

Cost-Effectiveness Analysis of the High-Dose Trivalent Influenza Vaccine in the Elderly Population in Italy

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Purpose: Influenza is a significant public health concern, particularly among the elderly, contributing to high morbidity, hospitalizations, and mortality, in addition to increased economic burden sustained by the Italian National Health Service (SSN). Traditional vaccines, ie, standard-dose trivalent inactivated influenza vaccine (TIV-SD), showed lower immunogenicity and effectiveness in older adults than in younger adults, as a result of the immunosenescence process and increased comorbidities. Enhanced formulations, such as the high-dose trivalent influenza vaccine (TIV-HD), have been introduced to address this gap. This study evaluates the cost-effectiveness of TIV-HD compared to TIV-SD for individuals ≥ 65 years of age in Italy.

Patients and Methods: A cost-effectiveness analysis was performed using a population-based decision-analytic model from the perspective of the SSN, over a one-year time horizon. The model simulated clinical pathways for influenza-related events, including general practitioner visits, emergency department consultations, hospitalizations for cardiorespiratory complications, and mortality. Epidemiological and cost data were sourced from national databases and peer-reviewed literature. Three pricing scenarios were explored. The outcomes included life-years (LYs), quality-adjusted life years (QALYs), and healthcare costs, allowing the calculation of the incremental cost-effectiveness ratio (ICER).

Results: Model-based results showed that TIV-HD is a dominant strategy over TIV-SD, yielding both improved health outcomes (14,070 LYs and 13,678 QALYs) and cost savings in all the pricing scenarios explored. When applied to the Italian elderly population eligible for seasonal influenza vaccination, TIV-HD was estimated to generate overall savings ranging from €82.3 million and €135.0 million for the National Health Service, driven by the prevention of approximately 50,000 influenza-related hospitalizations.

Conclusion: This analysis indicates that TIV-HD was associated with improved outcomes and lower overall costs compared with TIV-SD under the modeled assumptions. The enhanced clinical effectiveness combined with significant cost reductions underscores TIV-HD as a cost-effective intervention, contributing to sustainable healthcare management in Italy.

Plain Language Summary:

Why was this study done?

Every year in Italy, thousands of people aged 65 and over are hospitalized or die from flu-related complications. Standard flu vaccines may not work as well in older people because the immune system becomes weaker with age. A vaccine called the “high-dose trivalent influenza vaccine” (TIV-HD) was developed to improve the immune response in this age group. This study examined whether this vaccine offers good value for money for the Italian healthcare system.

What did the researchers do and find?

The researchers used a computer model to compare the standard-dose vaccine (TIV-SD) with the high-dose vaccine (TIV-HD) in people aged 65 and older. They looked at the number of flu cases, hospital visits, and deaths, as well as the costs to the National Health Service.

The model estimated that, compared with TIV-SD, TIV-HD was associated with about 70,000 fewer flu cases, 50,000 fewer hospitalizations, and 1,400 fewer deaths each year. Although the high-dose vaccine costs more per dose, it was associated with estimated net cost savings ranging from €82 to €135 million, mainly due to fewer influenza-related events and hospitalizations.



What do these results mean?

The findings suggest that the high-dose vaccine may improve health outcomes while reducing healthcare costs in people aged 65 and over in Italy. These results indicate that the high-dose vaccine may represent an effective option to prevent flu in this age group, with potential savings for the healthcare system.

Keywords: TIV-HD, influenza vaccination, cardiovascular worsening, costs, quality of life

Introduction

Globally, the influenza virus causes an estimated one billion infections annually, with 3–5 million severe cases particularly among vulnerable populations such as the elderly and individuals with chronic conditions.^{1,2} The burden of disease is considerable, with respiratory complications accounting for an estimated 290,000 to 650,000 deaths each year.²

In Italy, influenza remains a critical public health issue. Annually, approximately 9% of the population contracts influenza, leading to between 8,000 and 17,000 deaths, 84% of which occur among individuals ≥ 65 years of age.^{3–5} In the elderly, aging is associated with a gradual and physiological decline in immune function, a phenomenon referred to as “immunosenescence”. This process leads to diminished immunological responsiveness, whereby immune cells exhibit reduced capacity to recognize and respond to pathogens unless strongly stimulated.⁶ Immunosenescence has been identified as a key factor contributing to increased susceptibility to infectious diseases such as influenza, and is strongly associated with a heightened risk of severe complications—particularly those of a cardiorespiratory nature.^{3–5} In addition, elderly have more comorbidities than the general population, making them more susceptible to influenza-related complications.⁷

Influenza vaccination, aimed at preventing seasonal flu epidemics, is one of the most widely implemented and significant public health interventions. Given the reduced immunogenicity of standard influenza vaccines in older adults, enhanced vaccine approaches have been developed over the years.⁸ These include the MF59-adjuvanted vaccine, the recombinant vaccine, and the high-dose vaccine.⁸ In Italy, MF59-adjuvanted and high-dose vaccines are preferentially recommended for individuals ≥ 65 years of age.⁹

Beyond the direct health threat posed by influenza, the virus also carries a significant economic burden on healthcare systems and national economies. Consequently, vaccination campaigns must be meticulously planned, weighing both the clinical benefits of the vaccines and the economic sustainability of these interventions.¹

To ensure efficient allocation of healthcare resources and maximize health benefits for the population, it is essential to use vaccine-specific evaluation frameworks. The evaluation of vaccines should be conducted on the basis of solid, robust, and high-quality evidence. In line with the evolving European HTA framework,^{10,11} which emphasizes robust comparative effectiveness evidence to inform healthcare decision-making, this analysis prioritized high-quality randomized controlled trials (RCTs) for relative vaccine efficacy estimates, complemented by meta-analyses and observational data where appropriate.

Several studies have evaluated the clinical and economic value of the high-dose vaccine in various healthcare settings, highlighting important advantages over standard-dose vaccines, including superior protection against influenza and a marked reduction in influenza-related hospitalizations, cardiorespiratory complications, and mortality.^{12–20}

Building upon this evidence, the present study aims to further assess the cost-effectiveness and cost-utility of the high-dose trivalent influenza vaccine—TIV-HD (Efluelda[®], Sanofi Winthrop Industrie, Gentilly, France) in comparison with the standard-dose trivalent vaccine (TIV-SD) in the Italian elderly population (≥ 65 years of age). The analysis is intended to provide additional insights to support evidence-based healthcare policy and optimize resource allocation strategies.

Materials and Methods

A cost-effectiveness analysis was conducted to evaluate different influenza vaccination strategies in the Italian elderly population (≥ 65 years of age). The analysis compared two alternative scenarios, assuming the same proportion of the

elderly population—reflecting the average seasonal vaccination coverage—would receive either the TIV-SD (SD vaccination strategy) or the TIV-HD (HD vaccination strategy). Clinical and economic outcomes were estimated for the entire national elderly cohort to assess the overall impact at the population level.

Study Design

A static decision-analytic model (Figure 1) was developed to simulate the clinical course of influenza and estimate both clinical outcomes and healthcare costs associated with vaccination strategies in the target population (≥ 65 years of age).

The model captured three distinct influenza-related clinical pathways, which were not mutually exclusive, reflecting the possibility that an individual could experience multiple influenza-related events. The first pathway estimated the number of influenza cases, as well as the associated healthcare resource use, including General Practitioner (GP) consultations and Emergency Department (ED) visits among symptomatic individuals. The second pathway focused on complications possibly associated with influenza and estimated the number of hospitalizations across the entire target population, including those due to respiratory and cardiovascular events. This approach allowed for the independent assessment of influenza cases and hospitalizations. The third pathway estimated influenza-attributable mortality, applying a conditional probability to influenza cases. This framework enabled influenza-related mortality to be modeled as a function of influenza cases, while remaining independent from the occurrence of other clinical events.

Time Horizon and Perspective

The analysis was conducted from the perspective of the Italian National Health Service (SSN), taking into account only direct medical costs, considering vaccine acquisition and administration, outpatient visits, ED consultations, and hospitalizations. A one-year time horizon was adopted to capture the clinical and economic outcomes related to influenza and corresponds to a single influenza season. However, to account for the long-term health impact of influenza-related premature mortality, the model estimated life years (LYs) lost beyond the specified time horizon. These estimates were adjusted for health-related quality of life to derive quality-adjusted life years (QALYs). LYs, QALYs, and costs constituted the basis for calculating the incremental cost-effectiveness ratio (ICER).

A 3% annual discount rate was applied to calculate the present value of future costs and outcomes.²¹

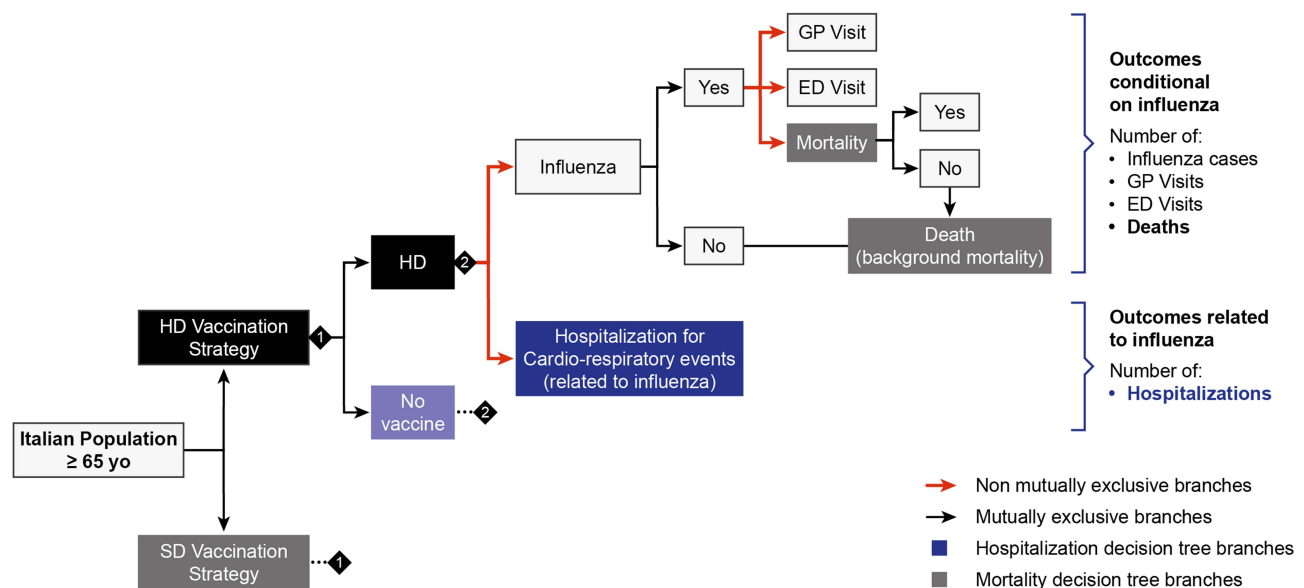


Figure 1 Model structure.

Abbreviations: ED, Emergency Department; GP, General Practitioner; HD, high-dose; SD, standard dose; yo, years old.

Epidemiological Inputs

Table 1 presents the input data of the model. The modeled cohort included all individuals ≥ 65 years of age residing in Italy as of January 1, 2025, according to official demographic data from the Italian National Institute of Statistics (ISTAT)²² (Table 1).

The distribution of underlying comorbidities within this population was assumed to reflect that observed in the general elderly Italian population, as reported by the most recent epidemiological data and national health sources. In

Table 1 Demographic, Vaccination Coverage, and Influenza-Related Outcome Data for the Italian Elderly Population Used in the Model

Demographics		
Age Group (years)	Population Size	Source
65–74	6,996,716	[22]
≥ 75	7,576,457	[22]
Total	14,573,173	[22]
High-risk elderly population (with ≥ 1 chronic condition) (%)		
65–74	34.2	[23]
≥ 75	52.2	[23]
Influenza vaccination coverage rates		
	Coverage Rate (%)	Source
Overall (≥ 65 years of age; 2023-2024)	53.3	[24]
• High-risk (with ≥ 1 chronic conditions) ^a	58.0	[24,25]
• Low-risk (without chronic conditions) ^a	46.9	[24,25]
Influenza-related outcome indicators		
Attack rate, %	7.2	[26]
GP visit, %	38.6	[28]
Cardiorespiratory hospitalization/100,000 inhabitants	7,839.7	[29]
Excess mortality rate/100,000 inhabitants	108.14	[5]
Age Group	Risk Group	Probability of ED visit (%)
65–74 years	Low-risk	0.21
	High-risk	0.90
≥ 75 years	Low-risk	0.36
	High-risk	1.88
Risk Group	Probability of death conditional on developing influenza (%)	
Low-risk	1.91	
High-risk	2.05	

Notes: a Vaccination coverage stratified by the elderly population with and without chronic conditions was estimated by applying the same proportional distribution observed in the previous influenza season, as reported in the PASSI d'Argento surveillance report (overall 65.3%; with ≥ 1 chronic disease 71.0%; without comorbidities 57.4%).²⁵

Abbreviations: ED, Emergency Department

particular, in the age groups 65–74 and ≥ 75 , 34.2% and 52.2% of subjects, respectively, have at least 1 chronic condition²³ (Table 1). The presence of ≥ 1 comorbidities defines the abovementioned subsets as high-risk population.

The vaccine coverage rate, applied identically across both vaccination strategies (TIV-HD and TIV-SD), was set at 53.3%, based on national data from the 2023/2024 influenza season for the elderly population (≥ 65 years of age)²⁴ (Table 1). Additionally, coverage was stratified according to risk groups, using data from the Passi d'Argento surveillance system for the 2022/2023 season.²⁵ Specifically, the observed coverage ratio between high-risk and low-risk groups in the 2022/2023 season was assumed to remain constant for the 2023/2024 season (Table 1).

The expected number of influenza cases in the target population was estimated by applying a seasonal attack rate of 7.2%²⁶ (Table 1), derived from published literature representative of the unvaccinated population. For vaccinated individuals, infection risk was adjusted according to the vaccine-specific effectiveness of TIV-HD and TIV-SD (see the “Efficacy and Effectiveness Inputs” section). Consequently, the overall incidence of influenza was modeled as a function of both the vaccination coverage rate and the differential effectiveness of the two vaccines.

All-cause mortality (background mortality) was applied to both the influenza-free population and individuals who survived an influenza episode during the modeled influenza season.³⁰ Age-stratified mortality rates (ie, 1.13% and 4.44% in the 65–74 and ≥ 75 age groups, respectively) were used to project residual life expectancy and survival in the absence of influenza-related events.³⁰

Influenza-Related Healthcare Events

As previously described, the model simulated different clinical pathways to estimate influenza-related healthcare events, including outpatient care, ED visits, possibly influenza-related hospitalizations, and influenza-attributable mortality.

Outpatient GP visits and ED presentations were modeled as conditional events upon the development of symptomatic influenza. The probability of a GP visit was set at 38.6%, applied uniformly across all age and risk groups²⁸ (Table 1). In contrast, ED access was modeled according to age and risk group distributions.²⁷ The total number of ED accesses was calculated by applying these probabilities to the estimated number of influenza cases for each vaccination strategy (Table 1).

Possibly influenza-related hospitalizations, associated with respiratory or cardiovascular complications, were estimated using an annual hospitalization rate of 7,839.7 per 100,000 individuals,²⁹ applied uniformly across the target population (Table 1). In the absence of Italy-specific seasonal data, it was assumed—based on observed winter patterns—that 60% of these hospitalizations occurred during the influenza season. Among all cardiorespiratory hospitalizations, 49.7% were attributed to respiratory infections,³¹ and 83.0% of total hospital admissions were considered to involve complications.^{32,33} These rates were used to define the baseline risk of hospitalization due to influenza-related cardiorespiratory complications for a hypothetical unvaccinated cohort and subsequently adjusted according to the vaccine-specific effectiveness of TIV-SD and TIV-HD in preventing severe outcomes.

To account for the probability of death conditional on influenza, an excess mortality rate of 108.14 deaths per 100,000 individuals⁵ was applied uniformly across both age groups (Table 1). This rate reflects the elevated risk of death among older adults, particularly those with comorbidities or frailty, when exposed to influenza infection.

Efficacy and Effectiveness Inputs

In adults ≥ 65 years of age, the absolute effectiveness of TIV-SD in reducing the risk of symptomatic influenza compared to no vaccination was estimated at 46%.^{32,33} This effect was modeled to produce a proportional decrease in influenza cases and related healthcare utilization, including GP visits and ED access. The incremental relative efficacy of TIV-HD to TIV-SD in preventing symptomatic influenza was estimated at 24.2%, according to the phase IIIb-IV RCT by DiazGranados et al.³⁴

For influenza-related hospitalizations due to respiratory and cardiovascular complications, the absolute effectiveness of TIV-SD was assumed to be 28.0%,^{35,36} applied uniformly across all age and risk categories. According to a systematic review and meta-analysis of randomized and observational studies conducted over 12 influenza seasons, including over 45 million individuals ≥ 65 years of age,¹² the incremental effectiveness of TIV-HD over TIV-SD in reducing these

hospitalizations was 16.7%. This rate was applied consistently across all modeled strata in the present analysis (ages 65–74 and ≥ 75 years; high- and low-risk groups).

Cost Inputs

Direct medical costs for each vaccination strategy were estimated by quantifying healthcare resource utilization associated with clinical events along each modeled pathway. These included theoretical vaccine procurement and administration, as well as the costs associated with the management of influenza-related events (Table 2).

Influenza vaccines are not reimbursed as standard pharmaceutical products in Italy; however, their cost is fully covered by regional health authorities for defined target populations. Doses are procured annually through public tenders based on estimated coverage needs. The base-case analysis was structured into three distinct scenarios, each reflecting a different assumed premium price per dose of TIV-HD relative to the TIV-SD. The analyses considered three theoretical scenarios: a minimum gap of €15, an intermediate gap of €17, and a maximum gap of €22 between the two vaccines. These values were selected to represent theoretical differences in acquisition costs.

Utility Inputs

Utility inputs were derived from age-specific health-related quality of life estimates reported in the literature.⁴² In cases of symptomatic influenza, baseline utility was temporarily reduced to reflect the disutility associated with acute illness, assumed to last an average of six days. As a consequence, by applying the utility per day with influenza of 0.2947,⁴³ the utility loss due to influenza case for 65–74 and ≥ 75 age groups were estimated to be 0.0099 and 0.0091, respectively. For patients hospitalized due to cardiorespiratory complications, an additional disutility was applied per episode (0.018), as documented in the literature.³² Disutility values per episode (including hospital length of stay) were specific to each clinical event (eg, uncomplicated influenza, hospitalization, complications) and were used to quantify the associated loss in QALYs within the model. QALY losses due to premature mortality were also considered, as per standard cost-effectiveness modelling practice, ie, calculated by multiplying the remaining life expectancy at time of death by age-specific quality of life scores from population norms and applying a 3% discount rate.

Sensitivity Analyses

Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were conducted to assess the uncertainties associated with the base-case inputs.

To assess the robustness of the model outcomes to variations in individual input parameters, the DSA was performed and presented as a tornado diagram. The Incremental Net Monetary Benefit (INMB) was selected as the central outcome. For each input, the INMB was recalculated by varying the parameter within a plausible range or, where appropriate, by

Table 2 Unit Costs (€) Associated with Vaccination Strategies and Healthcare Resource Utilization for Influenza-Related Events in the Elderly Population

Healthcare Resource	Unit Cost (€) ^a	Source
Administration	6.16	Colamesta et al, 2019 ³⁷
Prescription drugs (antibiotics, corticosteroids, aerosols)	16.18	Dal Negro et al, 2018 ³⁸
GP visit	19.84	Updated from DYSCO project data
ED visit	261.35	Regional Decree N°U00265, September 1, 2014 ³⁹
Hospitalization without complications ^b	3,514.30	DRG 80, 86, 90, 93, 97, 100, 102 ⁴⁰
Hospitalization with complications ^b	5,237.41	DRG 79, 85, 87, 89, 92, 96, 99, 101, 565, 566 ⁴⁰

Notes: ^aUnit costs refer to the cost per single dose (for vaccines and drugs) or per clinical event (for healthcare resources). ^bThe average cost per hospitalization was calculated using tariffs assigned to Diagnosis Related Groups (DRGs),⁴⁰ weighted based on the relative frequency of each DRG observed among relevant hospital admissions, using data from the Italian Hospital Discharge Records (SDO).⁴¹ The selected DRGs reflect the most common respiratory and systemic clinical conditions linked to influenza-related complications in the elderly population.

applying at least an arbitrary $\pm 20\%$ deviation from the mean value. [Supplementary Table 1](#) reports the range of the parameters varied in the deterministic sensitivity analysis. The resulting scenario-specific INMBs were then compared to the base-case estimate, allowing for the identification of parameters with the greatest influence on decision uncertainty.

The PSA was conducted with 1,000 iterations to capture the uncertainty surrounding the ICER in the base-case scenario. The results are represented on the incremental cost-effectiveness (CE) plane, displaying the dispersion of the 1,000 ICER estimates as the ratio of incremental costs to incremental benefits between TIV-HD and TIV-SD.

Results

The differences in total clinical outcomes and healthcare expenditure between the HD vaccination strategy (with TIV-HD) and the SD vaccination strategy (with TIV-SD) across the three base-case price gap scenarios are reported in [Tables 3–6](#).

Table 3 Comparison of Specific (I.e, with Positive Swab) Influenza Outcomes, I.e, Influenza Cases, Outpatient Visits for Influenza, and ED Visits for Influenza Between the HD Vaccination Strategy and the SD Vaccination Strategy in the Elderly Italian Population Results are Presented at Population Level

Clinical Outcome	SD Vaccination Strategy (TIV-SD)	HD Vaccination Strategy (TIV-HD)	Difference (TIV-HD vs TIV-SD)
Influenza cases	799,797	728,925	-70,872
GP visits for influenza	308,721	281,365	-27,356
ED visits for influenza	6338	5716	-622

Abbreviations: ED, Emergency Department; GP, General Practitioner; TIV-HD, high-dose trivalent influenza vaccine; TIV-SD, standard-dose trivalent influenza vaccine.

Table 4 Comparison of Less Specific (Without Swab Confirmation) Influenza Outcomes, I.e, Hospitalizations for Cardiorespiratory Events Between the HD Vaccination Strategy and the SD Vaccination Strategy in the Elderly Italian Population. Results are Presented at Population Level

Clinical Outcome	SD Vaccination Strategy (TIV-SD)	HD Vaccination Strategy (TIV-HD)	Difference (TIV-HD vs. TIV-SD)
Hospitalizations for cardiorespiratory events	685,496	635,573	-49,923
• Without complications	116,534	108,047	-8487
• With complications	568,962	527,525	-41,436

Abbreviations: TIV-HD, high-dose trivalent influenza vaccine; TIV-SD, standard-dose trivalent influenza vaccine.

Table 5 Comparison of Mortality, Life years, and QALYs Between the HD Vaccination Strategy and the SD Vaccination Strategy in the Elderly Italian Population. Results are Presented at Population Level

Clinical Outcome	SD Vaccination Strategy (TIV-SD)	HD Vaccination Strategy (TIV-HD)	Difference (TIV-HD vs. TIV-SD)
Death events			
Influenza-specific mortality	15,759	14,356	-1403
Background mortality	415,515	415,556	41
Incremental Life Years per cohort	14,070 years		
Incremental QALYs per cohort	13,678 years		

Abbreviations: QALY, quality-adjusted life-years; TIV-HD, high-dose trivalent influenza vaccine; TIV-SD, standard-dose trivalent influenza vaccine.

Table 6 Comparison of Healthcare Costs Between the HD Vaccination Strategy and the SD Vaccination Strategy in the Elderly Italian Population. Differences are Presented at Population Level

Cost Category	Difference (HD Vaccination Strategy vs. SD Vaccination Strategy) (€)		
	Gap price €15	Gap price €17	Gap price €22
Vaccination	112,985,467	128,050,196	165,712,018
Vaccine administration	0	0	0
Prescription drugs	-442,628	-442,628	-442,628
Outpatient visits for influenza	-542,753	-542,753 €	-542,753
ED visits for influenza	-162,654	-162,654 €	-162,654
Hospitalizations for cardiorespiratory events	-246,844,158	-246,844,158	-246,844,158
• Without complications	-29,825,626	-29,825,626	-29,825,626
• With complications	-217,018,532	-217,018,532	-217,018,532
Total healthcare costs for SSN	-135,006,725	-119,941,996	-82,280,174

Abbreviations: ED, Emergency Department; SSN, Italian National Health Service; TIV-HD, high-dose trivalent influenza vaccine; TIV-SD, standard-dose trivalent influenza vaccine.

From a clinical standpoint, the TIV-HD strategy was associated with a meaningful reduction in the burden of disease. Compared to TIV-SD, the use of TIV-HD resulted in fewer influenza cases, outpatient consultations, ED visits, hospitalizations for cardiorespiratory complications, and influenza-related deaths (Tables 3–5). The use of TIV-HD lead to 13,678 additional QALYs and 14,070 life-years gained at the cohort level, compared to TIV-SD (Table 5).

Across all base-case scenarios, TIV-HD was associated with substantial cost savings for the Italian National Health Service, with projected reductions ranging from €135 million (minimum price gap between the two vaccines) to €82 million (maximum price gap between the two vaccines) over a one-year time horizon (Table 7).

Although the vaccination cost for TIV-HD was higher than for TIV-SD, this was largely offset by reductions in downstream healthcare costs, particularly those associated with the treatment of influenza-related complications (Table 6). Significant cost savings were observed in the management of hospitalizations for cardiorespiratory events, as well as in prescription drug use, outpatient visits, and ED accesses.

In conclusion, TIV-HD was a dominant strategy in all scenarios considered compared to TIV-SD (Table 7).

A threshold analysis was conducted to identify the maximum unit price at which TIV-HD would remain the dominant strategy over TIV-SD, under the current base-case assumptions. Results showed that TIV-HD maintained its dominance—being both more effective and less costly—up to a gap price of €32.92.

Most simulations across all three pricing scenarios confirmed the base-case findings in the probabilistic sensitivity analysis. As shown in Figure 2, the incremental cost-effectiveness pairs are predominantly distributed in the southeast quadrant, indicating that TIV-HD remains more effective and less costly than TIV-SD. The dispersion around each base-case point increases with the assumed per-dose price gap, though most simulations consistently confirm dominance.

Table 7 Base Case Cost-Effectiveness Results Comparing High-Dose Trivalent Influenza Vaccine with Standard-Dose Trivalent Influenza Vaccine in the Elderly Italian Population

Scenario ^a	Incremental Cost (€)	Incremental LYs	Incremental QALYs	ICER/ICUR
Minimum gap price (€15)	-135,006,725	14,070	13,678	Dominant
Mid gap price (€17)	-119,941,996	14,070	13,678	Dominant
Maximum gap price (€22)	-82,280,174	14,070	13,678	Dominant

Notes: ^aAll outcomes are presented on a cohort basis and are discounted at an annual rate of 3.0%.

Abbreviations: ICER, Incremental Cost-Effectiveness Ratio; ICUR, Incremental Cost-Utility Ratio; LY, Life-Year; QALY, Quality-Adjusted Life-Year.

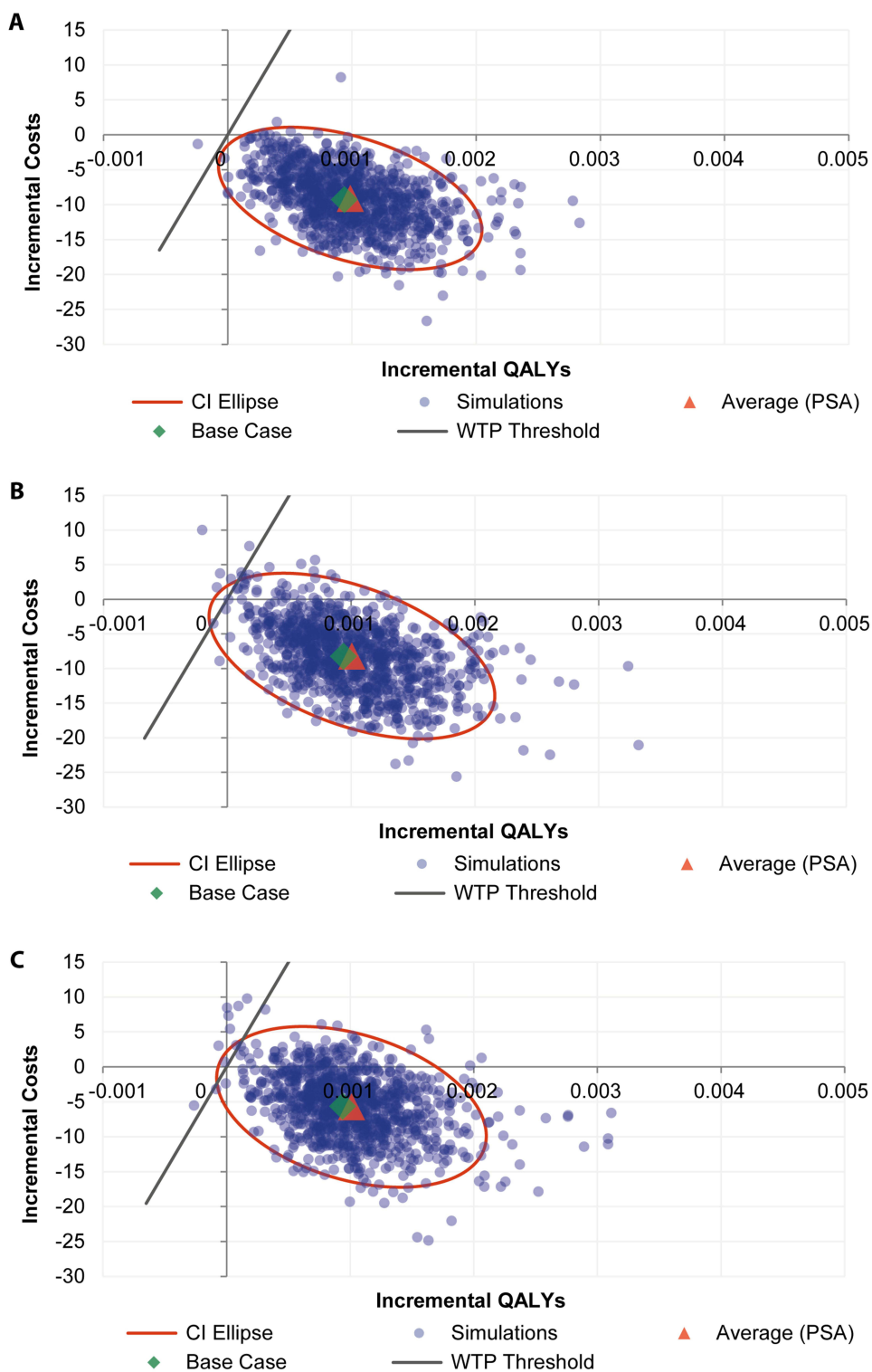


Figure 2 (A) Probabilistic sensitivity analysis (PSA): scatterplot of 1,000 simulations for the price gap scenario with incremental cost per dose €15, comparing TIV-HD vs. TIV-SD. Each point represents an ICER estimate based on randomly sampled input parameters; **(B)** Probabilistic sensitivity analysis (PSA): scatterplot of 1,000 simulations for the price gap scenario with incremental cost per dose €17, comparing TIV-HD vs. TIV-SD. Each point represents an ICER estimate based on randomly sampled input parameters; **(C)** Probabilistic sensitivity analysis (PSA): scatterplot of 1,000 simulations for the price gap scenario with incremental cost per dose €22, comparing TIV-HD vs. TIV-SD. Each point represents an ICER estimate based on randomly sampled input parameters.

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years; TIV-HD, high-dose trivalent influenza vaccine; TIV-SD, standard-dose trivalent influenza vaccine; WTP, willingness-to-pay.

The key drivers influencing the INMB of vaccination with TIV-HD versus TIV-SD across the three price gap scenarios are illustrated in the tornado diagram (Figure 3). The parameter with the greatest impact on INMB variation is the TIV-HD vaccination coverage.



Figure 3 (A) Deterministic sensitivity analysis (DSA) for incremental cost per dose scenario €15. The adjustment factor is the proportion of hospitalizations for cardiovascular events that occur during the influenza season; **(B)** Deterministic sensitivity analysis (DSA) for incremental cost per dose scenarios €17. The adjustment factor is the proportion of hospitalizations for cardiovascular events that occur during the influenza season. **(C)** Deterministic sensitivity analysis (DSA) for incremental cost per dose scenario €22. The adjustment factor is the proportion of hospitalizations for cardiovascular events that occur during the influenza season. **Abbreviations:** HD, high-dose trivalent influenza vaccine; INMB, incremental net monetary benefit; SD, standard-dose trivalent influenza vaccine.

Table 8 Scenario Analysis Assuming a 10% Increase in Vaccine Coverage

	Minimum Gap Price (€15)	Mid Gap Price (€17)	Maximum Gap Price (€22)
Influenza cases (n)	-77,959		
Hospitalizations for cardiorespiratory events (n)	-54,915		
All-cause mortality (n)	-1499		
Incremental health care cost (€)	-148,398,499	-131,839,439	-90,508,191

An additional scenario analysis was conducted to assess the impact of increased vaccine coverage on clinical and economic outcomes. In this analysis, a 10% increase in vaccination coverage was associated with a further reduction in influenza-related clinical events, along with an approximately 9% increase in cost savings across all three evaluated price gap scenarios relative to the base cases (Table 8).

Discussion

According to this model, TIV-HD represents a dominant strategy compared to the TIV-SD for the prevention of seasonal influenza in the Italian elderly population. By combining greater clinical effectiveness with overall cost savings, the use of TIV-HD was estimated to improve individual health outcomes while contributing to the more sustainable management of healthcare resources within the SSN.

Although the acquisition cost of TIV-HD was higher than that of TIV-SD, the alternative strategy was estimated to result in substantial cost offsets, particularly through the prevention of hospitalizations for cardiorespiratory complications, which represent a major component of influenza-related healthcare burden in older adults. These findings were consistent with previous economic evaluations conducted in Italy, such as the model-based analysis by Rumi et al and the real-world data assessment by Cicchetti et al, both of which highlighted the favorable cost-effectiveness profile of TIV-HD when considering direct and indirect influenza-related complications.^{44,45}

The clinical superiority of TIV-HD over TIV-SD has been robustly demonstrated across multiple settings. In a large-scale RCT, DiazGranados et al reported a 24.2% higher efficacy of TIV-HD in preventing laboratory-confirmed influenza in people aged 65 and over.³⁴ Complementing these results, a systematic review and meta-analysis of both randomized and observational studies conducted in the United States by Lee et al confirmed the sustained effectiveness of TIV-HD across various age groups (≥ 65 , ≥ 75 , and ≥ 85) and circulating viral strains.¹² Furthermore, by capturing not only respiratory but also cardiovascular complications triggered by influenza infection, this analysis aims at offering a more comprehensive estimate of the disease burden. This approach is aligned with findings from a retrospective Italian study by Bertolani et al, who emphasized the frequent underestimation of influenza-related hospitalizations in routine reporting.³¹ The risk of acute myocardial infarction within 7 days after detection of influenza B and influenza A was calculated as 10- and 5-fold higher than without influenza infection. This is the reason why cardiovascular societies such as the European Society of Cardiology (ESC)⁴⁶ and the American College of Cardiology (ACC)⁴⁷ recommend influenza vaccination to cardiovascular patients. The results of Bertolani et al were also consistent with clinical trial data, such as the RCT by Fröbert et al conducted in Sweden,³⁶ which demonstrated that influenza vaccination can significantly reduce major adverse cardiovascular events in high-risk populations.

Importantly, while this analysis is limited to the direct comparison between TIV-HD and TIV-SD, a broader public health priority is the urgent need to expand influenza vaccination coverage among the elderly.⁴⁸ Despite the availability of more effective vaccines, vaccination uptake in this high-risk population remains suboptimal in Italy,²⁴ limiting the potential clinical and economic benefits achievable through preventive strategies. Increasing coverage in the elderly would not only reduce preventable morbidity, mortality, and healthcare costs but also contribute to the resilience and sustainability of the healthcare system.⁴⁸ In Italy, influenza vaccination strategies for adults aged ≥ 65 years also include other enhanced vaccine formulations, such as MF59-adjuvanted influenza vaccines.⁴⁹ The present analysis focused on the comparison between high-dose and standard-dose trivalent vaccines in order to evaluate the incremental value associated

with the increased antigen content of the high-dose formulation. Direct comparisons with other enhanced vaccines, including MF59-adjuvanted formulations, were beyond the scope of the present model and would require dedicated analyses incorporating vaccine-specific effectiveness data and comparative evidence.

Furthermore, the regulatory landscape for healthcare technologies in Europe is undergoing a major transformation. Regulation (EU) 2021/2282 on HTA will progressively harmonize the evaluation of new drugs and vaccines across EU member states.¹⁰ In this evolving framework, generating robust, locally contextualized evidence—such as cost-effectiveness analyses tailored to national healthcare systems—becomes increasingly critical. The present study, by providing a comprehensive economic and clinical evaluation of TIV-HD, based on robust effectiveness data coming from RCTs, within the Italian healthcare setting, anticipates these regulatory requirements, thus supporting future decision-making processes aligned with European standards.

This study presented several strengths. The model was grounded on Italian-specific epidemiological, demographic, and healthcare cost data, ensuring high contextual relevance for national decision-making. Additionally, the model comprehensively captured both specific and less specific influenza-related outcomes, including cardiorespiratory complications, which are often underrepresented in traditional burden assessments. In fact, influenza proved to worsen any underlying cardiorespiratory condition.³ We deem that if swabs were performed to every patient presenting with cardiorespiratory disease worsening, an important increase in the number of influenza cases would emerge. To be precise, swabs in these cases are recommended,⁵⁰ but in clinical practice, they are often omitted due to cost reasons. Therefore, the inclusion of cardiorespiratory exacerbations may offer a better overview of the true impact of influenza. In fact, the clinical trials on high-dose influenza vaccines by Gravenstein et al⁵¹ and Palmu et al¹³ considered both specific and less specific outcomes for influenza. Data on vaccine effectiveness were based on clinical trial findings and updated real-world evidence, further reinforcing the credibility of the results. In fact, the best available evidence level was chosen, whether coming from clinical trials, observational studies, or meta-analyses including both randomized and observational studies. In our opinion, the latter source is the most reliable, as it combines both the strongest evidence in experimental conditions and real-world data, which best represent the general population.

This study has also some limitations. In particular, the inclusion of hospitalizations for cardiorespiratory complications which were not necessarily stemming from laboratory-confirmed influenza cases. Because influenza testing is not routinely performed for all patients presenting with respiratory or cardiovascular complications, some of the hospitalizations included in the model may not have been directly attributable to influenza infection. This approach may therefore lead to an overestimation of the influenza-attributable burden and, consequently, of the potential benefits associated with vaccination. At the same time, data about the influenza-related hospitalizations tend to underestimate the disease burden, as several studies have shown that influenza-related complications are often underdiagnosed in routine clinical practice. Furthermore, the data on the probability of GP visits were applied uniformly across the population, without accounting for differences between age or risk groups, potentially resulting in both under- and over-estimations. In addition, while the model evaluates TIV-HD, some effectiveness estimates—particularly those related to hospitalization outcomes—were informed by meta-analyses including both trivalent and quadrivalent high-dose influenza vaccines. These vaccines share the same high-dose antigen content per strain, and the inclusion of QIV-HD data reflects the broader evidence base of the high-dose platform rather than a shift in the evaluated intervention. However, the quadrivalent formulation maintains the same antigen dose for shared strains as the trivalent high-dose vaccine, with the addition of a second B lineage, supporting the clinical continuity of the high-dose platform. Notably, WHO has recently indicated that inclusion of the B/Yamagata lineage in quadrivalent vaccines is no longer warranted due to its apparent absence since 2020,⁵² further reducing potential differences between trivalent and quadrivalent formulations in current epidemiological contexts.

Conclusion

In conclusion, this analysis indicates that TIV-HD was associated with improved outcomes and lower overall costs compared with TIV-SD under the modelled assumptions. Broader adoption of TIV-HD, combined with strategies to enhance vaccination coverage among older adults, may improve public health outcomes and generate economic benefits, thus possibly contributing to a more effective and sustainable healthcare system.

Abbreviations

ACC, American College of Cardiology; CE, cost-effectiveness; DRGs, Diagnosis Related Groups; DSA, Deterministic sensitivity analysis; ED, Emergency Department; ESC, European Society of Cardiology; GP, General Practitioner; HTA, Health Technology Assessment; ICER, incremental cost-effectiveness ratio; ICER, Incremental Cost-Effectiveness Ratio; ICUR, Incremental Cost-Utility Ratio; INMB, Incremental Net Monetary Benefit; ISTAT, Italian National Institute of Statistics; LYs, included life-years; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; RCTs, randomized controlled trials; SSN, Italian National Health Service; TIV-HD, high-dose trivalent influenza vaccine; TIV-SD, standard-dose trivalent influenza vaccine; WTP, willingness-to-pay.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, MB, upon reasonable request.

Ethics Approval and Informed Consent

Due to its design, this study did not require institutional review board approval. It was conducted in compliance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Calabrò GE, D'Ambrosio F, Fallani E, Ricciardi W. Influenza vaccination assessment according to a value-based health care approach. *Vaccines*. 2022;10(10):1675. doi:10.3390/vaccines10101675
2. World Health Organization. Influenza (seasonal). 2023. Available from: [https://www.who.int/news-room/fact-sheets/detail/influenza-\(seasonal\)](https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)). Accessed June 9, 2025.
3. EpiCentro. [Mortality due to influenza] Mortalità per influenza. 2024. Available from: <https://www.epicentro.iss.it/influenza/sorveglianza-mortalita-influenza>. Accessed June 9, 2025.
4. Rizzo C, Bella A, Viboud C, et al. Trends for influenza-related deaths during pandemic and epidemic seasons, Italy, 1969–2001. *Emerg Infect Dis*. 2007;13(5):694–699. doi:10.3201/eid1305.061309
5. Rosano A, Bella A, Gesualdo F, et al. Investigating the impact of influenza on excess mortality in all ages in Italy during recent seasons (2013/14–2016/17 seasons). *Inter J Infect Dis*. 2019;88:127–134. doi:10.1016/j.ijid.2019.08.003
6. Lang PO, Mendes A, Socquet J, Assir N, Govind S, Aspinall R. Effectiveness of influenza vaccine in aging and older adults: comprehensive analysis of the evidence. *Clin Interv Aging*. 2012;7:55–64. doi:10.2147/CIA.S25215
7. Near AM, Tse J, Young-Xu Y, Hong DK, Reyes CM. Burden of influenza hospitalization among high-risk groups in the United States. *BMC Health Serv Res*. 2022;22(1):1209. doi:10.1186/s12913-022-08586-y

8. 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*. 2018. doi:10.1093/infdis/jiy720
9. Ministero della Salute. [Prevention and control of influenza: recommendations for the 2023–2024 season] Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2023–2024. 2023. Available from: <https://www.quotidianosanita.it/allegati/allegato1691170597.pdf>. Accessed June 9, 2025.
10. European Parliament. Regulation - 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU. 2021. Available from: <https://eur-lex.europa.eu/eli/reg/2021/2282/oj/eng>. Accessed June 9, 2025.
11. Member State Coordination Group on Health Technology Assessment. Guidance on validity of clinical studies. 2024. Available from: https://health.ec.europa.eu/document/download/9f9dbfe4-078b-4959-9a07-df9167258772_en?filename=hta_clinical-studies-validity_guidance_en.pdf. Accessed March 3, 2026.
12. Lee JKH, Lam GKL, Yin JK, Loiacono MM, Samson SI. High-dose influenza vaccine in older adults by age and seasonal characteristics: systematic review and meta-analysis update. *Vaccine X*. 2023;14:100327. doi:10.1016/j.jvaxc.2023.100327
13. Palmu AA, Pepin S, Syrjänen RK, et al. High-dose quadrivalent influenza vaccine for prevention of cardiovascular and respiratory hospitalizations in older adults. *Influenza Respir Viruses*. 2024;18(4):e13270. doi:10.1111/irv.13270
14. Chit A, Becker DL, DiazGranados CA, Maschio M, Yau E, Drummond M. Cost-effectiveness of high-dose versus standard-dose inactivated influenza vaccine in adults aged 65 years and older: an economic evaluation of data from a randomised controlled trial. *Lancet Infect Dis*. 2015;15(12):1459–1466. doi:10.1016/S1473-3099(15)00249-2
15. Becker DL, Chit A, DiazGranados CA, Maschio M, Yau E, Drummond M. High-dose inactivated influenza vaccine is associated with cost savings and better outcomes compared to standard-dose inactivated influenza vaccine in Canadian seniors. *Hum Vaccines Immunother*. 2016;12(12):3036–3042. doi:10.1080/21645515.2016.1215395
16. Shireman TI, Ogarek J, Gozalo P, et al. Cost benefit of high-dose vs standard-dose influenza vaccine in a long-term care population during an A/H1N1-predominant influenza season. *J Am Med Directors Assoc*. 2019;20(7):874–878. doi:10.1016/j.jamda.2018.12.003
17. Van Aalst R, Russo EM, Neupane N, et al. Economic assessment of a high-dose versus a standard-dose influenza vaccine in the US Veteran population: estimating the impact on hospitalization cost for cardio-respiratory disease. *Vaccine*. 2019;37(32):4499–4503. doi:10.1016/j.vaccine.2019.06.066
18. Colrat F, Thommes E, LARGERON N, Alvarez FP. Economic evaluation of high-dose inactivated influenza vaccine in adults aged ≥65 years: a systematic literature review. *Vaccine*. 2021;39:A42–A50. doi:10.1016/j.vaccine.2020.12.036
19. De Fougerolles TR, Baïssas T, Perquier G, et al. Public health and economic benefits of seasonal influenza vaccination in risk groups in France, Italy, Spain and the UK: state of play and perspectives. *BMC Public Health*. 2024;24(1):1222. doi:10.1186/s12889-024-18694-5
20. Chit A, Roiz J, Briquet B, Greenberg DP. 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
21. Capri S, Ceci A, Terranova L, Merlo F, Mantovani L; The Members of the Italian Group for Pharmacoeconomic Studies. Guidelines for economic evaluations in Italy: recommendations from The Italian Group of Pharmacoeconomic Studies | Therapeutic Innovation & Regulatory Science. *Drug Inf J*. 2001;35:189–201.
22. Istituto Italiano di Statistica. [Resident population in Italy as of January 1, 2025] Popolazione residente in Italia al 1 gennaio 2025. 2025. Available from: <https://demo.istat.it/app/?i=POS>. Accessed June 9, 2025.
23. Istituto Italiano di Statistica. [Health of older adults] Salute degli anziani. 2021. Available from: <https://www.istat.it/comunicato-stampa/le-condizioni-di-salute-della-popolazione-anziana-in-italia-anno-2019/>. Accessed June 9, 2025.
24. EpiCentro. [Influenza vaccination coverage in Italy] Coperture della vaccinazione antinfluenzale in Italia. 2024. Available from: <https://www.epicentro.iss.it/influenza/coperture-vaccinali>. Accessed June 9, 2025.
25. Istituto Superiore di Sanità. [Passi d'Argento data: in the 2022–2023 two-year period, 59% of adults over 65 had one or more diseases] Dati Passi d'Argento, nel biennio 2022–2023 una o più patologie per il 59% degli over 65. ISS; 2024. Available from: <https://www.iss.it/-/dati-passi-d-argento-nel-biennio-2022-2023-una-o-piu-patologie-per-il-59-degli-over-65-bene-la-vaccinazione-antinfluenzale>. Accessed June 9, 2025.
26. Somes MP, Turner RM, Dwyer LJ, Newall AT. 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
27. Trucchi C, Paganino C, Orsi A, et al. Hospital and economic burden of influenza-like illness and lower respiratory tract infection in adults ≥50 years-old. *BMC Health Serv Res*. 2019;19(1):585. doi:10.1186/s12913-019-4412-7
28. Capri S, Barbieri M, De Waure C, Boccalini S, Panatto D. Cost-effectiveness analysis of different seasonal influenza vaccines in the elderly Italian population. *Hum Vaccines Immunother*. 2018;14(6):1331–1341. doi:10.1080/21645515.2018.1438792
29. Fattore G, Pongiglione B, Vezzosi L. Excess hospitalizations and in-hospital mortality associated with seasonal influenza in Italy: a 11-year retrospective study. *BMC Infect Dis*. 2024;24(1):227. doi:10.1186/s12879-024-09071-z
30. Istituto Italiano di Statistica. [Deaths and mortality] Decessi e mortalità. 2025. Available from: <https://www.istat.it/notizia/dati-di-mortalita-cosa-produce-listat/>. Accessed June 9, 2025.
31. Bertolani A, Fattore G, Pregliasco F. The hospitalization burden of influenza: just the tip of the iceberg? *Glob Reg Health Technol Assess*. 2018;2018:228424031877714. doi:10.1177/2284240318777148
32. Baguelin M, Camacho A, Flasche S, Edmunds WJ. Extending the elderly- and risk-group programme of vaccination against seasonal influenza in England and Wales: a cost-effectiveness study. *BMC Med*. 2015;13(1):236. doi:10.1186/s12916-015-0452-y
33. Fleming DM, Andrews NJ, Ellis JS, et al. Estimating influenza vaccine effectiveness using routinely collected laboratory data. *J Epidemiol Community Health*. 2010;64(12):1062–1067. doi:10.1136/jech.2009.093450
34. 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
35. Beyer WEP, Nauta JJP, Palache AM, Giezeman KM, Osterhaus ADME. Immunogenicity and safety of inactivated influenza vaccines in primed populations: a systematic literature review and meta-analysis. *Vaccine*. 2011;29(34):5785–5792. doi:10.1016/j.vaccine.2011.05.040
36. 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

37. Colamesta V, Tamburrano A, Barbara A, et al. Cost-consequence analysis of influenza vaccination among the staff of a large teaching hospital in Rome, Italy: a pilot study. *PLoS One*. 2019;14(11):e0225326. doi:10.1371/journal.pone.0225326
38. Dal Negro RW, Turco P, Povero M. Cost of influenza and influenza-like syndromes (I-LSs) in Italy: results of a cross-sectional telephone survey on a representative sample of general population. *Respir Med*. 2018;141:144–149. doi:10.1016/j.rmed.2018.07.001
39. Regione Lazio. [Correction to Commissioner's Decree No. U00265 of September 1, 2014] Rettifica Decreto commissariale n. U00265 del 1 settembre 2014. 2015. Available from: https://www.regione.lazio.it/sites/default/files/decreti-commissario-ad-acta/SAN_DCA_U00064_18_02_2015.pdf. Accessed March 9, 2026.
40. Ministero della Salute. [Remuneration for acute inpatient hospital care, rehabilitation hospital care, post-acute long-term care, and outpatient specialist care services] Remunerazione prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di riabilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale. Decreto 10/2012Gazzetta Ufficiale. 2013. Available from: <https://www.gazzettaufficiale.it/eli/id/2013/01/28/13A00528/sg>. Accessed June 9, 2025.
41. Ministero della Salute. [Annual reports on hospital admissions. SDO Report 2021] Rapporti annuali sui ricoveri ospedalieri. Rapporto SDO. 2021. Available from: <https://www.salute.gov.it/new/it/tema/assistenza-ospedaliera/rapporti-annuali-sui-ricoveri-ospedalieri/>. Accessed March 6, 2026.
42. Scalone L, Cortesi PA, Ciampichini R, Cesana G, Mantovani LG. Health related quality of life norm data of the Italian general population: results using the EQ-5D-3L and EQ-5D-5L instruments. *EBPH*. 2022;12(3). doi:10.2427/11457
43. Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. *Health Technol Assess*. 2003;7(35):iii–iv, xi–xiii, 1–170. doi:10.3310/hta7350
44. Cicchetti A, Rumi F, Basile M, et al. Report HTA del vaccino quadrivalente ad alto dosaggio (QIV-HD) EFLUELDA® per la prevenzione dell'influenza stagionale e delle sue complicanze nella popolazione over 65. *Ital J Public Health World*. 2021;10:1–70. Available from: <https://www.ijph.it/hta-vaccino-quadrivalente-qiv-hd-efluelda>.
45. Rumi F, Basile M, Cicchetti A. Cost-effectiveness and budget impact analysis for high dose quadrivalent influenza vaccine in the Italian elderly population. *Grhta*. 2021;8:105–113. doi:10.33393/grhta.2021.2247
46. Heidecker B, Libby P, Vassiliou VS, et al. Vaccination as a new form of cardiovascular prevention: a European Society of Cardiology clinical consensus statement: with the contribution of the European Association of Preventive Cardiology (EAPC), the Association for Acute Cardiovascular Care (ACVC), and the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2025;46(36):3518–3531. doi:10.1093/eurheartj/ehaf384
47. Heidenreich PA, Bhatt A, Nazir NT, Schaffner W, Vardeny O. 2025 concise clinical guidance: an ACC expert consensus statement on adult immunizations as part of cardiovascular care: a report of the American College of Cardiology Solution Set Oversight Committee. *JACC*. 2025;86(21):2085–2098. doi:10.1016/j.jacc.2025.07.003
48. EpiCentro. [National Vaccine Prevention Plan (PNPV) 2023–2025] Piano nazionale di prevenzione vaccinale (PNPV) 2023–2025. 2021. Available from: <https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2025&codLeg=107011&parte=1%20&serie=null>. Accessed June 9, 2025.
49. Ministero della Salute. Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2025–2026. 2025.
50. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the infectious diseases society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):e1–e47. doi:10.1093/cid/ciy866
51. Gravenstein S, Davidson HE, Taljaard M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. *Lancet Respir Med*. 2017;5(9):738–746. doi:10.1016/S2213-2600(17)30235-7
52. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2025–2026 northern hemisphere influenza season. 2025. Available from: https://cdn.who.int/media/docs/default-source/influenza/who-influenza-recommendations/vcm-northern-hemisphere-recommendation-2025-2026/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2025-2026-northern-hemisphere-influenza-season.pdf?sfvrsn=857c2e9b_13&download=true. Accessed March 3, 2026.

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