza-related mortality was only linked to CAP in our model, it was more important to us to predict a conservative number of deaths than accurately predicting the number of influenza deaths that are due to CAP. The range of 1,500-2,000 deaths per year on which our model was calibrated can be extrapolated to an excess mortality of about 8,000 deaths per influenza season: according to several studies, the ratio between the direct mortality and indirect mortality (fatal influenza-related complications caused by pre-existing cardiovascular or neurologic conditions) is comprised between 2 and 8 [31, 32, 37].

The duration of immunity, be it after infection or after vaccination, is still a source of debate. As these durations have not yet been measured in appropriate studies, we used previously published assumptions on naturally-acquired immunity [5] derived from the Tecumseh study [38]. The average immunity duration after influenza A had a large impact on our results, and although B-epidemics only occur once or twice every 10 years, the immunity duration after influenza B sensibly impacted the results. The impact of QLAIV acquired immunity duration was limited because the same individuals tend to be vaccinated every year. To account for a higher uncertainty, extreme values around the central estimates of immunity durations were tested in sensitivity analyses, i.e. beyond the +/-25% variation used for other parameters. To not excessively increase the complexity of the analyses, partial immunity and genetic drift were not modelled.

Children exposed yearly to new influenza strains tend to be infected more easily than adults and might develop symptoms more often once infected; in our model, we used a common value across age classes (66.9%) in absence of more specific studies. The use of challenge studies is not appropriate in children or at-risk persons for safety and ethical reasons. Contact patterns may change when individuals become sick [39], yet our model uses the same contact matrix throughout the season, independent of the health status of the individuals. Noteworthy, a contact matrix developed specifically for the French population has been released after we performed our analyses [40]. The impact of using a non-French matrix from the Polymod study on our results is likely to be attenuated given the similarities between both studies, and the fact that the highest number of contact was always concentrated on children and teenagers. Finally, vaccine-related adverse events were not taken into account as they were generally mild and not different between TIV and LAIV used in their respective indications.

Our simulation tool was able to reproduce a credible, conservative outcome with the current vaccination strategy and TIV coverage rate, and showed both direct and indirect benefits of additionally protecting healthy children against influenza with a live-attenuated quadrivalent influenza vaccine specifically developed for a paediatric population. In the French context, the paediatric influenza vaccination with QLAIV appears to be cost-effective.

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Compliance with Ethical Standards

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Conflict of interest

LG and ML are employees of IMS Health which received consulting fees from AstraZeneca. SG is employed by AstraZeneca. OD has conducted studies for and received honoraria from Herescon GmbH, which has received research support and consulting fees from AstraZeneca and MedImmune. MS is employee and shareholder of ExploSYS GmbH, which has received payments from Epimos GmbH, a contract research and consulting institute, which has received research support and consulting fees from AstraZeneca. ME is partner and shareholder of the contract research and consulting institute Epimos GmbH, which received consulting fees and research support from AstraZeneca, Novartis and GlaxoSmithKline. FC has received consulting fees from AstraZeneca and GlaxoSmithKline. XL has received consulting fees from AstraZeneca. CWO has received grants for congresses and honoraria for conferences and meetings from AstraZeneca, GlaxoSmithKline, Novartis, Pfizer, Sanofi-Pasteur, and Sanofi-Pasteur MSD.

Authorship

ME and OD conceptualised the study, carried out the simulations and interpreted the results. MS designed and developed the simulation tool and provided technical support. LG provided local data input, analysed the simulation results and drafted the manuscript; CWO, FC, XL were part of the Scientific Committee of the project; they provided expertise and guidance on data input and assumptions; SG provided clinical data inputs and coordinated the discussions with

the Scientific Committee; all authors critically appraised, corrected and validated the manuscript.

Tables and Figures (*to be submitted as separate files*):

Table 1: Epidemiological model input values and sources

Table 2: Medical resources and unit cost input values and sources

Table 3: Base case epidemiology, public health and economic results over 10 years in mainland France

Figure 1: Tornado diagrams (univariate sensitivity analysis):
a) Number of averted cases of confirmed influenza in children aged 0-17 years (combining direct and indirect effects)
b) Number of averted cases of confirmed influenza in adults aged ≥18 years (indirect effect)
c) Incremental cost-effectiveness ratio (ICER), 'all-payer' perspective

VE: vaccine efficacy; (Q)LAIV: (quadrivalent) live-attenuated influenza vaccine; pct: percent; R_0: basic reproduction number; durations are in years. 1,000 simulations were performed with each tested value (low and high).

Because of the stochasticity caused by the random composition of the trivalent inactivated vaccine (TIV), the results of univariate sensitivity analyses are given as averages over several simulation runs (N=1,000).

The range of averted cases obtained with R_0 values around the base case value of 1.27 does not contain the base case number of averted cases. This might happen when studying the indirect effect, given the non-linear association between the different parameters.

Figure 2: Cost-effectiveness plane of the evaluated versus the current strategy

Current strategy: vaccination of at-risk individuals and elderly (aged ≥65 years) with trivalent inactivated vaccine.

Evaluated strategy: vaccination of 50% of children aged 2-17 years with quadrivalent live-attenuated influenza vaccine, add-on to the current vaccination strategy.

The red dotted line indicates a willingness-to-pay (WTP) threshold of €31,000 per life-year gained (LYG): 98.5% of the simulations are acceptable.

5,000 simulations were performed per vaccination strategy.

Information on parameters and distributions used are available in supplementary material S4.

Figure 3: Scenario analyses on quadrivalent live-attenuated influenza vaccine coverage rate and targeted age:

a) Percentage of averted cases in adults aged ≥18 years depending on the coverage scenario (indirect effect)

b) Percentage of averted cases in the total population depending on the coverage scenario

c) Incremental cost-effectiveness ratio (ICER) in € per life-year gained depending on the coverage scenario

1,000 simulations were performed per vaccination strategy.

Table 1: Epidemiologic model inputs values and sources

Parameter s	Age (years)	Value base case	Source
Population mainland France	All ages	2014: 63.9 million 2024: 67.0 million	[13]
	2-17	2014: 22.0% of the population; 2024: 21.2%	[13]
Risk factor for severe influenza complications	0-9 10-17 18-44 45-64	6.2% (at-risk, without severe asthma) 4.4% (at-risk, without severe asthma) 5.4% 10.2%	[14]
	0-9 10-17	0.7% (at-risk, with severe asthma) 0.5% (at-risk, with severe asthma)	[15]
Transmission dynamics	5y age groups	Number of contacts between individuals, per day 'Polymod' contact matrix, 'all reported contacts', Belgium	[16]
	All ages	Basic reproduction number $R_0 = 1.27$ (annual average)	Calibration
	All ages	Infection introduction rate, per patient per year: 1/1,000	Assumption
Natural history of influenza	All ages	Proportion of infected individuals developing symptoms: 66.9%	[17]
	All ages	Duration of latency: 1 day	[17]
	All ages	Duration of contagiousness: 5 days	[17]
	All ages	Duration of symptoms: 6 days	[18]
	All ages	Duration of naturally-acquired immunity after infection: Influenza A: 6 years; Influenza B: 12 years	[5]
Complications of symptomatic influenza	0-1 2-8 9-17 <18 at-risk ≥18 at-risk	39.7% 19.6% 4.4% 19.6% 1.1%	[19], [37]
	0-1 2-8	2.8% 2.5%	[19], [37] , expert opinion

	9-17 18-64 no risk <18 at-risk ≥18 at-risk	1.0% 0.4% 6.0% 2.5%	Community-acquired pneumonia (CAP)		
	No risk <18 at-risk ≥18 at-risk	0.02% 5.00% 10.00%	Probability of dying in case of CAP		Calibration
Calibration	All ages	2.2 million influenza visits/year:			[31], expert opinion
	All ages At-risk	1,500-2,000 influenza-related deaths/year 90% of influenza deaths occurring in at-risk adults			[2]
Vaccination coverage		**Current strategy**	**Evaluated strategy**		
		TIV	**TIV**	**QLAIV**	[21]
	<2, no risk	3.4%	3.4%	0%	
	2-8, no risk	3.4%	0%	From 3.4% to 50%*	
	9-17, no risk	8.0%	0%	From 8.0% to 50%	
	18-34, no risk	7.0%	7.0%	0%	
	35-49, no risk	10.0%	10.0%	0%	
	50-64, no risk	21.0%	21.0%	0%	
	<2, at-risk	17.3%	17.3%	0%	
	2-8, at-risk	17.3%	0%	From 17.3% to 50%	
	9-17, at-risk	19.5%	0%	From 19.5% to 50%	
	18-64, at-risk	31.9%	31.9%	0%	
	65+, at-risk	54.0%	54.0%	0%	
	<2, severe asthma	17.3%	17.3%	0%	
	2-8, severe asthma	17.3%	From 17.3% to 50%	0%	
	9-17, severe asthma	19.5%	From 19.5% to 50%	0%	

Vaccine efficacy		**TIV**	**QLAIV**	
	1	11%	NA	[41]
	2-17	59%	80%	[23, 24]
	>18, no risk	68%	NA	[25]
	>18, at-risk	58%	NA	[26]
Immunity duration	All ages	100% immunity lost at end of 1st season	% lost at end of : 1st season: 30% 2nd season: 100%	[23, 24], [27]
Re-vaccination factor	All Ages	RR=6.0 of being vaccinated, when vaccinated in previous year		[14]
Time horizon	Initialisation period: 1994/95-2008/09 (time to build up immunity status, arbitrary)			
	Transition period: 2009/10-2013/14 (to adjust coverage rates post-pandemia)			
	Evaluation period: 2014/15-2023/24			
Perspective	Base case analysis: 'all-payer', direct medical costs only (sick fund + patient co-payments)			[15]
	Scenario analysis: Societal ('all-payer' + costs of productivity losses)			[15]
Discounting	Disaggregated outcomes: undiscounted			[15]
	ICER calculation: 4% per year (costs, effects)			[15]

ILI: influenza-like illness; INSEE: institut national de la statistique et de l'évaluation économique (http://www.insee.fr/fr/); NA: not applicable; OR: odds ratio; QLAIV: quadrivalent live-attenuated influenza vaccine; RR: relative risk; TIV: trivalent inactivated vaccine

*Maximum coverage reached in 3 years

Table 2: Medical resources and unit costs inputs values and sources

Treatments	CH1	CH2	CH3	CH4	OHA	ARA	ARC	Source
Symptomatic influenza								
Physician consultation given symptomatic flu	70.0%	70.0%	52.5%	35.0%	35.0%	52.5%	90.0%	[42], expert opinion
Drug prescriptions given consultation:								
Antivirals (oseltamivir)	5.0%	5.0%	5.0%	5.0%	5.0%	45.0%	45.0%	[43-44]
of which experiencing a beneficial effect:	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	Assumption: median 1 day reduction of symptoms duration
Antibiotics	23.7%	15.6%	15.6%	5.0%	5.8%	33.7%	33.7%	[19], [45-47]
Analgesics and antipyretics	90.0%	90.0%	90.0%	90.0%	90.0%	90.0%	90.0%	[45-47]
Antitussives	43.9%	43.9%	43.9%	43.9%	3.6%	51.2%	51.2%	[45-47]
Self-medication (OTC)	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	[45-47]
Hospitalisation (influenza)	0.05%	0.05%	0.05%	0.05%	0.05%	0.35%	0.35%	[48], calibration
AOM								
Antibiotic therapy	80.0%	80.0%	25.0%	25.0%	25.0%	80.0%	80.0%	[49], expert opinion
Analgesics and antipyretics	90.0%	90.0%	90.0%	90.0%	90.0%	90.0%	90.0%	[45-47]
Nasal spray	16.2%	16.2%	16.2%	16.2%	14.0%	24.4%	24.4%	[45-47]
CAP								
Antibiotic therapy	95.0%	95.0%	80.0%	80.0%	80.0%	95.0%	95.0%	[49], expert opinion
Analgesics and antipyretics	90.0%	90.0%	90.0%	90.0%	90.0%	90.0%	90.0%	[45-47]
Antitussives	43.9%	43.9%	43.9%	43.9%	3.60%	51.2%	51.2%	[45-47]
Outpatient chest x-ray	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	[50]

Hospitalisation (CAP)	50.0%	25.0%	25.0%	25.0%	25.0%	50.0%	90.0%	Expert opinion, calibration
Productivity loss								
% of employed with sick leave given symptomatic influenza*	25.0%	25.0%	25.0%	25.0%	70.0%	70.0%	25.0%	[44]
Average duration (days)	3.0	3.0	3.0	3.0	4.8	4.8	3.0	
Employment rate*	81.6%	81.6%	81.6%	81.6%	18-24y: 29.9% 25-49 y: 81.6% 50-64 y: 54.8%		81.6%	[13]
Unit cost (2014; in €), 'all-payer'	**CH1**	**CH2**	**CH3**	**CH4**	**OHA**	**ARA**	**ARC**	**Source**
TIV dose	6.14	6.14	6.14	6.14	6.14	6.14	6.14	[29] BdM_IT
QLAIV dose	NA	30.37	30.37	30.37	NA	NA	30.37	Public Price (manufacturer)
Vaccine administration	25	23	23	23	23	23	23	[29] (CH1: paediatrician, else GP tariff)
Chest X-ray, outpatient	21.28	21.28	21.28	21.28	21.28	21.28	21.28	[29], procedure ZBQK002
Hospitalisation								
Influenza	4467	4467	4467	4467	4467	4467	4467	[30], GHM 04M25
CAP	2357	2357	2357	2357	5414	5414	2357	[30], GHM 04M04, 04M05
Medications								[29] BdM_IT
Antivirals	12.40	12.40	18.34	24.27	24.27	24.27	24.27	
Antibiotics (influenza)	2.20	5.24	5.24	5.24	5.24	5.24	5.24	
Antibiotics (AOM, CAP)	8.99	8.99	8.99	8.99	9.03	9.03	9.03	
Analgesics, antipyretics	2.02	2.02	2.02	2.02	2.08	2.08	2.08	
Antitussives	2.89	2.89	2.89	2.89	2.89	2.89	2.89	
Nasal spray	5.09	5.09	5.09	5.09	4.95	4.95	4.95	
Self-medication	10.00	10.00	10.00	10.00	10.00	10.00	10.00	Assumption

Indirect costs	142.5	142.5	142.5	142.5	142.5	142.5	142.5	[13]

* CH1-4, ARC: assuming parents aged 25-49 years

AOM: acute otitis media; ATIH: agence technique de l'information sur l'hospitalisation (technical agency for hospital information); BdM_IT: base des médicaments et informations tarifaires (medication and costs database); CAP: community-acquired pneumonia; GHM: groupe homogène de maladies (diagnosis related group); OTC: over-the-counter medication; T2A: tarification à l'activité (fee-per-service); CH1: children without risk factors, aged 0-1 year; CH2: children without risk factors, aged 2-6 years; CH3: children without risk factors, aged 7-8 years; CH4: children without risk factors, aged 9-17 years; OHA: otherwise healthy adults; ARA: at-risk adults, including elderly aged ≥65 years; ARC: at-risk children, including children with severe asthma, aged 0-17 years.

Table 3: Base case epidemiology, public health and economic results over 10 years in mainland France

Outcome	Current strategy	Evaluated strategy	Difference Evaluated – Current (absolute numbers)	Difference Evaluated – Current (%)
Aged <18 years (N=14.1 million)				
Epidemiology	**N (attack rate)**	**N (attack rate)**	**N (attack rate)**	**Relative change**
Infections (A + B)	22,146,156 (15.7%)	9,222,177 (6.5%)	-12,923,979 (-9.1%)	-58.4%
Symptomatic cases	14,815,778 (10.5%)	6,169,636 (4.4%))	-8,646,142 (-6.1%)	-58.4%
Influenza complications	**N (rate /100,000 /year)**	**N (rate /100,000 /year)**	**N (rate /100,000 /year)**	**Relative change**
AOM	1,742,660 (1,233.6)	783,975 (554.9)	-958,684 (-678.6)	-55.0%
CAP	271,002 (191.8)	116,132 (82.2)	-154,869 (-109.6)	-57.1%
Antibiotics courses	2,257,205 (1597.8)	1,025,027 (725.6)	-1,232,178 (-872.2)	-54.6%
Hospitalisations	115,217 (81.6)	50,714 (35.9)	-64,503 (-45.7)	-56.0%
Deaths	2,505 (1.8)	1,091 (0.8)	-1,414 (-1.0)	-56.5%
Life-years lost	204,570 (144.8)	89,402 (63.3)	-115,168 (-81.5)	-56.3%
Health economics	**€**	**€**	**€**	**Relative change**
Vaccination costs	312,004,074	3,136,288,658	2,824,284,584	905.2%
Influenza treatments costs	656,994,058	283,423,078	-373,570,980	-56.9%
Outpatient visits and procedures	172,338,741	73,465,479	-98,873,262	-57.4%
Medication	165,520,617	69,924,636	-95,595,981	-57.8%
Hospitalisation	319,134,700	140,032,963	-179,101,737	-56.1%
Total direct costs	**968,998,131**	**3,419,711,736**	**2,450,713,604**	**252.9%**
Indirect costs	872,996,713	363,022,476	-509,974,237	-58.4%
Total society costs	**1,841,994,844**	**3,782,734,212**	**1,940,739,368**	**105.4%**

Aged ≥ 18 years (N=51.6 million)				
Epidemiology	**N (attack rate)**	**N (attack rate)**	**N (attack rate)**	**Relative change**
Infections (A + B)	62,597,202 (12.1%)	45,332,446 (8.8%)	-17,264,757 (-3.3%)	-27.6%
Symptomatic cases	41,877,528 (8.1%)	30,327,406 (5.9%)	-11,550,122 (-2.2%)	-27.6%
Influenza complications	**N (rate /100,000 /year)**	**N (rate /100,000 /year)**	**N (rate /100,000 /year)**	**Relative change**
AOM	439,714 (85.2)	318,438 (61.7)	-121,276 (-23.5)	-27.6%
CAP	303,868 (58.9)	220,068 (42.6)	-83,800 (-16.2)	-27.6%
Antibiotics courses	2,337,449 (452.8)	1,692,841 (327.9)	-644,607 (-124.9)	-27.6%
Hospitalisations	160,056 (31.0)	115,917 (22.5)	-44,138 (-8.6)	-27.6%
Deaths	17,094 (3.3)	12,381 (2.4)	-4,714 (-0.9)	-27.6%
Life-years lost	471,645 (91.4)	340,727 (66.0)	-130,919 (-25.4)	-27.8%
Health economics	**€**	**€**	**€**	**Relative change**
Vaccination costs	3,715,337,163	3,715,337,162	0	0.0%
Influenza treatments costs	1,658,586,189	1,201,175,803	-457,410,386	-27.6%
Outpatient visits and procedures	369,765,975	267,783,734	-101,982,242	-27.6%
Medication	420,198,241	304,307,750	-115,890,492	-27.6%
Hospitalisation	868,621,972	629,084,320	-239,537,652	-27.6%
Total direct costs	**5,373,923,352**	**4,916,512,966**	**-457,410,386**	**-8.5%**
Indirect costs	4,343,631,701	3,151,427,197	-1,192,204,504	-27.4%
Total societal costs	**9,717,555,052**	**8,067,940,162**	**-1,649,614,890**	**-17.0%**
Total population (N=65.8 million)				
Epidemiology	**N (attack rate)**	**N (attack rate)**	**N (attack rate)**	**Relative change**
Infections (A + B)	84,743,359 (12.9%)	54,554,623 (8.3%)	-30,188,736 (-4.6%)	-35.6%
Symptomatic cases	56,693,307 (8.6%)	36,497,043 (5.6%)	-20,196,264 (-3.1%)	-35.6%

Influenza complications	**N (rate /100,000 /year)**	**N (rate /100,000 /year)**	**N (rate /100,000 /year)**	**Relative change**
AOM	2,182,374 (331.9)	1,102,413 (167.7)	-1,079,961 (-164.2)	-49.5%
CAP	574,869 (87.4)	336,200 (51.1)	-238,669 (-36.3)	-41.5%
Deaths	19,599 (3.0)	13,471 (2.1)	-6,128 (-0.9)	-31.3%
Life-years lost	676,216 (102.8)	430,129 (65.4)	-246,087 (-37.4)	-36.4%
Antibiotics courses	4,594,653 (698.8)	2,717,868 (413.3)	-1,876,785 (-285.4)	-40.8%
Hospitalisations	275,273 (41.9)	166,631 (25.3)	-108,642 (-16.5)	-39.5%
Health economics	**€**	**€**	**€**	**Relative change**
Vaccination costs	**4,027,341,236**	**6,851,625,820**	**2,824,284,584**	**70.1%**
Influenza treatments costs	2,315,580,247	1,484,598,881	-830,981,365	-35.9%
Outpatient visits and procedures	542,104,716	341,249,213	-200,855,504	-37.1%
Medication	585,718,858	374,232,386	-211,486,473	-36.1%
Hospitalisation	1,187,756,672	769,117,283	-418,639,389	-35.2%
Total direct costs	**6,342,921,483**	**8,336,224,701**	**1,993,303,219**	**31.4%**
Indirect costs	5,216,628,414	3,514,449,673	-1,702,178,741	-32.6%
Total societal costs	**11,559,549,897**	**11,850,674,374**	**291,124,478**	**2.5%**
Cost-effectiveness				
Discounted life-years lost	242,210	160,092	-82,117	
Discounted total direct costs	€4,934,088,196	€6,412,265,983	€1,478,177,787	
ICER, 'all-payer' perspective		**€18,001 per life-year gained**		
Discounted total societal costs	€9,001,073,262	€9,132,103,178	€131,029,916	
ICER, societal perspective		**€1,596 per life-year gained**		

AOM: acute otitis media; CAP: community acquired pneumonia; ICER: incremental cost-effectiveness ratio.

N: mainland France population size on average over 2014-2023; results were averaged over 1,000 simulations.

Current strategy: vaccination of at-risk individuals and elderly (aged ≥65 years) with trivalent inactivated vaccine.

Evaluated strategy: vaccination of 50% of children aged 2-17 years with quadrivalent live-attenuated influenza vaccine, add-on to the current vaccination strategy.

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Figure 1a

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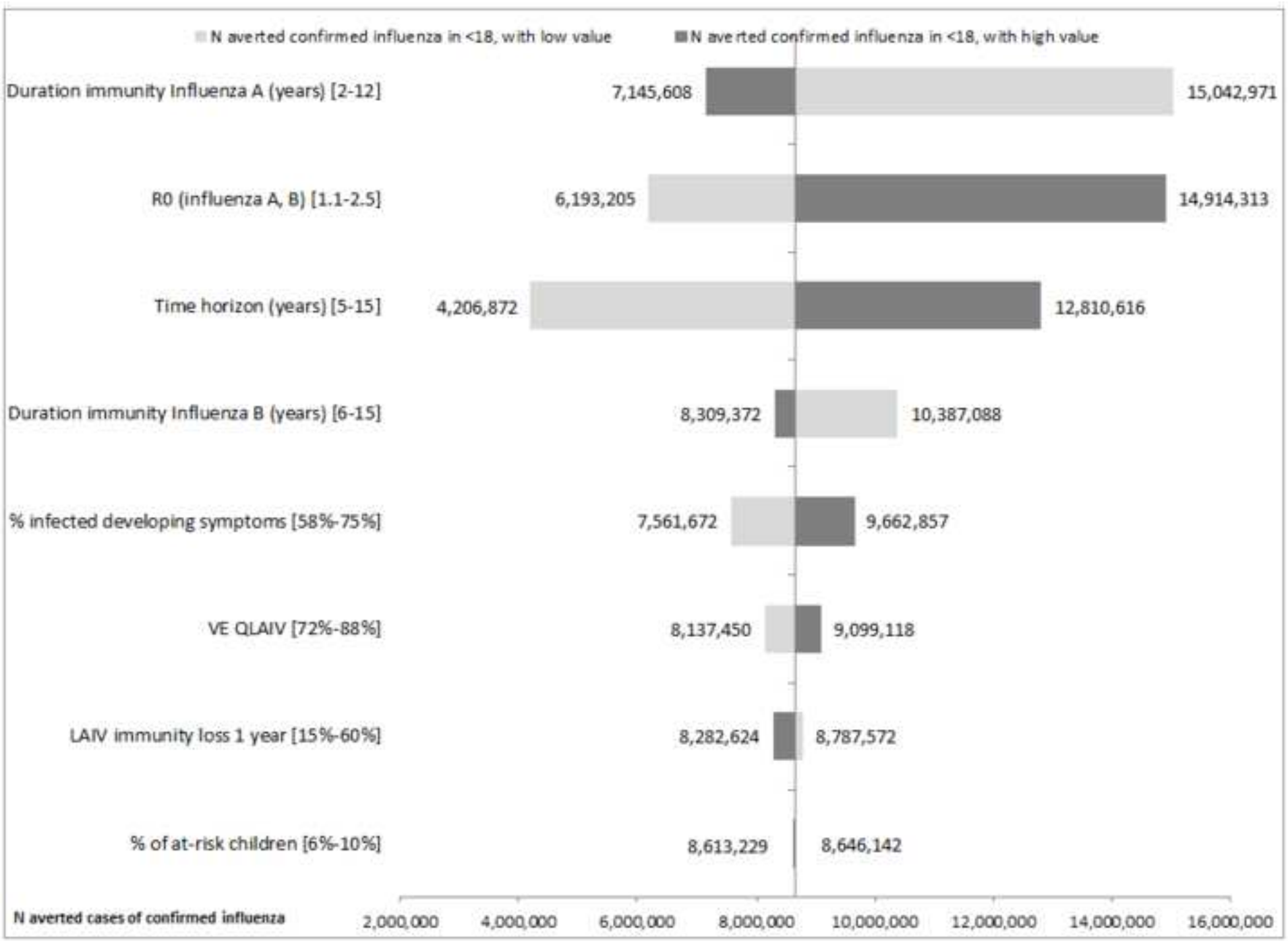

Figure 1b

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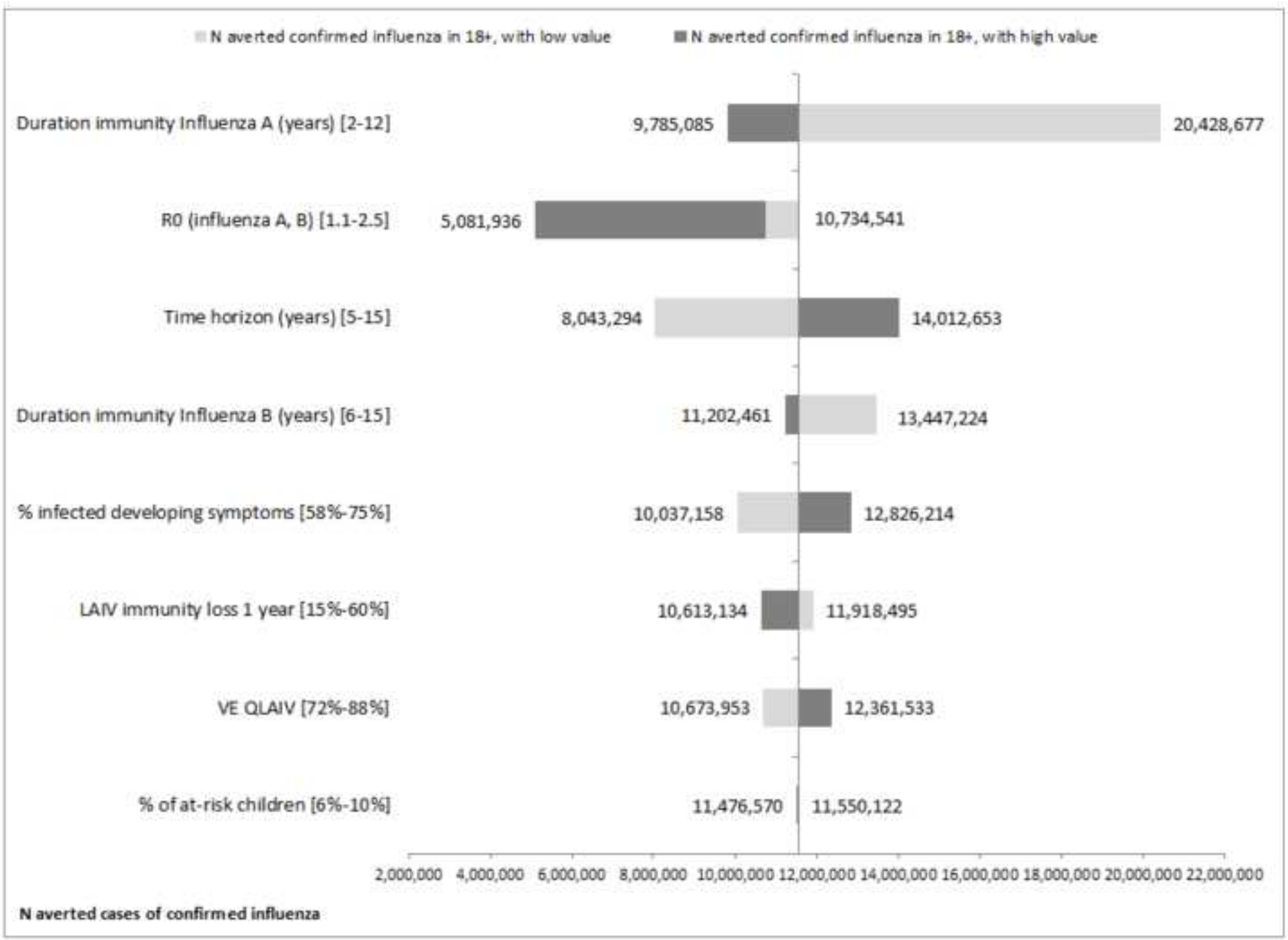

Figure 1c

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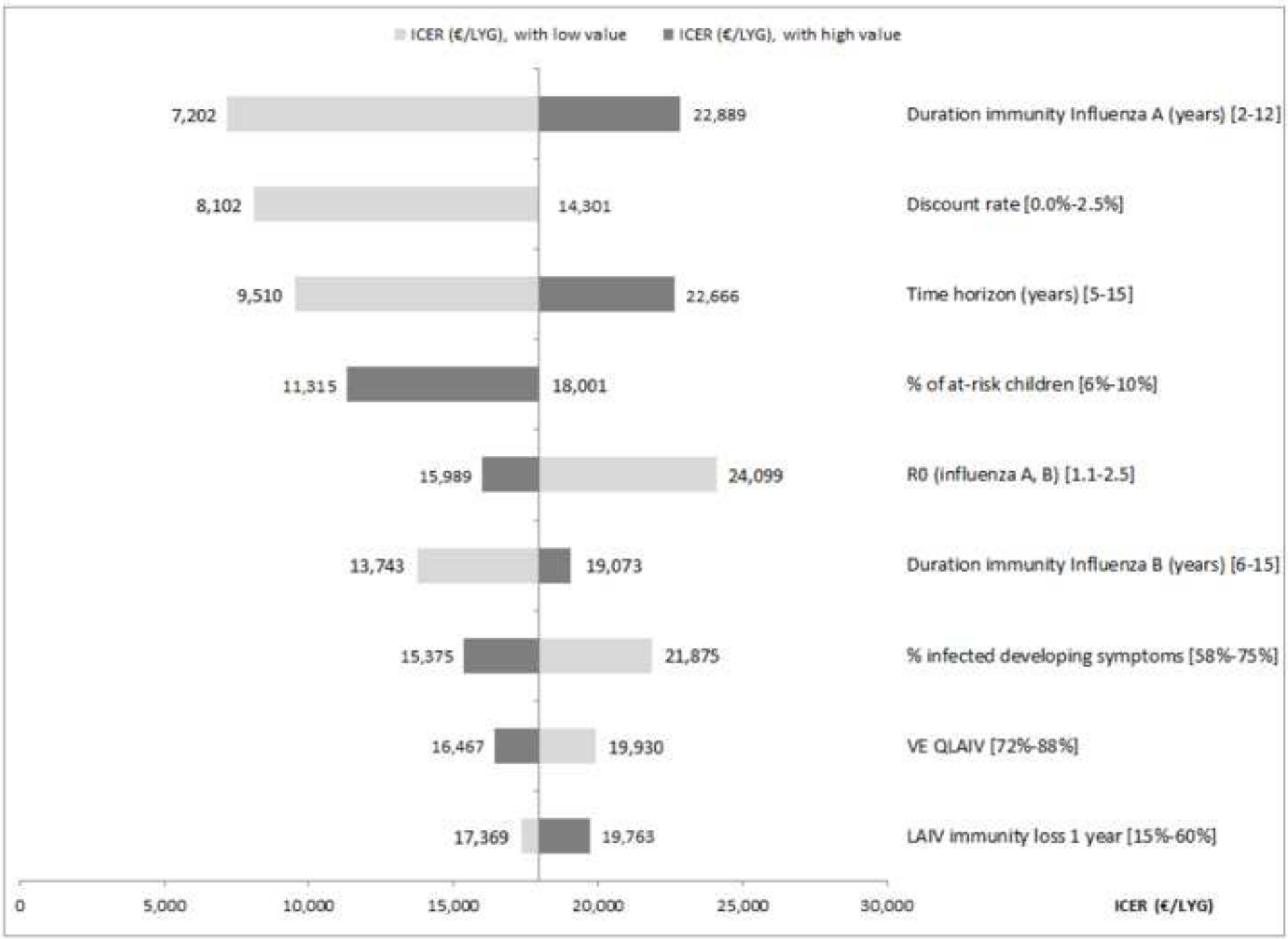

Figure 2

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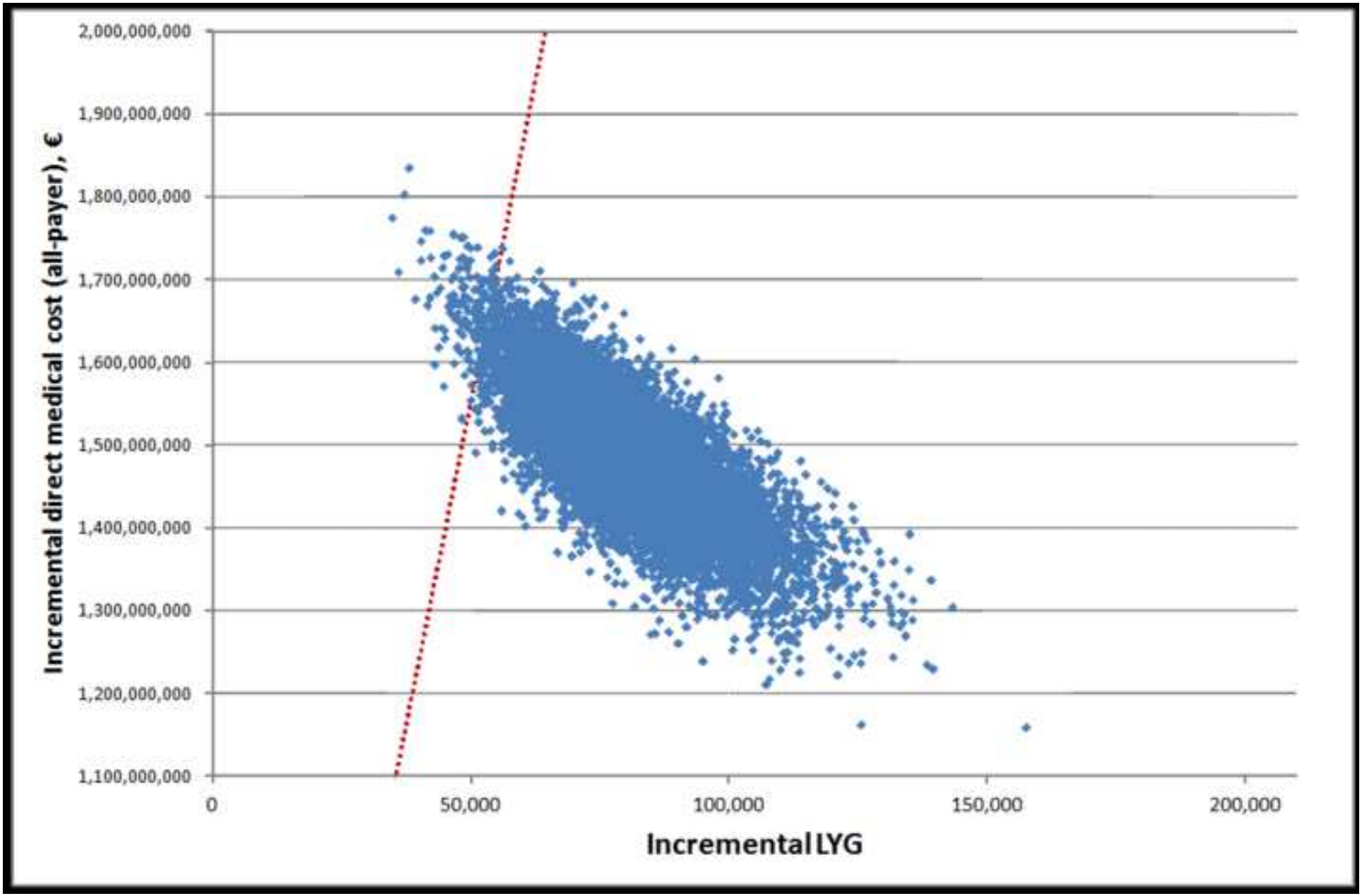

Figure 3a

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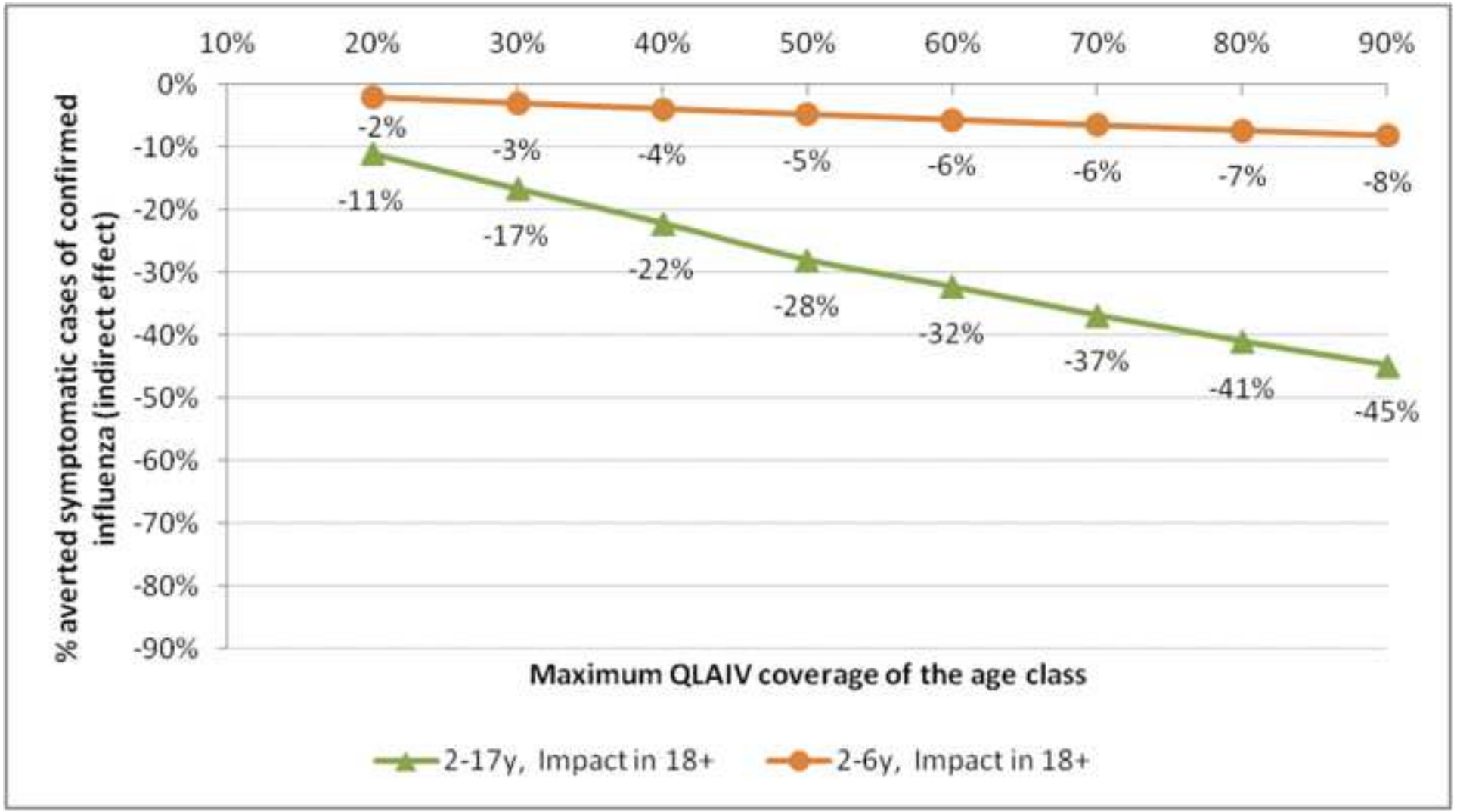

Figure 3b

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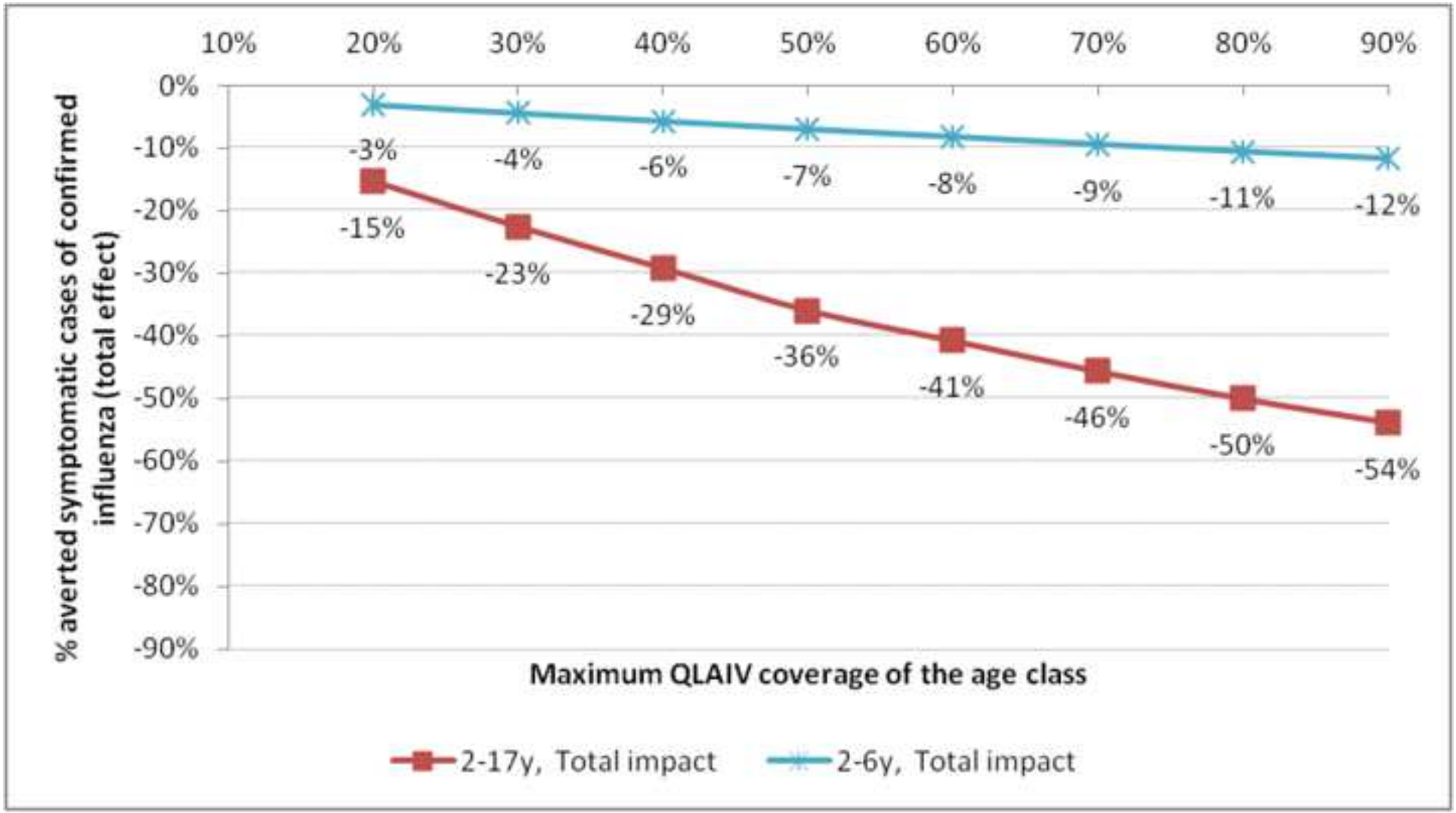

Figure 3c

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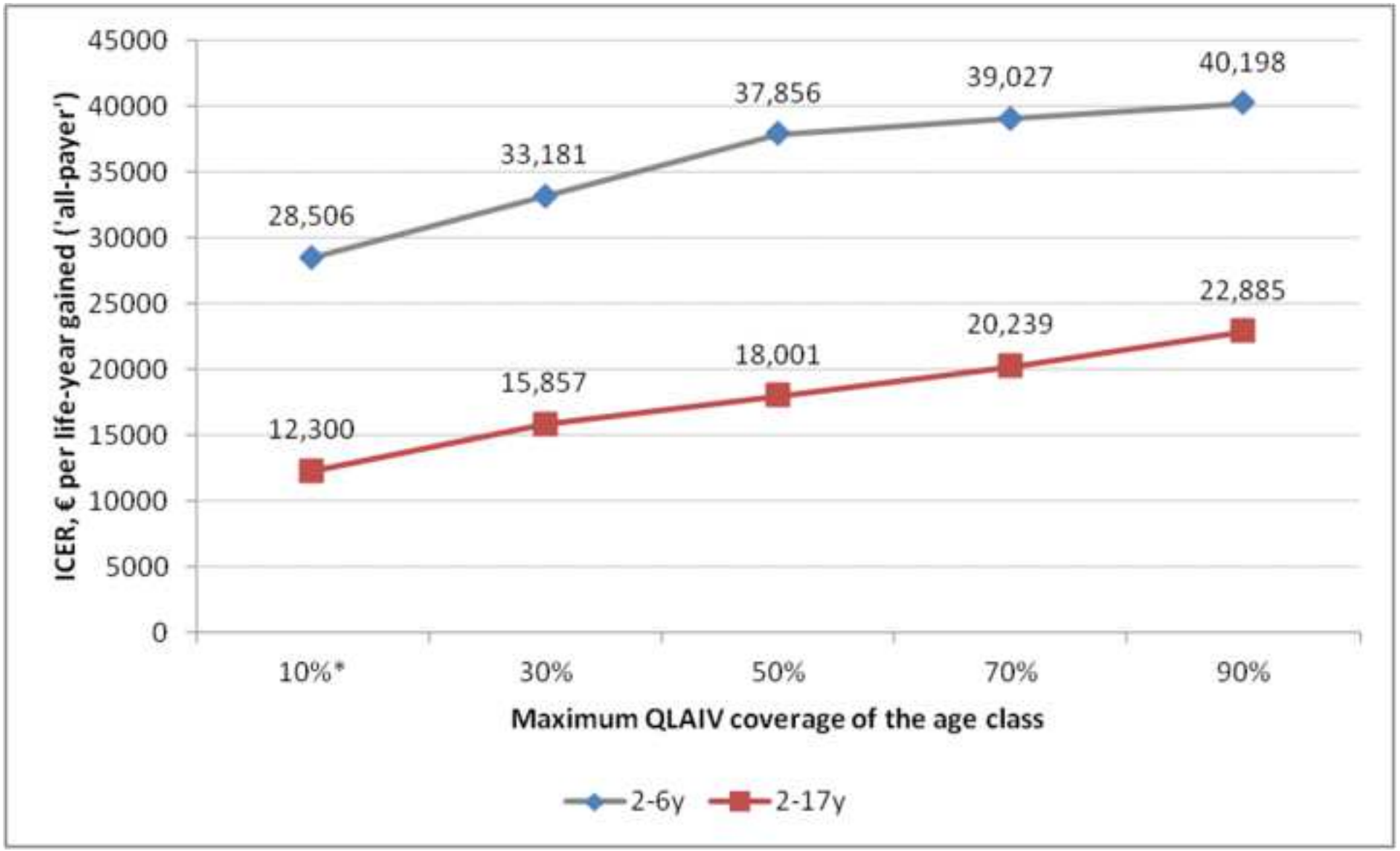


Supplementary material

[Assessment of public health and economic impact of intranasal live-attenuated influenza vaccination of children in France using a dynamic transmission model]

S1 Consolidated Health Economic Evaluation Reporting Standards ('CHEERS') checklist

S2 Comparison of influenza A+B incidence with current and evaluated strategies in a single randomly selected simulation (10-year time horizon)

S3 Comparison of influenza A+B incidence with current and evaluated strategies in a single randomly selected simulation (15-year time horizon)

S4 Parameter values and distributions used in the probabilistic sensitivity analysis

S1 Consolidated Health Economic Evaluation Reporting Standards ('CHEERS') checklist

Table 1 – CHEERS checklist—Items to include when reporting economic evaluations of health interventions.

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pages 6-7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Pages 6 to 9 & Table 1
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA[a]
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA[b]
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 8 Table 2
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Table 2
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 6[a]
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Pages 6-9[a]
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	NA[a]

Table 1 – *continued*

Section/item	Item No	Recommendation	Reported on page No/ line No
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 Table 2 Sup. S4
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Pages 10-11 Figure 1 Figure 2
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pages 12-13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 14
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

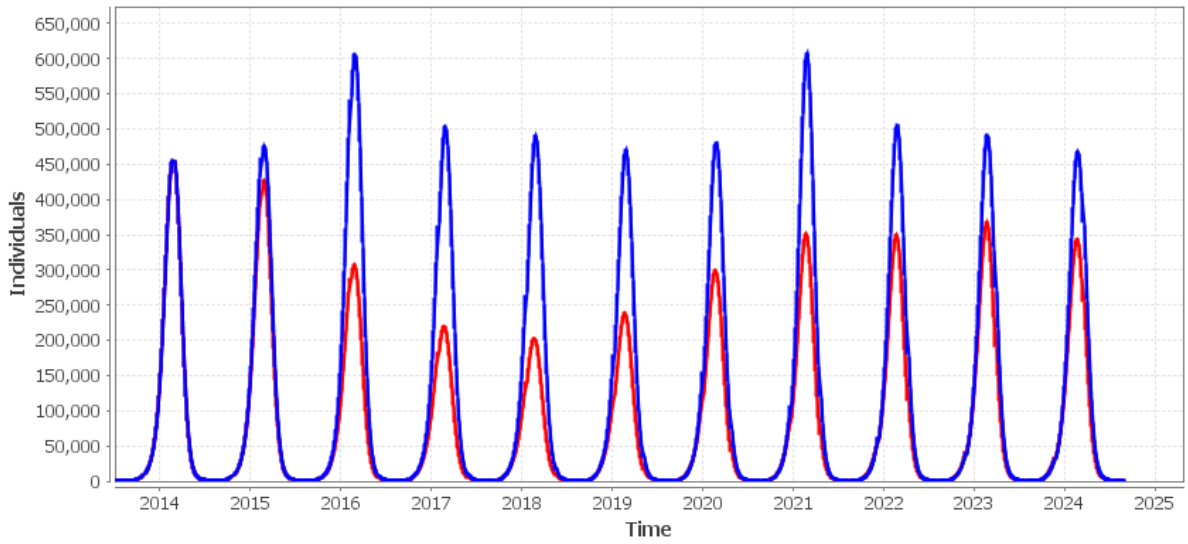
For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist.

a: Detailed method description of the model used, including model structure chart, was published earlier (Damm et al 2014, Rose et al 2014).

b: No quality-adjusted life-years (QALYs) were used in our model; incremental cost-effectiveness ratio (ICER) was based on life-years gained.

Reference: Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E; ISPOR Health Economic Evaluation Publication Guidelines-CHEERS Good Reporting Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013 Mar-Apr;16(2):231-50. doi: 10.1016/j.jval.2013.02.002.

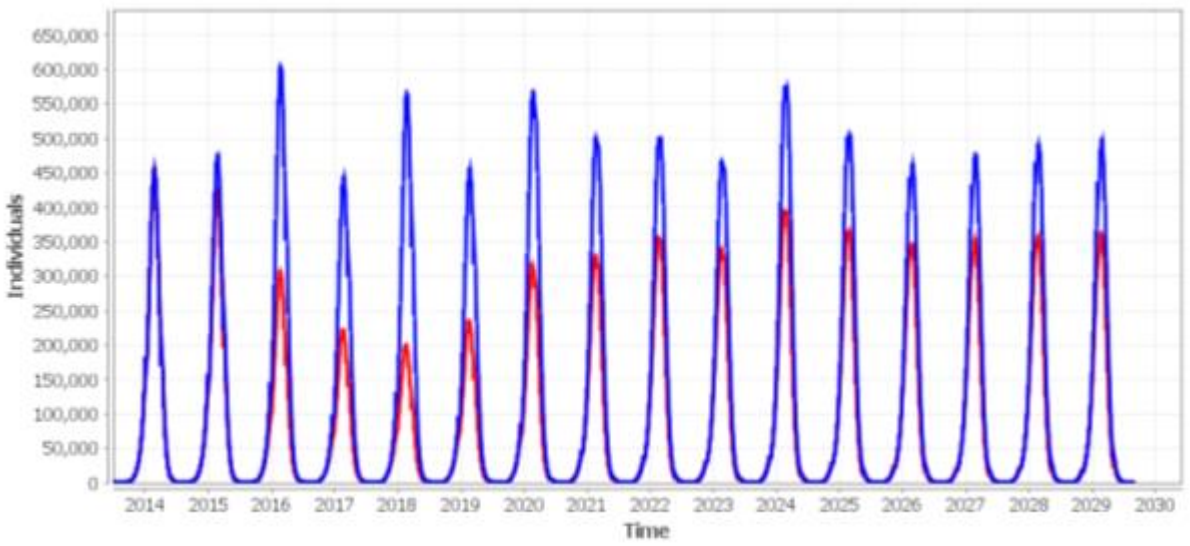
S2 Comparison of influenza A+B incidence with current and evaluated strategies in a single randomly selected simulation (10-year time horizon)



Blue curve: Current strategy (vaccination of at-risk individuals and elderly [aged ≥65 years] with trivalent inactivated vaccine; current vaccination coverage)

Red curve: Evaluated strategy (vaccination of 50% of children aged 2-17 years with quadrivalent live-attenuated influenza vaccine, add-on to the current vaccination strategy).

S3 Comparison of influenza A+B incidence with current and evaluated strategies in a single randomly selected simulation (15-year time horizon)



Blue curve: Current strategy (vaccination of at-risk individuals and elderly [aged ≥65 years] with trivalent inactivated vaccine; current vaccination coverage)

Red curve: Evaluated strategy (vaccination of 50% of children aged 2-17 years with quadrivalent live-attenuated influenza vaccine, add-on to the current vaccination strategy).

The maximum effect of the new vaccination strategy is seen during the fourth season: first, it takes three seasons for the new coverage to reach 50%. Second, the rather long-lasting natural immunity acquired by the large annual infection incidence during the previous seasons still persists during the first years of the evaluation period, but as influenza transmission declines following QLAIV vaccination, the acquisition of natural immunity also diminishes, and the number of susceptible individuals increases again after a transitory phase of maximum immunity (caused by the combination of old natural immunity and new vaccination-derived immunity). This phenomenon has also been called the "honeymoon period" as described elsewhere (Scherer and McLean 2002).

S4 Parameter values and distributions used in the probabilistic sensitivity analysis

Parameter	Distribution	Parameter 1	Parameter 2	Mean	SD	Low	High
Basic reproduction number R_0	Lognormal	0.24	0.19	1.27	0.31	1.10	2.30
Duration of contagiousness	Lognormal	1.61	0.13	5.00	0.64	3.75	6.25
Proportion of infected developing symptoms	Beta	66.90	33.10	66.90	8.53	50.18	83.63
Duration of naturally-acquired immunity, after inf A	Lognormal	1.79	0.13	6.00	0.77	4.50	7.50
Duration of naturally-acquired immunity, after inf B	Lognormal	2.48	0.13	12.00	1.53	9.00	15.00
Duration of vaccination-acquired immunity QLAIV (% immunity lost after first season)	Beta	30.00	70.00	30.00	11.48	15.00	60.00
Vaccine efficacy TIV, aged 0-1 year	Beta	11.00	89.00	11.00	0.56	9.90	12.10
Vaccine efficacy TIV, aged 2-17 years	Beta	59.00	41.00	59.00	3.01	53.10	64.90
Vaccine efficacy TIV, aged 18-64 years, low risk	Beta	68.00	32.00	68.00	3.47	61.20	74.80
Vaccine efficacy TIV, high risk	Beta	58.00	42.00	58.00	2.96	52.20	63.80
Vaccine efficacy QLAIV, aged 2-17 years	Beta	80.00	20.00	80.00	4.08	72.00	88.00
Proportion of symptomatic visiting GP, CH1	Beta	70.00	30.00	70.00	8.93	52.50	87.50
Proportion of symptomatic visiting GP, CH2	Beta	70.00	30.00	70.00	8.93	52.50	87.50
Proportion of symptomatic visiting GP, CH3	Beta	52.50	47.50	52.50	6.70	39.38	65.63
Proportion of symptomatic visiting GP, CH4	Beta	35.00	65.00	35.00	4.46	26.25	43.75
Proportion of symptomatic visiting GP, OHA	Beta	35.00	65.00	35.00	4.46	26.25	43.75
Proportion of symptomatic visiting GP, ARA	Beta	52.50	47.50	52.50	6.70	39.38	65.63
Proportion of symptomatic visiting GP, ARC	Beta	90.00	10.00	90.00	11.48	67.50	112.50
Proportion of symptomatic developing AOM, CH1	Beta	39.70	60.30	39.70	5.06	29.78	49.63
Proportion of symptomatic developing AOM, CH2	Beta	19.60	80.40	19.60	2.50	14.70	24.50
Proportion of symptomatic developing AOM, CH3	Beta	19.60	80.40	19.60	2.50	14.70	24.50
Proportion of symptomatic developing AOM, CH4	Beta	4.40	95.60	4.40	0.56	3.30	5.50
Proportion of symptomatic developing AOM, ARC	Beta	19.60	80.40	19.60	2.50	14.70	24.50
Proportion of symptomatic developing CAP, CH1	Beta	28.00	972.00	2.80	0.36	2.10	3.50
Proportion of symptomatic developing CAP, CH2	Beta	25.00	975.00	2.50	0.32	1.88	3.13
Proportion of symptomatic developing CAP, CH3	Beta	25.00	975.00	2.50	0.32	1.88	3.13
Proportion of symptomatic developing CAP, CH4	Beta	10.00	990.00	1.00	0.13	0.75	1.25
Proportion of symptomatic developing CAP, OHA	Beta	4.00	996.00	0.40	0.05	0.30	0.50

Proportion of symptomatic developing CAP, ARA	Beta	25.00	975.00	2.50	0.32	1.88	3.13
Proportion of symptomatic developing CAP, ARC	Beta	60.00	940.00	6.00	0.77	4.50	7.50
Cost of hospitalisation for influenza (Public)	Gamma	61.47	44.97	2764.00	352.55	2073.00	3455.00
Cost of hospitalisation for influenza (Patient)	Gamma	61.47	27.71	1703.00	217.22	1277.25	2128.75
Cost of hospitalisation for CAP, regular, aged <18 years (Public)	Gamma	61.47	34.28	2107.00	268.75	1580.25	2633.75
Cost of hospitalisation for CAP, regular, aged <18 years (Patient)	Gamma	61.47	4.07	250.00	31.89	187.50	312.50
Cost of hospitalisation for CAP, regular, aged ≥18 years (Public)	Gamma	61.47	60.34	3709.00	473.09	2781.75	4636.25
Cost of hospitalisation for CAP, regular, aged ≥18 years (Patient)	Gamma	61.47	27.74	1705.00	217.47	1278.75	2131.25
Cost of hospitalisation for CAP, ICU, aged <18 years (Public)	Gamma	61.47	65.86	4048.00	516.33	3036.00	5060.00
Cost of hospitalisation for CAP, ICU, aged <18 years (Patient)	Gamma	61.47	11.96	250.00	31.89	187.50	312.50
Cost of hospitalisation for CAP, ICU, aged ≥18 years (Public)	Gamma	61.47	91.92	3709.00	473.09	2781.75	4636.25
Cost of hospitalisation for CAP, ICU, aged ≥18 years (Patient)	Gamma	61.47	35.63	2190.00	279.34	1642.50	2737.50

AOM: acute otitis media; CAP: community acquired pneumonia; CH1: children without risk factors, aged 0-1 year; CH2: children without risk factors, aged 2-5 years; CH3: children without risk factors, aged 6-11 years; CH4: children without risk factors, aged 12-17 years; GP: general practitioner; HRA: high-risk adults; OHA: otherwise healthy adults; ARA: at-risk adults, including elderly aged ≥65 years; ARC: at-risk children, including children with severe asthma, aged 0-17 years; TIV: trivalent inactivated vaccine QLAIV: quadrivalent live-attenuated influenza vaccine.

The parameters 1 and 2 presented in the table below are depending on the chosen distribution, respectively:

-Lognormal: log(mean) and Standard error (SE) of the log(mean). Used for the basic reproduction number R_0 and durations.

-Beta: alpha and beta. Used for probabilities; alpha being estimated as the number of events and beta the number of "non-events", assuming a sample size of 100 or 1,000 in case of probabilities <5%.

-Gamma: alpha and beta. Used for costs.

Low and high values were obtained by applying variations around the central estimates of -/+ 10% for vaccine efficacy values or -/+25% for durations, for probabilities of developing symptoms, of requiring a GP visit and of complications and for costs. Larger variations encompassing clinically relevant values were used for basic reproduction number (1.1-2.5) and for loss of QLAIV-induced immunity after 1 season (15%-60%).