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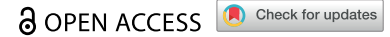


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




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ORIGINAL RESEARCH



Cost-effectiveness and public health impact of using high dose quadrivalent influenza vaccine in the French older adults population

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ABSTRACT

Background: Seasonal influenza outbreaks in France cause a surge in patients, exacerbating the overburdened healthcare system each winter. Older adults are particularly vulnerable to serious events related to influenza. Quadrivalent influenza high dose (QIV HD) vaccines have been developed to offer better clinical protection in older adults, who often exhibit suboptimal immune response to quadrivalent influenza standard dose vaccines (QIV SD). This study aims to evaluate the public health impact and cost-effectiveness of administering HD versus SD vaccines to individuals aged 65+ in France.

Methodology: Using a static model and decision-tree approach, the study analyzed health outcomes such as influenza cases, GP (general practitioner) visits, hospitalizations, and mortality; relative vaccine efficacy (rVE) estimates were derived from a pivotal randomized-controlled trial and a meta-analysis comparing HD to SD vaccines. Two approaches were implemented to model hospitalizations (conditional on influenza or not), and analyses on bed occupancy were performed.

Results: Results showed that using QIV HD instead of QIV SD during an average influenza season in France led to the prevention of 57,209 additional cases of influenza, 13,704 GP visits, and 764 influenza-related deaths. Moreover, switching to QIV HD resulted in an additional 1,728–15,970 hospitalizations avoided and 15,124–138,367 reduced days of hospitalization depending on the hospitalization approach used. The cost-utility analysis showed a cost per quality-adjusted life year (QALY) gained ranging from 24,020 €/QALY to 5,036 €/QALY.

Conclusions: Switching to QIV HD in older adults was shown to be cost-effective, with even greater public health benefits at a higher coverage rate, regardless of the season severity.

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CLASSIFICATION CODES

I: Health, Education, and Welfare; I11: Analysis of Health Care Markets; I18: Government Policy, Regulation, Public Health

Introduction


Influenza viruses undergo continuous antigenic changes leading to seasonal epidemics commonly observed during winter in temperate climates¹. The fluctuations in influenza incidence and circulation are major contributing factors to the variability and unpredictability in influenza burden each season, making the prediction of future influenza epidemics difficult^{2–4}.

Influenza epidemics have a major medical impact on the French healthcare system as they lead to an influx of patients who require urgent medical attention. This creates disruptions as it coincides with a period where hospitals are already under pressure with a peak of Intensive Care Unit (ICU) admissions and hospitalizations from other winter pathogens such as norovirus or rotavirus³. Assessing the full influenza burden is challenging due to the lack of systematic testing and consistent diagnoses of cases. For instance,

patients hospitalized for respiratory and cardiorespiratory reasons triggered by influenza infection are often not recorded as such, leading to underestimation of the actual influenza burden^{2,5}.

Influenza can indeed trigger secondary bacterial infections and various complications, which can be caused by the virus itself (such as acute pulmonary edema, pneumonia, respiratory failure, encephalitis, and myocarditis), or by the worsening of pre-existing chronic conditions, especially cardiovascular diseases (such as stroke and myocardial infarction) and diabetes^{5–8}. In particular, older adults are at higher risk of influenza complications, various anatomical and physiological alterations related to aging, but also malnutrition and comorbidities. To protect this at-risk population, the *Haut Conseil de la Santé Publique* recommends influenza vaccination to adults aged 65 and over (13.5 million people in France in 2020⁹) and calls for improved vaccine prevention strategies¹⁰.

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Quadrivalent influenza vaccines (QIV) contain two type A (A/H1N1 and A/H3N2) and two type B (B/Yamagata and B/Victoria)¹¹. QIV HD is a “high dose” (HD) vaccine as it contains 60 µg of hemagglutinin for each of the four viral strains, i.e. four times the antigens per strain on the standard dose (SD) vaccines currently available in France¹². HD vaccine has been developed to specifically enhance protection in older adults who – due to immunosenescence – exhibit a suboptimal immune response to SD vaccines. A higher protection against influenza also reduces the probability of influenza-related complications when compared to SD vaccines¹³. HD has consistently shown superior relative efficacy vs SD against influenza infections and influenza-related hospitalizations across multiple seasons in randomized and observational settings¹³.

QIV HD was included for the first time in the French vaccination schedule from the influenza vaccination campaign 2021/22¹⁴. Despite the influenza vaccination being recommended and funded in the population aged 65 years and above, the influenza vaccination coverage rate (VCR) in this population has remained suboptimal. Although the World Health Organization (WHO) and European guidelines recommend a VCR of at least 75%, it has remained around 50% over the last 10 years in France (with a peak at 59.9% in 2020/21 during the COVID pandemic)^{3,15}. The French surveillance data on seasonal influenza from 2011/12 to 2021/22 showed influenza to cause, on average, over 1 million primary care consultations, 20,000 hospitalizations, and 9,000 deaths per year, with 90% of these deaths occurring in the population aged 65 years and above⁴. Increasing the confidence in influenza vaccination thanks to demonstrated vaccine superior efficacy compared to the standard dose in the age group 65 years and above could contribute to increase the coverage rate and provide greater protection in this particularly vulnerable population¹⁶.

The main objective of this analysis is to estimate the potential public health impact and cost-effectiveness of QIV HD versus QIV SD in the French population aged 65 and over, from a healthcare payer perspective. Additionally, this study quantifies the reduced hospital bed occupancy, which adds critical information about vaccination impact compared to previously published HD cost-effectiveness analyses.

Methodology

Model structure

A static model using a decision-tree approach was developed to assess the public health impact and cost-effectiveness of switching from QIV SD to QIV HD in the French older adults population (65 years and above). The model structure has been previously described, and is consistent with WHO guidance and requirements on the evaluation of influenza vaccinations (Supplementary Figure S1)¹⁷.

The model considered the following set of clinical events: (i) influenza cases, (ii) General Practitioner (GP) visits, (iii) Emergency Department (ED) presentations, (iv) hospitalizations, and (v) mortality. For each vaccination strategy, the model calculated the number of influenza cases based on an

attack rate in an unvaccinated population aged 65 and above¹⁸, VCR, and vaccine efficacies (VE) parameters. Visits and hospitalizations were modelled independently and were not mutually dependent events (i.e. patients can experience a GP visit and/or a hospitalization episode). Influenza-related deaths were conditional on developing influenza, and individuals surviving influenza were subject to background mortality.

The model offers two distinct approaches for hospitalization, as illustrated in Figure 1 and Supplementary Figure S1: either hospitalizations were conditional to influenza cases (Approach 1) or they were considered independently of influenza cases (Approach 2). These two distinct modeling approaches allowed for several hospitalization definitions to be tested.

In Approach 1, hospitalizations were modeled as a probability applied to influenza cases. With this approach, only hospitalizations directly related or associated to influenza were included in the analysis. As a result, the hospitalization outcomes were linked to the parameters used in determining the number of influenza cases, including vaccine efficacy against influenza cases. Since this approach is conditional on influenza cases, the hospitalization data informing the model were obtained either by identifying hospitalizations with ICD-10 codes specific to influenza, or through regression models assessing the excess hospitalizations associated to influenza, such as the Fardogrip study².

In Approach 2, the hospitalizations considered are those possibly related to influenza and therefore are not linked to laboratory-confirmed influenza cases. This approach directly models the impact of vaccination on hospitalization outcomes using specific vaccine effectiveness estimates, and captures the improved efficacy of HD versus SD vaccines against broader endpoints, including cardiorespiratory hospitalizations possibly related to influenza regardless of laboratory confirmation^{13,19}. This approach is justified in particular by the absence of systematic testing for influenza viruses in France before the COVID-19 pandemic, which means that hospitalizations due to influenza or its complications are not systematically identified as such.

The model assumed all events of interest arose within an average influenza season (assumed to last 6 months).

Model inputs

The detailed list of inputs and description can be found in Supplementary Table S1.

Vaccination

Depending on the hospitalization modeling approach, the model considered one or two inputs of VE: VE against influenza cases, with and without VE against hospitalizations. To reflect the additional clinical benefit of HD vaccine versus SD, a relative vaccine efficacy (rVE) of HD versus SD was applied to the absolute VE of SD.

- *VE against influenza cases (in both approaches):* Absolute VE of SD vaccine against any circulating influenza strain

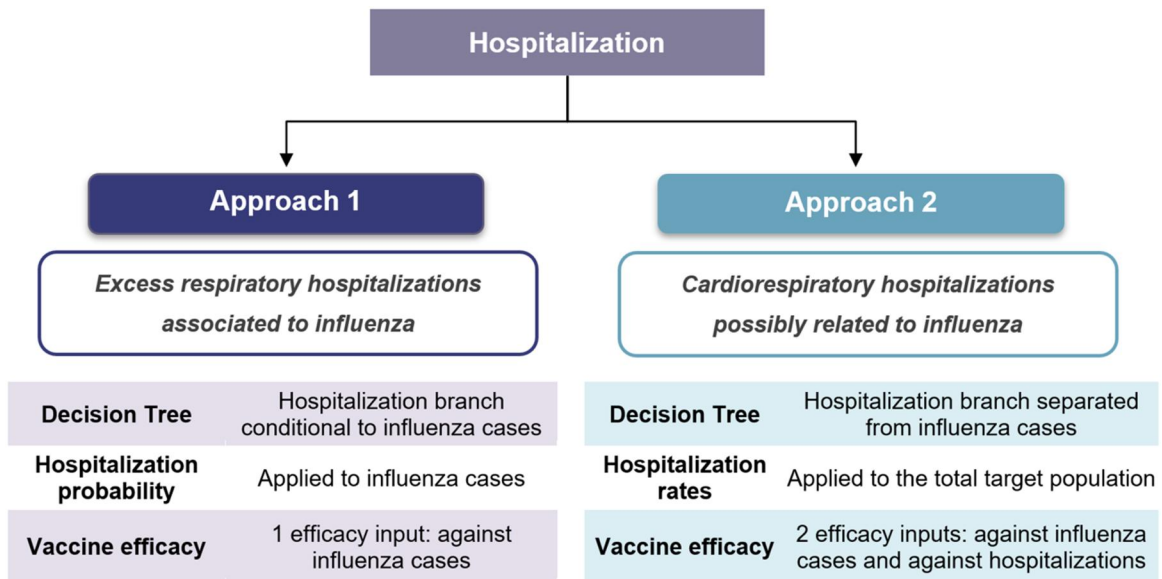


Figure 1. Hospitalization modeling approaches.

of 50% was applied in the model²⁰. The rVE of HD versus SD against influenza cases was 24.2% based on the FIM12 randomized clinical trial (prespecified superiority primary endpoint)^{21,22}.

- *VE against hospitalizations (in Approach 2):* As hospitalization outcomes were estimated separately from influenza cases in Approach 2, additional VE data against hospitalizations were required:
 - VE of QIV SD: The model used a vaccine effectiveness value for QIV SD on the prevention of respiratory hospitalizations of 29.3%²³, and a vaccine efficacy of 28% on cardiovascular hospitalizations²⁴ (see [Supplementary material](#)).
 - rVE of HD vs SD: The model applied a rVE of HD over SD against hospitalizations for cardio-respiratory causes of 17.9% sourced from the Lee et al. study¹³. Lee et al. conducted a meta-analysis of four randomized controlled trials (RCTs) and 12 retrospective cohort studies over 10 consecutive seasons, reporting outcomes of approximately 34 million people aged 65+. This was the most recent study at the time of analysis, with the highest level of evidence to inform the relative vaccine effectiveness of QIV HD vs QIV SD; in addition, it reported different estimates depending on the definition of hospitalization considered¹³.

Healthcare resources

For approach 1, excess respiratory hospitalizations were sourced from *Fardogrip* that estimated the admissions for ICD10 codes J00–J99 associated to influenza from cyclic regression models over the period 2013/14–2017/18 in France^{2,25}.

In approach 2, cardio-respiratory hospitalizations were collected from a French Hospital National Database – PMSI (*Programme de médicalisation des systèmes d'information*) using hospital admissions over five seasons for episodes

coded as respiratory (ICD10: J00–99) and cardiovascular (ICD10: I00–99) events²⁶.

Based on the mean length of stay (LoS) per hospitalization episode sourced from the *Fardogrip* study, hospital bed occupancy days were computed and served as evidence of the burden of influenza on the hospital units and healthcare system². The same length of stay was assumed across hospitalization definitions, considered as a conservative assumption.

Analyses

The base case analysis used the excess respiratory hospitalizations definition (approach 1). The model estimated clinical events and assessed the public health impact of using QIV HD over SD in the 65+ population, reporting costs, Life Years (LYs), and Quality-Adjusted Life Years (QALYs), leading to ICER (Incremental Cost-Effectiveness Ratio) calculation. Complementary analysis considered HD vaccine improved efficacy against cardiorespiratory hospitalizations using hospitalization approach 2^{13,19}. Scenario analyses reflected influenza season variability and assessed the public health impact of increasing vaccine coverage up to WHO's target of 75%. Uncertainty was explored on the base case through deterministic and probabilistic sensitivity analyses to assess results robustness.

Results

Base case analysis

The use of QIV HD instead of SD in older adults prevented an additional 57,209 influenza cases, 13,704 GP visits, and 764 deaths annually. Switching to HD also reduced the hospitalization burden by avoiding 1,728 additional excess respiratory hospitalizations, resulting in a reduction in bed occupancy of 15,124 days ([Table 1](#)). Vaccinating this

Table 1. Clinical population-level outcomes.

| | QIV SD | QIV HD | Events avoided |
|---|-----------|-----------|------------------|
| Outcomes | | | |
| Influenza cases | 709,196 | 651,987 | -57,209 (-8.1%) |
| GP visits | 169,881 | 156,178 | -13,704 (-8.1%) |
| Hospitalizations (Excess Respiratory) | 21,426 | 19,697 | -1,728 (-8.1%) |
| Hospitalizations (Cardiorespiratory) | 213,882 | 197,912 | -15,970 (-7.5%) |
| Bed occupancy days (Excess Respiratory) | 187,492 | 172,367 | -15,124 (-8.1%) |
| Bed occupancy days (Cardiorespiratory) | 1,853,167 | 1,714,800 | -138,367 (-7.5%) |
| Deaths associated to influenza | 9,471 | 8,707 | -764 (-8.1%) |

Abbreviations: GP, General Practitioner; QIV HD, Quadrivalent Influenza Vaccine High Dose; QIV SD, Quadrivalent Influenza Vaccine Standard Dose.

Table 2. Cost-effectiveness results (LYs and QALYs).

| | Base case analysis | | | Complementary analysis | | |
|---------------------------------|---|-------------|-------------|--|-------------|-------------|
| | Hospitalization approach 1 – Excess Respiratory | | | Hospitalization approach 2 – Cardiorespiratory | | |
| | Total Costs (€) | Total LYs | Total QALYs | Total Costs (€) | Total LYs | Total QALYs |
| Population-level results | | | | | | |
| QIV SD | 308,513,246 | 130,534,775 | 98,980,092 | 1,514,527,555 | 130,534,775 | 98,976,628 |
| QIV HD | 423,061,539 | 130,540,543 | 98,984,861 | 1,539,832,172 | 130,540,543 | 98,981,653 |
| | | Cost/LY | Cost/QALY | | Cost/LY | Cost/QALY |
| ICER | | 19,861 | 24,020 | | 4,387 | 5,036 |

Abbreviations: ICER, Incremental Cost-Effectiveness Ratio; LY, Life Year; QALY, Quality-Adjusted Life Year; QIV HD, Quadrivalent Influenza Vaccine High Dose; QIV SD, Quadrivalent Influenza Vaccine Standard Dose.

population with QIV HD vs QIV SD was found to have an incremental cost per QALY gained of 24,020 € (Table 2).

Complementary analysis

Considering the improved efficacy of HD compared to SD against cardiorespiratory hospitalizations, the use of HD led to a greater annual reduction of 15,970 hospitalizations and 138,367 hospital days (Table 1). Under this scenario, the incremental cost per QALY of using HD instead of SD in the older adults population was found to be 5,036 € (Table 2).

Scenario analyses

Scenario analysis using hospitalization data across five consecutive influenza seasons

The lowest hospitalization rates were reported for 2013/2014 in both approaches, while the highest hospitalization rates were for 2016/2017 and 2017/2018, respectively, for approach 1 and approach 2, mostly pronounced in the age group 75+. The benefits of QIV HD vs SD were observed in every modeled season, even in the lowest intensity influenza season. For the highest intensity influenza season, the model predicted up to 2,801 excess respiratory hospitalizations and 19,701 cardiorespiratory hospitalizations avoided compared to SD and up to 24,670 and 172,554 hospital days avoided for approach 1 and approach 2, respectively (see Supplementary Tables S4 and S5).

Scenario analysis testing higher coverage rate

The benefits of QIV HD vs SD were also tested by varying VCR from 50% to the WHO objective of 75%. The predicted avoided events per VCR level and per influenza season were reported in a heatmap in Supplementary Tables S4 and S5.

The linear relationship between the VCR and the outcomes is explained by the static approach of the model.

On average, the combined benefit of achieving the recommended VCR and switching to QIV HD was estimated to prevent an additional 2,592 excess respiratory hospitalizations in approach 1 and 23,955 cardiorespiratory hospitalizations in approach 2, resulting in 22,687 and 207,550 hospital days avoided, respectively. As the VCR increased, the predicted reduction in hospitalizations and bed occupancy days became more substantial, and this is particularly visible during the seasons of high influenza circulation.

Sensitivity analyses

The results of the sensitivity analyses can be found in Supplementary Figures S2–S5.

Discussion

This study provides the first estimates of the public health and economic benefits of switching to QIV HD over QIV SD in the French population 65 and above. The findings revealed a significant reduction in healthcare burden, including the prevention of influenza cases, hospitalizations, and bed occupancy days and confirmed the favorable economic profile of the QIV HD vaccine^{27–29}.

In the base case scenario, hospitalizations were modeled conditionally to influenza cases, using the definition of *excess respiratory hospitalizations associated to influenza*². The switch from QIV SD to QIV HD vaccine resulted in significant annual additional reductions in influenza cases (~57,000), excess respiratory hospitalizations (~1,700), and bed occupancy days (~15,000), and an incremental cost-utility ratio of 24,020 €/QALY. The main drivers of the cost-effectiveness outcomes were the relative efficacy of QIV HD vs SD against influenza cases and the parameters assessing the economic

benefits of the prevention of excess respiratory hospitalizations associated with the HD vaccine adoption (hospitalization rates and costs).

Several studies have highlighted the complexity of assessing the broad burden of influenza^{2,5}. Influenza-related hospitalizations are often underreported in the surveillance systems since they are not systematically coded as influenza. These hospitalizations are frequently associated with underlying illnesses and/or superinfections, some of which may manifest 1 or 2 weeks after the initial infection. Furthermore, there is no systematic testing to detect influenza in these cases. Considering these challenges and the demonstration of HD superior clinical data against those complications, a complementary analysis was conducted using a broader definition of hospitalization (*cardio-respiratory hospitalization possibly related to influenza*), which showed even greater impact of QIV HD vaccination on the health system. This analysis concluded that ~16,000 additional hospitalizations and ~138,000 bed occupancy days were avoided with QIV HD, leading to an incremental cost per QALY gained (5,036 €/QALY) lower than the one for *excess respiratory hospitalization* approach (24,020 €/QALY). Of note, in economic evaluations vaccine costs are based on published prices, higher for innovative products than actual net price paid by authorities, which is confidential (it holds for France and most countries) and might lead to better economic profile.

The first scenario analysis confirmed that the benefits of using HD vaccine over SD on excess respiratory and cardio-respiratory hospitalizations and bed occupancy was demonstrated in every season tested, whatever the severity and/or the intensity of the season. The second scenario analysis revealed that the combined benefit of reaching the WHO VCR recommended threshold and switching to HD vaccine would prevent on average up to ~2,600 additional excess respiratory hospitalizations and ~24,000 cardiorespiratory hospitalizations, resulting in ~22,700 and ~208,000 bed days avoided, respectively, for each approach, for each season.

Our study reinforces the existing evidence on the public health impact and cost-effectiveness of QIV HD compared to SD in reducing influenza burden among the older adults population. Similar cost-effectiveness analyses (CEAs) conducted in Belgium, Finland, and Portugal²⁹ have shown QIV HD vs SD to improve health outcomes and to be cost-effective in preventing influenza-related complications in this population; a CEA in Italy³⁰ has proved QIV HD to be even cost-saving when considering the cardiorespiratory hospitalizations. Multiple studies have consistently demonstrated the use of HD vaccine to improve health impact by reducing influenza-related burden, and to save healthcare resources and costs, resulting in strong cost-effectiveness profile^{27,28,31,32}.

In comparison of the previous publications, this model included a new measure of the influenza-related healthcare burden: the length of hospital stay. The fact that hospital beds are in short supply due to other seasonal infection, especially in older adults who tend to require longer stays, stresses the importance of using hospital bed occupancy as an indicator of a disease impact on the national healthcare

system. This model demonstrated that QIV HD was associated with an additional decrease in the number of bed days needed over the influenza season compared to QIV SD and allowed to demonstrate that QIV HD is an effective tool to help in controlling the overall winter pressure on health care services.

The reliability and validity of our findings was enhanced by the quality and robustness of the clinical and epidemiological data used to inform the model parameters. The pivotal FIM12 trial provided robust evidence, which was further supported by real-world data demonstrating the efficacy of QIV HD in preventing influenza-related events and chronic conditions^{13,19}. In addition, recent data from a retrospective cohort study in France estimated the rVE of QIV HD vs QIV SD in the 2021/2022 season to prevent influenza hospitalizations at 23.3% (95% confidence interval = 8.4–35.8), in line with the model assumptions³³. To assess the rVE of QIV HD against cardiorespiratory hospitalizations, we incorporated a meta-analysis by Lee et al. encompassing data from multiple studies and influenza seasons¹³. To accurately capture the burden of disease in France, we leveraged recent real-world evidence generated from the French PMSI and cyclic regression models over multiple influenza seasons².

In addition to its strengths, several limitations to our study should be mentioned. First, the use of a static model in the infectious disease area could lead to less precise estimates compared to a dynamic approach, which could capture the value of herd immunity and consequently the additional indirect effects of increasing the VCR. However, our choice to apply a conservative modeling approach was based on the WHO guidelines for economic evaluations for infectious diseases. These guidelines recommend considering static models in two contexts, both fulfilled in this work: when assessing the costs and consequences of an intervention over short periods of time, and when there is a low disease transmission within the different age groups¹⁷.

Secondly, our study did not capture ED visits and subsequent healthcare resource utilization related to functional decline, such as specialist consultations and readaptation stays^{34–36}. Functional decline following hospitalization with influenza is commonly observed in older adults and can sometimes result in persistent, catastrophic disability³⁷. Similarly, recent data highlighted an increase in specialist consultations (physiotherapist, pneumologist, cardiologist, ...) following an influenza episode³⁸. For instance, the proportion of patients with influenza who consulted at least one specialist increased from 32.0% to 43.4% for cardiologists, from 21.6% to 48.0% for pulmonologists, from 5.5% to 8.4% for neurologists, and from 5.6% to 6.6% for psychiatrists between the year before and the year following ICU admission due to influenza infection³⁸. However, these healthcare resources used were not captured in the current analysis, which can be considered as a conservative approach. Regarding ED, it is expected that the use of HD vs SD would trigger a decline in admissions, as seasonal influenza regularly leads to overcrowding in ED, and that ED visits could replace consultations with GP. However, due to absence of

available solid French data this was not accounted for in this analysis.

Thirdly, our study's limitations arise from the challenges in obtaining a consensus on the epidemiological inputs to use, as they are influenced by the variability of influenza outbreaks from season to season and differences in surveillance methods across countries. Despite several sources on vaccine efficacy, the rVE of QIV HD compared to QIV SD was sourced from a RCT focusing on the prevention of laboratory confirmed influenza cases, not influenza-like illness, similarly to the assessment of QIV HD by the European Heads of Medicines Agencies³⁹. Additionally, while acknowledging the limitations of the source used for the influenza attack rate, this parameter was needed in an unvaccinated population for modeling purposes and was tested in the sensitivity analyses.

Another limitation of our study is the approach used for estimating the costs associated with hospitalizations. In the base case analysis (Approach 1) and the complementary analysis (Approach 2), we employed a conservative approach by applying the same average cost of hospitalization (the one for pneumonia and influenza causes) leading to a possible underestimation of the economic burden of hospital stays for cardio-respiratory complications.

Lastly, it should be noted that the model inputs were collected prior to the COVID-19 pandemic, which disrupted seasonal epidemics of all respiratory viruses (except rhinovirus). While it remains an open question if these seasonal epidemics will fully return to pre-pandemic dynamics, influenza continues to circulate at high levels, despite the extinction of the influenza B/Yamagata lineage that drove WHO to move back into trivalent formulations. Moreover, the massive use of PCR testing during and after the pandemic has likely increased the specificity of the coding of influenza hospitalizations, while conversely reducing the use of less specific codes (i.e. those related to non-specific influenza events). While these factors may lead to some differences on the incidence of influenza outcomes when comparing pre- and post-COVID incidence, it is unlikely that these changes are substantial. Based on the sensitivity analyses conducted in this study, we can reasonably assume that these potential changes fall under the scope of our findings, even as more data from post-COVID seasons become available.

Despite strong clinical evidence supporting more effective influenza vaccines, improving VCR remains a challenging task. Even if influenza VCR improved among older adults during the COVID-19 pandemic, reaching almost 60.0% in season 2021/22⁴⁰, the end of social distancing measures, and VCR decline resulted in a rebound in influenza activity^{4,41}.

All the above emphasizes the need to continue efforts to promote influenza prevention. The policy issued in 2019 authorizing pharmacists to prescribe and administer influenza vaccines to older adults population may represent a valuable lever to increase VCR and potentially improve the uptake of QIV HD^{42,43}.

Conclusion

The model highlights the substantial impact on public health in France of the introduction and increasing use of HD

vaccine among individuals 65 and above, regardless of the influenza season severity. Our analysis confirms that the switch to QIV HD is a cost-effective intervention, with an estimated incremental cost-utility ratio of 24,020 €/QALY and 5,036 €/QALY depending on the approach considered. Moreover, the use of HD vaccine will alleviate the burden on hospitals, by reducing bed occupancy. The burden of influenza can be further reduced by combining two levers – higher vaccination coverage and use of an enhanced vaccine – resulting in greater public health benefits in terms of avoided hospitalizations and bed occupancy.

Transparency

Declaration of funding

The study was funded by Sanofi.

Declaration of financial/other interests

MCL, HB, FA, and CDC are employees of Sanofi and may or may not hold shares in the company. PC reports to have participated in advisory committees organized by Sanofi and being a consultant for Sanofi. JG reports to have participated in advisory committees organized by GSK, MSD, Pfizer, and Sanofi. GG reports to have participated in advisory committees organized by Astellas, AstraZeneca, BioMérieux, MSD, Pfizer, Sanofi, Sanofi Pasteur, Sanofi Pasteur-MSD, and Vifor, acted as consultant and speaker for these companies, and participated in congresses on invitation by Eisai, MSD, Novartis, Pfizer, Sanofi, and Vifor. OL reports to be a principal investigator in vaccine trials sponsored by Sanofi, MSD, Pfizer, GSK, and Moderna. She received financial support for travel to medical congress and personal fees for participation in advisory boards for Sanofi, MSD, Pfizer, and GSK. AM reports to have participated in an advisory committee organized by Sanofi, Seqirus, and Viatrix and to be a member of the scientific board of the French Microbiology Society influenza group (GEIG). She received financial support from Sanofi for travel to medical congress. FB and DP are Syneos Health employees who have received funds from Sanofi for this study.

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Author contributions

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Ethical disclosures













Ethical approval was not sought for the present study as the different inputs used in this study were extracted from publicly available sources (either peer-reviewed publications or governmental websites). Hospitalization and mortality rates related to influenza disease are based on the Fardogrip study which was based on the PMSI database (Programme de Médicalisation des Systèmes d'Information). Data from the PMSI are anonymized and collected from patients who provide informed consent.

Previous presentations

Preliminary results of this research were presented at the JNI 2022 congress (Journées Nationales d'Infectiologie).

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References

- [1] Petrova VN, Russell CA. The evolution of seasonal influenza viruses. *Nat Rev Microbiol*. 2018;16(1):47–60. doi: [10.1038/nrmicro.2017.118](https://doi.org/10.1038/nrmicro.2017.118).
- [2] Lemaitre M, Fouad F, Carrat F, et al. Estimating the burden of influenza-related and associated hospitalizations and deaths in France: an eight-season data study, 2010–2018. *Influenza Other Respir Viruses*. 2022;16(4):717–725. doi: [10.1111/irv.12962](https://doi.org/10.1111/irv.12962).
- [3] Pivette M, Nicolay N, de Lauzun V, et al. Characteristics of hospitalizations with an influenza diagnosis, France, 2012–2013 to 2016–2017 influenza seasons. *Influenza Other Respir Viruses*. 2020;14(3):340–348. doi: [10.1111/irv.12719](https://doi.org/10.1111/irv.12719).
- [4] Santé Publique France. Fardeau de la grippe en France métropolitaine: bilan des données de surveillance des épidémies de 2011–2012 à 2021–2022. 2023 [cited 2024 Sep]. Available from: <https://www.santepubliquefrance.fr/content/download/509230/3781839?version=1>
- [5] Macias AE, McElhaney JE, Chaves SS, et al. The disease burden of influenza beyond respiratory illness. *Vaccine*. 2021;39 Suppl 1:A6–A14. doi: [10.1016/j.vaccine.2020.09.048](https://doi.org/10.1016/j.vaccine.2020.09.048).
- [6] Grimprel E, Cohen R. Relation entre la grippe et les infections bactériennes. *Méd Théor/Pédiatr*. 2010;13(4):316–321.
- [7] World Health Organization. A manual for estimating disease burden associated with seasonal influenza. 2015 [cited 2024 Sep]; p. 124. Available from: <https://www.who.int/publications/i/item/9789241549301>
- [8] Mertz D, Kim TH, Johnstone J, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ*. 2013;347:f5061. doi: [10.1136/bmj.f5061](https://doi.org/10.1136/bmj.f5061).
- [9] Institut national de la statistique et des études économiques. Population totale par sexe et âge au 1er janvier 2020, France métropolitaine. Bilan démographique 2019; 2020 [cited 2024 Sep]. Available from: <https://www.insee.fr/fr/statistiques/1892088?sommaire=1912926>
- [10] Haut Conseil de la Santé Publique. Vaccination des personnes âgées; 2016 [cited 2024 Sep]. Available from: <https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=559>
- [11] European Medicines Agency, C.B.G. Public assessment report. Scientific discussion. Eflueda, suspension for injection in pre-filled syringe. NL/H/4757/001/DC; 2020 [cited 2024 Sep]. Available from: <https://www.geneesmiddeleninformatiebank.nl/pars/h124920.pdf>
- [12] Robertson CA, DiazGranados CA, Decker MD, et al. Fluzone® high-dose influenza vaccine. *Expert Rev Vaccines*. 2016;15(12):1495–1505. doi: [10.1080/14760584.2016.1254044](https://doi.org/10.1080/14760584.2016.1254044).
- [13] Lee JKH, Lam GKL, Shin T, et al. Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: an updated systematic review and meta-analysis. *Vaccine*. 2021;39 Suppl 1:A24–A35. doi: [10.1016/j.vaccine.2020.09.004](https://doi.org/10.1016/j.vaccine.2020.09.004).
- [14] Ministère des Solidarités et de la Santé. Calendrier des vaccinations et recommandations vaccinales 2021. 2021 Apr [cited 2024 Sep]. Available from: <https://splf.fr/wp-content/uploads/2022/04/Calendrier-vaccinal-Ministere-de-la-sante-juillet-2021.pdf>
- [15] European Centre for Disease Prevention and Control. Seasonal influenza vaccination and antiviral use in EU/EEA Member States. Overview of vaccine recommendations for 2017–2018 and vaccination coverage rates for 2015–2016 and 2016–2017 influenza seasons; 2018 [cited 2024 Sep]. Available from: <https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/vaccination-coverage>
- [16] Santé Publique France. Face à la circulation active de virus dans la majorité des régions, la campagne de vaccination contre la grippe saisonnière est prolongée. 2022 [cited 2024 Sep]. Available from: <https://www.santepubliquefrance.fr/presse/2022/face-a-la-circulation-active-de-virus-dans-la-majorite-des-regions-la-campagne-de-vaccination-contre-la-grippe-saisonniere-est-prolongee>
- [17] World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. 2019 [cited 2024 Sep]; II. Available from: <https://www.who.int/publications/i/item/who-guide-for-standardization-of-economic-evaluations-of-immunization-programmes-2nd-ed>
- [18] Somes MP, Turner RM, Dwyer LJ, et al. Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: a systematic review and meta-analysis. *Vaccine*. 2018;36(23):3199–3207. doi: [10.1016/j.vaccine.2018.04.063](https://doi.org/10.1016/j.vaccine.2018.04.063).
- [19] DiazGranados CA, Robertson CA, Talbot HK, et al. Prevention of serious events in adults 65 years of age or older: a comparison between high-dose and standard-dose inactivated influenza vaccines. *Vaccine*. 2015;33(38):4988–4993. doi: [10.1016/j.vaccine.2015.07.006](https://doi.org/10.1016/j.vaccine.2015.07.006).
- [20] Govaert TM, Thijs CT, Masurel N, et al. The efficacy of influenza vaccination in elderly individuals: a randomized double-blind placebo-controlled trial. *JAMA*. 1994;272(21):1661–1665. doi: [10.1001/jama.1994.03520210045030](https://doi.org/10.1001/jama.1994.03520210045030).
- [21] DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med*. 2014;371(7):635–645. doi: [10.1056/NEJMoa1315727](https://doi.org/10.1056/NEJMoa1315727).

- [22] Chang L-J, Meng Y, Janoszyk H, et al. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥ 65 years of age: a phase 3 randomized clinical trial. *Vaccine*. 2019;37(39):5825–5834. doi: [10.1016/j.vaccine.2019.08.016](https://doi.org/10.1016/j.vaccine.2019.08.016).
- [23] Chit A, Roiz J, Briquet B, et al. Expected cost effectiveness of high-dose trivalent influenza vaccine in US seniors. *Vaccine*. 2015; 33(5):734–741. doi: [10.1016/j.vaccine.2014.10.079](https://doi.org/10.1016/j.vaccine.2014.10.079).
- [24] Fröbert O, Götberg M, Erlinge D, et al. Influenza vaccination after myocardial infarction: a randomized, double-blind, placebo-controlled, multicenter trial. *Circulation*. 2021;144(18):1476–1484. doi: [10.1161/CIRCULATIONAHA.121.057042](https://doi.org/10.1161/CIRCULATIONAHA.121.057042).
- [25] IQVIA. FARDOGRIP: Etude du fardeau de la grippe en France. Data on file, Influenza-associated excess respiratory hospitalization rates per influenza season. 2019.
- [26] IQVIA. Fardogrip Etude du fardeau de la grippe en France. Data on file, Cardiorespiratory hospitalization rates possibly related to influenza per influenza season. 2019.
- [27] Redondo E, Drago G, López-Belmonte JL, et al. Cost-utility analysis of influenza vaccination in a population aged 65 years or older in Spain with a high-dose vaccine versus an adjuvanted vaccine. *Vaccine*. 2021;39(36):5138–5145. doi: [10.1016/j.vaccine.2021.07.048](https://doi.org/10.1016/j.vaccine.2021.07.048).
- [28] Mattock R, Gibbons I, Moss J, et al. Cost-effectiveness of high dose versus adjuvanted trivalent influenza vaccines in England and Wales. *J Med Econ*. 2021;24(1):1261–1271. doi: [10.1080/13696998.2021.2000780](https://doi.org/10.1080/13696998.2021.2000780).
- [29] Alvarez FP, Chevalier P, Borms M, et al. Cost-effectiveness of influenza vaccination with a high dose quadrivalent vaccine of the elderly population in Belgium, Finland, and Portugal. *J Med Econ*. 2023;26(1):710–719. doi: [10.1080/13696998.2023.2194193](https://doi.org/10.1080/13696998.2023.2194193).
- [30] Rumi F, Basile M, Cicchetti A. Cost-effectiveness and budget impact analysis for high dose quadrivalent influenza vaccine in the Italian elderly population. *Glob Reg Health Technol Assess*. 2021;8:105–113. doi: [10.33393/grhta.2021.2247](https://doi.org/10.33393/grhta.2021.2247).
- [31] Colrat F, Thommes E, LARGERON N, et al. Economic evaluation of high-dose inactivated influenza vaccine in adults aged ≥ 65 years: a systematic literature review. *Vaccine*. 2021;39 Suppl 1: A42–A50. doi: [10.1016/j.vaccine.2020.12.036](https://doi.org/10.1016/j.vaccine.2020.12.036).
- [32] Chit A, Roiz J, Aballea S. An assessment of the expected cost-effectiveness of quadrivalent influenza vaccines in Ontario, Canada using a static model. *PLoS One*. 2015;10(7):e0133606. doi: [10.1371/journal.pone.0133606](https://doi.org/10.1371/journal.pone.0133606).
- [33] Bricout H, Levant M-C, Assi N, et al. The relative effectiveness of a high-dose quadrivalent influenza vaccine vs standard-dose quadrivalent influenza vaccines in older adults in France: a retrospective cohort study during the 2021–22 influenza season. *Clin Microbiol Infect*. doi: [10.1016/j.cmi.2024.08.012](https://doi.org/10.1016/j.cmi.2024.08.012).
- [34] Liang C-Y, Hwang S-J, Lin K-C, et al. Effectiveness of influenza vaccination in the elderly: a population-based case-crossover study. *BMJ Open*. 2022;12(2):e050594. doi: [10.1136/bmjopen-2021-050594](https://doi.org/10.1136/bmjopen-2021-050594).
- [35] Gozalo PL, Pop-Vicas A, Feng Z, et al. Effect of influenza on functional decline. *J Am Geriatr Soc*. 2012;60(7):1260–1267. doi: [10.1111/j.1532-5415.2012.04048.x](https://doi.org/10.1111/j.1532-5415.2012.04048.x).
- [36] Yedlapati SH, Khan SU, Talluri S, et al. Effects of influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2021;10(6):e019636. doi: [10.1161/JAHA.120.019636](https://doi.org/10.1161/JAHA.120.019636).
- [37] Andrew MK, MacDonald S, Godin J, et al. Persistent functional decline following hospitalization with influenza or acute respiratory illness. *J Am Geriatr Soc*. 2021;69(3):696–703. doi: [10.1111/jgs.16950](https://doi.org/10.1111/jgs.16950).
- [38] Rapport Charges et Produits. Publication du rapport annuel 'Charges et Produits 2023': 30 propositions pour améliorer l'accès aux soins, renforcer la prévention et maîtriser les dépenses. 2023 [cited 2024 Jul]. Available from: <https://assurance-maladie.ameli.fr/presse/2022-07-13-cp-rapport-charges-et-produits-pour-2023>
- [39] Heads of Medicines Agencies. Product details | NL/H/4757/001. 2023 [cited 2024 Sep]. Available from: <https://mri.cts-mrp.eu/portal/details?productnumber=NL/H/4757/001>
- [40] Ngami A, Christie T, Guelfucci F, et al. EPH185 increased influenza vaccine coverage rate following COVID-19: durable trend or epiphenomenon? *Value Health*. 2022;25(12):S226. doi: [10.1016/j.jval.2022.09.1106](https://doi.org/10.1016/j.jval.2022.09.1106).
- [41] Santé publique France. Grippe. Bulletin hebdomadaire épidémiologique grippe semaine 17, saison 2022–23. 2022 [cited 2024 Sep]. Available from: <https://www.santepubliquefrance.fr/content/download/433053/3453328>
- [42] Proshenska D, Ménin G, Bianic F, et al. Public health and economic impact of influenza immunization by pharmacists: a systematic literature review and analysis of the French experience. *Value Health*. 2022;25(1):S132. doi: [10.1016/j.jval.2021.11.630](https://doi.org/10.1016/j.jval.2021.11.630).
- [43] O'Reilly DJ, Blackhouse G, Burns S, et al. Economic analysis of pharmacist-administered influenza vaccines in Ontario, Canada. *Clinicoecon Outcomes Res*. 2018;10:655–663. doi: [10.2147/CEOR.S167500](https://doi.org/10.2147/CEOR.S167500).