Supplementary File 2. Economic evaluation of the use of adjuvanted trivalent inactivated vaccine in the Italian elderly

The *objective* of the present study was to compare all seasonal influenza vaccines available in Italy for immunisation of the elderly in the 2018/19 influenza season in terms of cost-effectiveness and to quantify the health and budget impact of current and alternative recommendation-based scenarios of vaccinating the elderly.

Methods

Target population and subgroups. The study population consisted of a full cohort of about 13.4 million Italian subjects aged ≥65 years (henceforth referred to as "elderly").[1] Given that the elderly population is not homogeneous[2] in terms of developing influenza-related complications,[3] the study population was divided into two subgroups: those at lower risk of developing complications (henceforth referred to as "low risk") and those at higher risk of developing complications (henceforth referred to as "high risk"). This latter subgroup included subjects affected by the following health conditions: diabetes, myocardial infarction, angina pectoris, other cardiac diseases, stroke, intracerebral haemorrhage, chronic bronchitis, emphysema, cirrhosis, malignancies, parkinsonism, Alzheimer's disease and dementia.[4]

Setting and location. The Italian National Health Service (NHS) implements a Beveridge-like model with universal coverage. However, in the context of Italian fiscal federalism the 19 Regions and two Autonomous Provinces enjoy significant autonomy in organising and delivering healthcare services through local health units.[5] Regarding influenza vaccination policies, the latest National Immunisation Plan 2017–2019[6] recommends annual influenza vaccination for the elderly, for people aged 0.5–64 years with specific health conditions (similar to those listed in the previous subsection), healthcare professionals and some other population groups. According to the current essential levels of care,[7] the Italian elderly are entitled to receive annual vaccination free-of-charge.

Study perspective. Given that the study population involved only the elderly who are entitled to free-of-charge vaccination, the study was conducted from the third-payer (Italian NHS) perspective; therefore, only direct medical costs were considered.

Comparators. All types of vaccines available to the Italian elderly in the 2018/19 influenza season were considered in the present paper, namely trivalent inactivated vaccine (TIV), adjuvanted TIV (aTIV) and quadrivalent inactivated vaccine (QIV).[8]

Time horizon and discounting. The time horizon was set to one year. Indeed, as per World Health Organization (WHO) guidance on the economic evaluation of influenza vaccination,[9,10] most influenza-related costs and consequences occur within a single year; a 1-year time horizon is therefore appropriate. Considering the 1-year time horizon adopted, no discount rates were applied. However, the life expectancy of the study population was estimated in order to take into account benefits associated with deaths avoided due to vaccination. For this purpose, the total quality-adjusted life years (QALYs) gained were discounted at an annual rate of 3%, as per available Italian guidelines.[11]

Choice and evaluation of preference-based outcomes. In high-income countries like Italy, QALYs gained [and not disability-adjusted life years (DALYs) averted] are usually used as utility measures[9,10] and recommended by National guidelines.[11] Given that it was not possible to establish Italian disutility weights for laboratory-confirmed influenza (LCI) and its complications, international data,[12-15] which were mainly based on EuroQol EQ-5D social tariffs, were used.

Measurement of effectiveness. In this study, both single-study and synthesis-based estimates were used. Specifically, the absolute efficacy of TIVs against LCI was drawn from a Cochrane meta-analysis[16] of randomised placebo controlled trials (RCTs) that has been used in a previous Italian cost-effectiveness analysis (CEA).[17] Given that aTIV is more immunogenic than TIV[18-20],it is expected to provide greater protection against LCI. Analogously, given that QIV has an additional B strain, it is expected to provide broader protection.[17] Therefore, the vaccine effectiveness (VE) of aTIV and QIV was established as a function of absolute VE of TIV and relative VE (rVE) of aTIV/QIV. The VE of aTIV has been systematically explored by Domnich et al.[21] In one Canadian study[22] the rVE of aTIV vs TIV against LCI was 63% [adjusted odds ratio 0.37 (95% CI: 0.14-0.96)]. However, we decided to use a more conservative estimate of the rVE of aTIV vs TIV, i.e. 25%, as reported by Mannino et al.[23] By contrast, the rVE of QIV was established analytically, since no elderly-specific data were available. The analytical approach used methodology similar to that described by Chit et al.[24] Specifically, an advantage of QIV over TIV will depend on the frequency of B type detection in the elderly, the frequency of B lineage mismatch (regarding the B strain included in TIV) and the degree of cross-protection against the opposite B lineage provided by TIV. The frequency of B type detection was set to 17.9%, a value taken from in-house data of the Interuniversity Research Centre on Influenza and other Transmissible Infections (CIRI-IT; Genoa, Italy). An average level of B lineage mismatch (60.1%) was adopted from a previously published Italian Health Technology Assessment (HTA) report on the introduction of QIV,[17] and a 35% rVE estimate of QIV vs TIV against the mismatched B lineage was assumed from previously published[25,26] systematic reviews and meta-analyses.

Costs. All costs are expressed in 2017 Euro (€). As in previously published Italian HTA,[17] the present CEA adopts ex-factory prices of purchase of single vaccine types. The ex-factory price was derived from the official retail list price (RLP) by applying the following formula: ex-factory price = RLP – VAT10% – [(RLP – VAT10%)*0.3335], where RLP is the retail list price and VAT is the reduced value added tax imposed on pharmaceuticals. Costs relative to ambulatory services and treatments including vaccine administration came from normative documents[27,28] whenever possible; otherwise, previously published Italian studies[29] were consulted. Diagnosis-related group (DRG) reimbursement tariffs[30] were applied for hospitalizations following influenza complications.

Choice of model, basic assumptions and model parameters. The CEA used the static approach, which is more conservative; indeed, some population groups, such as the elderly, contribute less to virus transmission in community.[9,10] For this purpose, a decisional-tree model was constructed in TreeAge Pro version 2017 (TreeAge Software Inc.); this is is schematically depicted in Fig. S1. Briefly, the model begins with a full cohort of Italian people aged ≥65 years; this population may be at lower or higher risk of developing influenza complications, as described above. The likelihood of being immunized with either vaccine depends on the average vaccination coverage of the Italian elderly and is different for subjects at lower and higher risk of developing influenza-related complications. In the vaccinated sub-cohorts, the risk of catching influenza will be, to some degree, lower than the baseline risk (i.e that of unvaccinated subjects), depending on the vaccine type). The subsequent influenza subtree follows a typical progression: complication outcomes -> hospitalization outcomes -> survival outcomes. An important assumption of the model is that deaths may occur only in hospitalized patients. We acknowledge some possibility of mortality in the community setting; however, as these data were not available, we adopted a conservative approach.

The model parameters, with references and derivation techniques, are listed in Table S1. The selection of input parameters was driven by systematic/scoping reviews conducted during the whole HTA process, previously published Italian HTA on the QIV introduction in Italy[17] and expert opinion. Italian data were always preferred, if available and sufficiently robust. In particular, epidemiological and virological data and all cost data are Italy-specific. By contrast, it was not possible to find robust Italian data on LCI-related complications, hospitalizations and mortality, nor on Italy-specific disutility weights.

Study outcome and data analysis. The study outcome was the incremental cost-effectiveness ratio (ICER) of aTIV vs comparators (i.e. TIV and QIV). Pairwise comparisons found to be cost-effective in the base-case scenario were subjected to both one-way deterministic and probabilistic sensitivity analyses. In the latter, 10,000 Monte Carlo rounds were computed; beta distributions were associated to demographic and influenza- and vaccination-related input parameters, while gamma distributions were associated to costs and disutility weights. A strategy was deemed to be cost-effective when ICER was <30,000/QALY gained in the base case scenario and <30,000/QALY gained in at least 50% of simulations in the probabilistic sensitivity analysis.

Health and budget impact analyses. To provide a complete picture of the health- and budget-related consequences of using aTIV in the Italian elderly, a budget impact analysis (BIA) was performed in addition to the above-described CEA model. The BIA adopted the same model structure and assumptions as the CEA model, with the exception of vaccine purchase price. Indeed, in Italy each Region procures seasonal influenza vaccines through a tender procedure and the final purchase price of single vaccine types is usually well below both list and ex-factory prices. In the present BIA, we used weighted-average regional procurement prices of TIV (€2.49), aTIV (€5.20) and QIV (€5.66) for the 2018/19 influenza season. Another peculiarity of BIA lies in the need to establish current and hypothetical market shares of single vaccines. For the 2018/19 influenza season, the elderly-specific market share was based on the analysis of allotments requested by single Italian Regions, i.e. 1%, 35% and 64% for TIV, aTIV and QIV, respectively. The hypothetical market share was based on the recent recommendations issued by the Italian Ministry of Health[8] on the preferential use of aTIV in all people aged ≥75 years, while the sub-cohort of subjects aged 65-74 years may receive QIV or TIV. However, TIV is likely to disappear in the upcoming season (its market share now is about 1%). Therefore, only aTIV and QIV were considered in the hypothetical scenario. To establish the hypothetical market share, we first found a vaccination coverage among the elderly aged ≥75 years that was likely to be higher than among those aged 65-74 years. Indeed, an Italian survey[38] has shown that subjects aged ≥75 years are approximately 30% more likely to be immunized than those aged 65-74 years. The resulting market share was 42% for QIV and 58% for aTIV.

Results

Base case. In the base case analysis, aTIV proved highly cost-effective in comparison with TIV (ICER=€4,527/QALY gained). By contrast, QIV was markedly dominated by aTIV (Table S2).

Uncertainty analysis. In the one-way deterministic analysis of aTIV vs TIV, only four parameters had a significant impact on ICER: the purchase price and VE of both vaccines. When the lower limit estimate of TIV VE (34%) was used, TIV was dominated by aTIV, while setting this parameter to 73% produced an ICER, as TIV was a dominant strategy. Likewise, the VE of aTIV had a great influence: at the maximum level (43%) ICER was €222/QALY, while at minimum levels (2%) it was €119,477/QALY. Finally, at the minimum TIV price, ICER became €24,479/QALY, while at the maximum level of TIV, aTIV was a dominant strategy. Given that the vaccine purchase price was highly influential on the economic outcome, we performed an additional *post-hoc* analysis of aTIV vs QIV in which the price of aTIV remained the same (€6.99) while that of QIV dropped to €5.54 (-50%). In this analysis, aTIV was still cost-effective, with an ICER of €10,750/QALY gained.

The probabilistic sensitivity analysis of aTIV vs TIV is shown in Fig. S2. aTIV was cost-effective in 58.3% of Monte Carlo rounds, dominant over TIV in 18.1 %, unlikely to be cost-effective (ICER>€30.000/QALY gained) in 13.1%, and dominated by TIV in the remaining 10.5% of cases.

Health and budget impact of current versus alternative scenario of vaccinating the Italian elderly. Nationwide adoption of the alternative scenario (in which all the elderly aged ≥75 years are given aTIV, while all people aged 65-74 years are given QIV) would prevent an additional 9,699 cases of LCI, 1,014 complications, 311 hospitalisations and 12 deaths. The alternative strategy would also save about € 0.53 million in vaccination campaigns, resulting in total budget savings of over € 1.67 million (Table S3).

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Fig S1. Stylised model structure

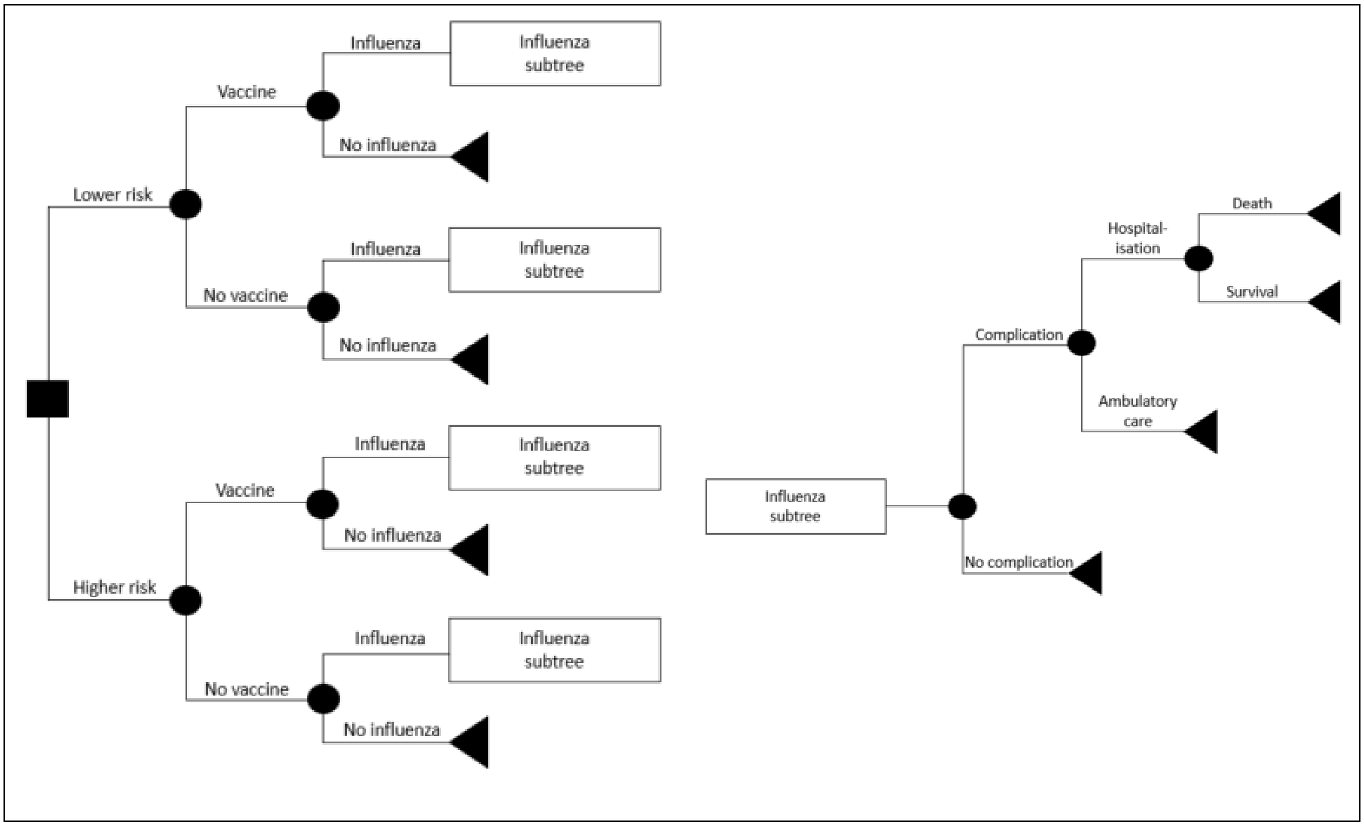

Fig S2. Cost-effectiveness plane of the probabilistic sensitivity analysis: aTIV vs TIV

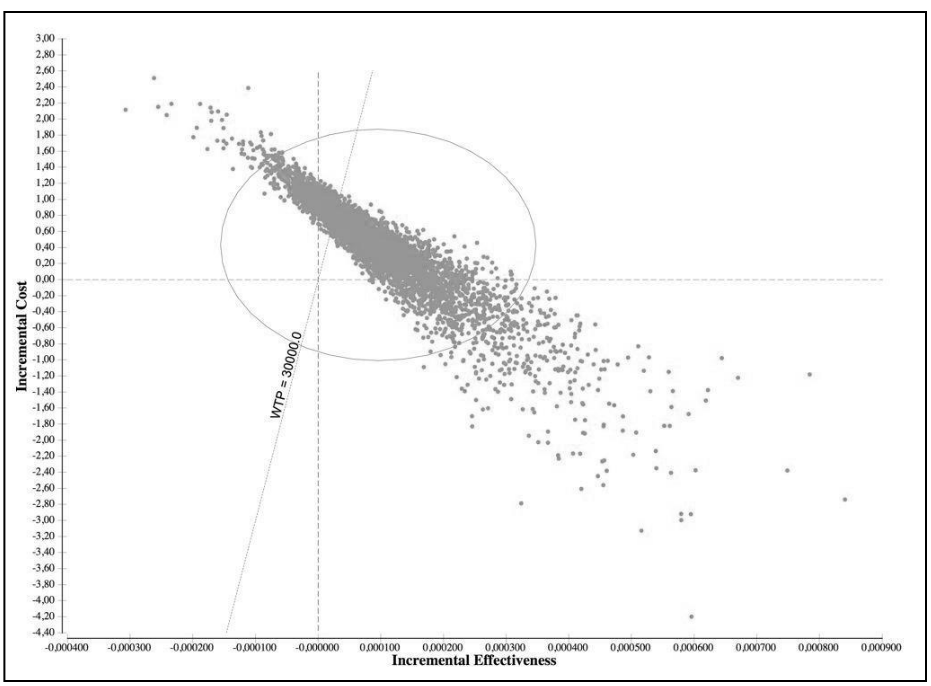

Table S1. Model input parameters

Parameter	Low risk		High risk		Ref
	Base case	Range	Base case	Range	
Population, million	7.47	5.98-8.97	5.90	4.72-7.07	1, 4
Influenza-related parameters, probability					
LCI	.0540	.0210-.1060	.0540	.0210-.1060	31, 32[a]
GP visit|LCI	.3860	.2900-.4100	.3860	.2900-.4100	33[b]
Bronchitis|LCI	.0269	.0238-.0302	.0346	.0305-.0390	3
Pneumonia|LCI	.0104	.0086-.0126	.0131	.0106-.0160	3
URTI|LCI	.0450	.0411-.0493	.0467	.0420-.0518	3
CV complications|LCI	.0009	.0004-.0017	.0080	.0061-.0103	3
CNS complications|LCI	.0021	.0013-.0032	.0031	.0020-.0047	3
Renal complications|LCI	.0005	.0002-0.011	.0016	.0008-.0028	3
Otitis media|LCI	.0021	.0013-.0032	.0015	.0007-.0027	3
GI bleeding|LCI	.0066	.0051-.0084	.0066	.0049-.0087	3
Hospitalisation|Complication	.2640	.2210-.3170	.3430	.2740-.4120	3, 34, 35[c]
Death|Hospitalisation	.0360	.1020-.1120	.0380	.0120-.1220	3, 36[d]
Vaccination-related parameters, probability					
Vaccination coverage	.551	.441-.661	.660	.528-.792	37, 38[e]
TIV VE	.58	.34-.73	.58	.34-.73	16
rVE QIV vs TIV	.07	0-.11	.07	0-.11	16, 17, 25, 26
rVE aTIV vs TIV	.25	.02-.43	.25	.02-.43	16, 23
Costs, €					
TIV ex-factory price	5.35	2.14-8.56	5.35	2.14-8.56	17
QIV ex-factory price	11.08	5.54-16.62	11.08	5.54-16.62	17
aTIV ex-factory price	6.99	4.89-9.09	6.99	4.89-9.09	17
Vaccine administration	6.16	4.31-8.00	6.16	4.31-8.00	28
GP visit	20.66	20.66-20.66	20.66	20.66-20.66	27
Outpatient treatment of complications (except for otitis media)	80.0	56.0-04.0	80.0	56.0-04.0	29
Outpatient treatment of otitis media	50.0	35.0-65.0	50.0	35.0-65.0	29
Inpatient treatment of bronchitis	1832.0	1282.4-2381.6	1832.0	1282.4-2381.6	17, 30
Inpatient treatment of pneumonia	2291.0	1603.7-2978.3	2291.0	1603.7-2978.3	17, 30
Inpatient treatment of URTI	4422.0	3095.4-5748.6	4422.0	3095.4-5748.6	17, 30
Inpatient treatment of CV complications	3544.0	2480.8-4607.2	3544.0	2480.8-4607.2	31
Inpatient treatment of renal complications	3734.0	2613.8-4854.2	3734.0	2613.8-4854.2	17, 30
Inpatient treatment of CNS complications	3507.0	3454.9-4559.1	3507.0	3454.9-4559.1	31
Inpatient treatment of otitis media	1247.0	899.9-1594.1	1247.0	899.9-1594.1	17, 30
Inpatient treatment of GI bleeding	2091.0	1463.7-2718.3	2091.0	1463.7-2718.3	17, 30
Disutilities, weight					
LCI episode	.00780	.00546-.10140	.00780	.00546-.10140	12, 13
Bronchitis	.00940	.00585-.01291	.00940	.00585-.01291	15
Pneumonia	.01041	.00674-.01487	.01041	.00674-.01487	15
URTI	.00904	.00585-.01291	.00904	.00585-.01291	15
Otitis media	.01382	.00894-.01974	.01382	.00894-.01974	15
CV complications	.10000	.06471-.14284	.10000	.06471-.14284	15
Outpatient treatment of CNS and renal complications	.03370	.02359-.04381	.03370	.02359-.04381	14
Inpatient treatment of CNS and renal complications	.03750	.02625-.04875	.03750	.02625-.04875	14

Notes:

aTIV, adjuvanted trivalent influenza vaccine; CNS, central nervous system; CV, cardiovascular; GI, gastrointestinal; GP, general practitioner; LCI, laboratory-confirmed influenza; QIV, quadrivalent influenza vaccine; rVE, relative vaccine effectiveness; TIV, trivalent influenza vaccine; URTI, unspecified respiratory tract infection; VE, vaccine effectiveness.
[a]Derived as a function of baseline influenza-like illness (ILI) attack rate and an average influenza virus detection rate among ILI patients. The baseline ILI attack rate among the Italian elderly was estimated in a meta-analysis[31] being .168 (95% CI: .066-.331). An average influenza virus detection rate among Italian ILI patients was .321.[32] [b]Average 3-season consultation rate for ILI. It was assumed that low- and high-risk elderly have the same LCI attack rate. [c]Analytically derived estimate. An average estimate (111.8 per 100.000) of hospitalizations due to LCI in the US elderly[34] was applied to the study population[1] and a total of 14,947 expected hospitalizations were calculated. This number was corrected for the sensitivity of polymerase chain reaction (PCR) test in the elderly (63.5% on average), by using the following formula *N*(hospitalizations corrected)=*N*(hospitalizations expected)×1/Sensitivity PCR.[35] This resulted in 23,539 hospitalizations. Considering the attack rate of 5.4% and a likelihood of developing any influenza related-complication of 10.9%[3] the probability of hospitalisation for the whole elderly population would be 29.9%. The elderly at high risk were assumed to have a 1.3-fold higher likelihood of being hospitalised;[3] to establish a risk-specific hospitalisation rate, the following formula was applied [*P*(low risk)×*h*) + [*P*(high risk)×1.3×*h*]=29.9%, where *h* is risk of hospitalisation among the low-risk elderly. [d]Analytically derived estimate. The probability of death in the high-risk elderly was derived from Arriola et al.[36] For the low-risk elderly, the parameter was deflated to 3.6%, by applying a correction factor derived from a ratio of the probability of death among low- and high-risk elderly reported by Meier et al.[3]
[e]Analytically derived estimate. An average 10-season vaccination coverage in the Italian elderly was 59.9%.[37] Given that it has been found[38] that the elderly at high risk have approximately 1.2-fold higher likelihood of being immunized, to establish a risk-specific coverage rate the following formula was applied [*P*(low risk)×VC) + [*P*(high risk)×1.2×VC]=59.9%, where VC is vaccination coverage among the low-risk elderly.

Table S2. Cost-effectiveness analysis of the influenza vaccines available to the Italian elderly: base-case results

Strategy	Total costs, €	Δ Total costs, €	Effectiveness, QALY	Δ Effectiveness, QALY×10^4	ICER, €/QALY
TIV	10.92	4.69	8.960839	–	–
aTIV	11.35	0.43	8.960935	0.96	4,527
QIV	14.21	2.86	8.960864	Negative	Dominated

Notes:

aTIV, adjuvanted trivalent influenza vaccine; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine

Table S3. Comparison of the current and alternative scenarios in terms of influenza-related events and costs

Parameter	Current scenario	Alternative scenario	Δ
LCI cases, N	482,545	472,846	-9,699
Complicated LCI cases, N	49,767	48,752	-1,014
Hospitalisations, N	14,970	14,659	-311
Deaths	555	543	-12
Total vaccination program cost, €	83,571,644	83,039,048	-532,596
Total event costs, €	15,723,809	14,584,627	-139,182
Total costs, €	99,295,453	97,623,675	-1,671,778

Notes:

LCI, laboratory-confirmed influenza