Exploring Cost-Effectiveness of Flu Vaccines

Heidi Kabler, MD, and Thomas Shin, MA, MPH, MA (stats)

Correspondence: Heidi.Kabler@sanofi.com, Thomas.Shin@sanofi.com

Influenza poses a major public health concern in the United States (US) and globally[1,2], particularly among high-risk groups such as individuals with chronic conditions, those with weakened immune systems, and older adults[3]. Influenza infections can lead to severe outcomes, exacerbating the economic burden of the disease[4,5]. In response, new vaccine technologies, including enhanced vaccines, have been developed to achieve greater effectiveness than that found with traditional standard dose (SD) influenza vaccines[1]. While these enhanced vaccines may be of particular benefit to high-risk populations, they also come with a relatively higher cost[1,6]. To assess the trade-offs between higher costs and effectiveness, cost-effectiveness or cost-utility analyses have been crucial for supporting and optimizing resource allocation among decision-makers worldwide.

Enhanced influenza vaccines, which include high-dose (HD) inactivated influenza vaccines (IIVs), adjuvanted influenza vaccines (Adj-IVs), cell-cultured IIVs, and recombinant influenza vaccines (RIVs), are designed to improve vaccine effectiveness (VE) [1,6,7,8]. Each of these vaccines has different manufacturing processes as well as

different properties. Traditional vaccine manufacturing processes, which have been used for >70 years, involve replicating candidate vaccine viruses in embryonated chicken eggs[9]. HD-IIVs and Adj-IVs are both egg-based influenza vaccines; HD-IIVs vaccines contain four times the amount of hemagglutinin (HA) protein as SD egg-based vaccines[10]. Adj-IVs are SD inactivated vaccines that contain adjuvant, an added ingredient to elicit a stronger immune response [11]. In contrast, cell-cultured vaccines, US Food and Drug Administration (FDA) approved since 2012, replicate in cultured mammalian cells, potentially allowing for a faster manufacturing process[9]. The fastest method involves recombinant influenza vaccines (FDA approved in 2013), which are synthetically manufactured by targeting HA genes, thus eliminating reliance on chicken-egg supply and susceptibility to antigenic drift during production[9,12].

Vaccination Strategies and Cost-Effectiveness

The Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices recommend the use of higher dose influenza vaccines (including HD inactivated and recombinant vaccines) or Adj-IVs over SD unadjuvanted vaccines for adults aged ≥65 years[13]. With rising health care costs, health systems are seeking to optimize their vaccine strategies to maximize both population health outcomes and cost efficiency[14]. Physician leaders and administrators are under significant pressures, including competing priorities and complex decisions that require attention to costs while maintaining the focus and goal of providing the best health care options to patients[14]. The annual economic burden of influenza in the US in 2015 was estimated at about $5.8 billion, accounting for ~65% of the total annual economic

burden caused by other vaccine-preventable diseases[5]. In another study, the average annual total economic burden of influenza to the health system and society was estimated at $11.2 billion[4]. Recent data indicate that nine out of ten influenza hospitalization cases involved at least one underlying chronic condition, highlighting the need for effective vaccination strategies in this demographic[3].

A greater number of patients aged ≥50 years have chronic conditions than in younger populations and influenza vaccination in adults aged 50–64 years has previously been shown to be cost-effective[15-21]; however, many individuals in this age group remain uninsured or face high health-related financial burdens[22]. This age group contributes significantly to the economic and societal implications of influenza, as evidenced by the fact that influenza infections accounted for 67% of the estimated annual economic burden of vaccine-preventable diseases in 2015[5].

Societal Perspective on the Cost-Effectiveness of an Enhanced Influenza Vaccine in Adults Younger Than Age 65 Years

In the analysis by Nowalk et al., among working-age adults aged 18–64 years, vaccination with recombinant quadrivalent influenza vaccine (RIV4) was associated with a cost of $94,186 per quality-adjusted life year (QALY) gained, while for the age 50–64-year subgroup, the cost was $61,329 per QALY gained[6]. Adopting a 100,000 per QALY threshold, RIV4 was more effective and cost-effective relative to SD quadrivalent IIV (SD-IIV4), which encompassed both egg and cell-based SD influenza vaccines. RIV4 was cost-effective among the group aged 18–64 years, particularly among those aged 50–64 years[6].

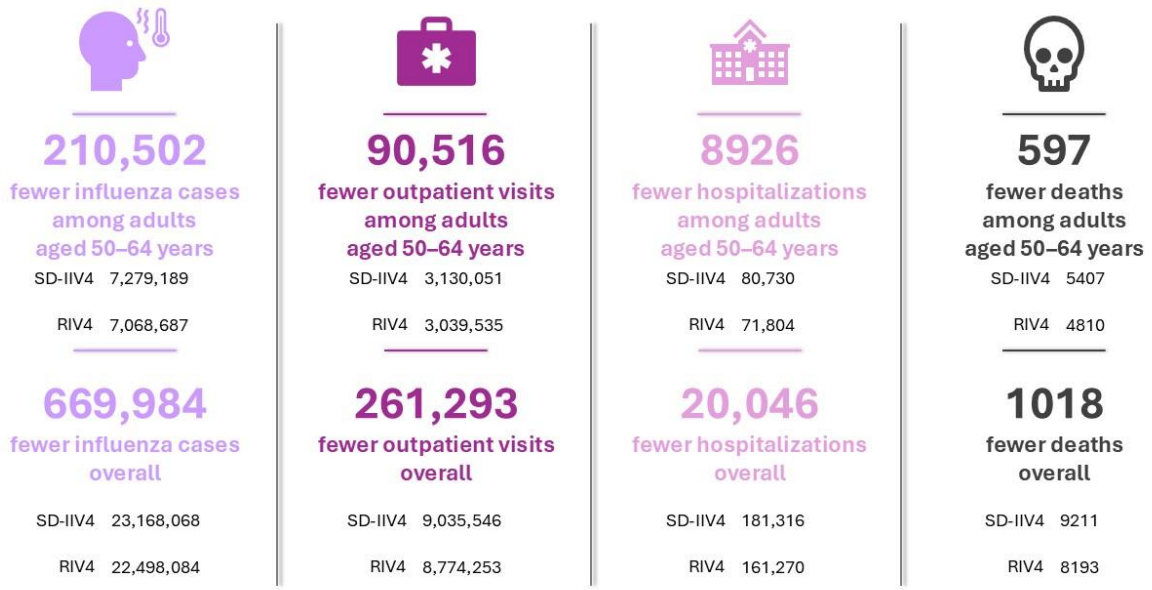
A sensitivity analysis of model parameters indicated significant variability in outcomes within the group aged 18–64 years, influenced by factors such as VE for inpatient hospitalization and outpatient RIV4, VE for inpatient hospitalization and outpatient SD-IIV4, the cost of RIV4, and influenza attack rates. A focused examination of cost-per-QALY (ICER) sensitivity to RIV4 VE for outpatient scenarios revealed that, for individuals aged 18–64 years, RIV4 ceased to be cost-effective at a threshold of $100,000 per QALY when the absolute VE of RIV4 relative to SD-IIV4 was 4% or less. Among those aged 50–64 years, however, RIV4 remained cost-effective under all conditions, likely because of the higher disease burden in this cohort[6].

Further analysis of inpatient-specific VE thresholds showed that RIV4 would not be cost-effective at more than $100,000 per QALY if the absolute VE relative to SD-IIV4 was <19% for the group aged 18–64 years or <13% for the cohort aged 50–64 years[6]. Comparing cost-per-dose of RIV4 with its absolute VE relative to SD-IIV4, sensitivity analysis demonstrated that with a VE difference of 5% for outpatients or 20% for inpatients, the cost-effective price was approximately $57.50 for those aged 18–64 years and >$70 for those aged 50–64 years[6].

The projected annual public health effects of influenza vaccination strategies indicate that the use of RIV4 instead of SD-IIV4 could result in thousands fewer influenza-related hospitalizations and hundreds of thousands of outpatient office visits and hundreds of thousands fewer infections (**Figure 1**), assuming 40% vaccine uptake[6]. While adults aged 50–64 years accounted for about 31% of the study population (62,788,435 of 199,841,852), and an equivalent proportion of the decrease in cases (~31%) occurred in this age group, a higher proportion of the decreases in hospitalizations (~44%) and

most of the decreases in deaths (~59%) occurred in those aged 50–64 years[6], assuming 40% vaccine uptake. The model did not capture information about the presence of chronic conditions; however, this finding may reflect the likelihood of chronic conditions observed in this age group and highlights the potential benefit of an enhanced vaccine strategy beyond a focus on adults aged ≥65 years. Future research could potentially quantify the effects of chronic conditions and may further elucidate the effectiveness and cost-effectiveness of using an enhanced vaccine strategy in the overall population, including younger (aged 18–64 years) adults. One study estimated that 14% of younger working age adults (aged 18–49 years) had clinical risk conditions for influenza but represented more than 28% of influenza hospitalizations in that age group[23]. Furthermore, the study model predicted that using RIV4 among adults with clinical risk conditions in the US could prevent nearly 9000 hospitalizations (in adults 50-64 years of age) and >1000 hospitalizations (in adults 18-49 years of age) due to influenza each season [23]. Accordingly, health systems and policymakers may opt for preferential product use in select age/risk groups (eg. 50–64-year-olds) to maximize cost-benefit ratios.

Figure 1. Annual Projected Public Health Benefits to a RIV4-Vaccination Strategy vs. Standard Dose Among Adults Aged 50–64 Years (N=62,788,435) and Aged 18–64 Years Overall (N=199,841,852)[6]*



*Assuming 40% vaccine uptake

Conclusion

Decision-making related to annual influenza vaccination challenges physician leaders and administrators to balance competing priorities between the improved effectiveness associated with new vaccine technologies with their relatively higher costs[24]. Consequently, health systems and policymakers may consider preferential use of enhanced vaccines such as recombinant influenza vaccine in select age and risk

groups, particularly individuals aged 50-64years, to optimize protection for the adult population[1].

Acknowledgments

Heidi Kabler, MD, and Thomas Shin, MA, MPH, MA, (stats) are employees of Sanofi. Medical writing support, under the direction of the authors, was provided by Ashfield MedComms, an Inizio company and funded by Sanofi.

References

1. Zimmerman RK, Patricia Nowalk M, Dauer K, Clarke L, Raviotta JM, Balasubramani GK. Vaccine effectiveness of recombinant and standard dose influenza vaccines against influenza related hospitalization using a retrospective test-negative design. *Vaccine.* 2023;41(35):5134-5140.
2. Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices - United States, 20242–25 influenza season*. MMWR Recomm Rep.* 2024:73(5)1–28.
3. Centers for Disease Control and Prevention. People at Increased Risk for Flu Complications. https://www.cdc.gov/flu/highrisk/index.htm. Published 2024. Updated September 11, 2024. Accessed April 1, 2025.
4. Putri WCWS, Muscatello DJ, Stockwell MS, Newall AT. Economic burden of seasonal influenza in the United States. *Vaccine.* 2018;36(27):3960–3966.
5. Ozawa S, Portnoy A, Getaneh H, et al. Modeling the economic burden of adult vaccine-preventable diseases in the United States. *Health Aff (Millwood).* 2016;35(11):2124–2132.
6. Nowalk MP, Smith KJ, Raviotta JM, Wateska A, Zimmerman RK. Cost-effectiveness of recombinant influenza vaccine compared with standard dose influenza vaccine in adults 18-64 years of age. *Vaccine.* 2024;42(24):126107.

7. Ng TWY, Cowling BJ, Gao HZ, Thompson MG. Comparative immunogenicity of enhanced seasonal influenza vaccines in older adults: a systematic review and meta-analysis. *J Infect Dis*. 2019;219(10):1525–1535.
8. Cowling BJ, Perera RAPM, Valkenburg SA, et al. Comparative immunogenicity of several enhanced influenza vaccine options for older adults: a randomized, controlled trial. *Clin Infect Dis*. 2020;71(7):1704–1714.
9. Centers for Disease Control and Prevention. How Influenza (Flu) Vaccines Are Made. https://www.cdc.gov/flu/vaccine-process/index.html. Published 2022. Updated November 3, 2022. Accessed April 1, 2025.
10. Center for Disease Control and Prevention. Fluzone High-Dose Seasonal Influenza Vaccine. https://www.cdc.gov/flu/vaccine-types/flu-zone.html. Published 2024. Updated September 6, 2024. Accessed April 1, 2025.
11. Centers for Disease Control and Prevention. Adjuvanted Flu Vaccine. https://www.cdc.gov/flu/vaccine-types/adjuvant.html. Published 2022. Updated August 25, 2022. Accessed April 1, 2025.
12. Hsiao A, Yee A, Fireman B, Hansen J, Lewis N, Klein NP. Recombinant or standard-dose influenza vaccine in adults under 65 years of age. *N Engl J Med.* 2023;389(24):2245–2255.
13. Centers for Disease Control and Prevention. Flu and People 65 Years and Older. https://www.cdc.gov/flu/highrisk/65over.htm. Published 2024. Updated September 5, 2024. Accessed April 1, 2025.
14. American Hospital Association. Report: Hospitals and health system squeezed by persistent economic challenges. 30 APR 2025. Accessed 19 MAY 2025.

15. Nguyen VH, Ashraf M, Mould-Quevedo JF. Estimating the impact of influenza vaccination of low-risk 50–64-year-olds on acute and ICU hospital bed usage in an influenza season under endemic COVID-19 in the UK. *Hum Vaccin Immunother.* 2023;19(1):2187592.
16. Choi EJ, Park JH, Chun BC. Cost effectiveness of trivalent and quadrivalent influenza vaccines in 50- to 64-year-old adults in Korea. *Vaccine.* 2020;38(32):5002–5008.
17. Maciosek MV, Solberg LI, Coffield AB, Edwards NM, Goodman MJ. Influenza vaccination health impact and cost effectiveness among adults aged 50 to 64 and 65 and older. *Am J Prev Med.* 2006;31(1):72–79.
18. Urueña A, Micone P, Magneres MC, et al. Cost-effectiveness analysis of cell versus egg-based seasonal influenza vaccination in children and adults in Argentina. *Vaccines (Basel).* 2022;10(10):1627.
19. De Luca, EK, et al. Cost-effectiveness of routine annual influenza vaccination by age and risk status. *Vaccine*. 2023; 41(29):4239-48.
20. de Waure C, Veneziano MA, Cadeddu C, et al. Economic value of influenza vaccination. *Hum Vaccin Immunother.* 2012;8(1):119–129.
21. Molinari N-AM, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine.* 2007;25(27):5086–5096.
22. Smolka G, Multack M, Figueiredo C. *Health Insurance Coverage for 50- to 64-Year-Olds.* AARP Public Policy Institute. *Insight on the Issues I59*, February 2012:1-16.

23. Torcel-Pagnon L, Coudeville L, Harris RC, Chaves SS. The impact of Influenza on Working-Age Adults ; Exploring the Benefits of the Recombinant Influenza Vaccine. Clin Infect Dis 2025. doi: 10.1093/cid/ciaf200.

24. WHO. Seasonal Influenza Vaccines: An overview for decision-makers. 2020. Accessed 23 May 2025.