Adjuvanted influenza vaccine for the Italian elderly in the 2018/19 season: an updated health technology assessment

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Background: The elderly, defined here as subjects aged $\geq$ 65 years, are among at-risk subjects for whom annual influenza vaccination is recommended. For the 2018/19 season, three vaccine types are available for the elderly in Italy: trivalent inactivated vaccine (TIV), adjuvanted TIV (aTIV) and quadrivalent inactivated vaccines (QIV). No health technology assessment (HTA) of seasonal influenza vaccination in the elderly has previously been conducted in Italy. **Methods:** An HTA was conducted in 2017 to analyze the burden of influenza illness, the characteristics, efficacy, safety and cost-effectiveness of available vaccines and the related organizational and ethical implications. This was then contextualized to the 2018/19 influenza season. Comprehensive literature reviews/analyses were performed and a static mathematical model developed in order to address the above issues. **Results:** In Italy, influenza is usually less common in the elderly than in other age-classes, but the burden of disease is the highest; >10% of infected elderly subjects develop complications, and about 90% of all influenza-related deaths occur in this age-class. All available vaccines are effective, safe and acceptable from an ethical standpoint. However, aTIV has proved more immunogenic and effective in the elderly. Furthermore, from the third payer's perspective, aTIV is highly cost-effective and cost-saving in comparison with TIV and QIV, respectively. Nevertheless, vaccination coverage needs to be improved. **Conclusions:** According to this HTA, aTIV appeared the vaccine of choice in the elderly. HTA should be reapplied whenever new relevant data become available.

Introduction

Each winter, influenza affects 5–10% of the population, and is responsible for considerable excess mortality. Since the virus was isolated, prevention made great progress and several types of vaccines were developed.[1]

Each year, the Italian Ministry of Health (MoH) issues recommendations[2] for seasonal influenza vaccination, identifying target groups and vaccination coverage (VC) goals. In the 2018/19 season,[2] three types of influenza vaccines are available in Italy: trivalent inactivated vaccines (TIVs), adjuvanted TIV (aTIV) and quadrivalent inactivated vaccines (QIVs). When compared with TIVs and aTIV, which contain A(H1N1), A(H3N2) and a B strain (belonging to Victoria or Yamagata lineage), QIVs may provide broader protection by including B strains of both lineages. In contrast, aTIV may provide better protection than unadjuvanted vaccines, since it contains an adjuvant that significantly enhances the immune response.[2]

In Italy, a health technology assessment (HTA)[3] including a cost-effectiveness analysis (CEA)[4] of the use of aTIV in the elderly was first conducted in 2016–17 by adopting a multidisciplinary policy-oriented approach to evaluating the clinical, economic, organizational and ethical implications of this health technology. Since then, major regulatory changes occurred, with the intradermal TIV being permanently withdrawn. Moreover, the latest MoH recommendations[2] for the first time advocated a preferential use of aTIV in the elderly aged $\geq$75

years and QIV in younger age-classes. Nevertheless, in the context of Italian fiscal federalism, the procurement of single vaccine types is inhomogeneous among Italian Regions.

In the original HTA report, we showed that aTIV could be considered the best choice for the elderly. However, given the above-mentioned regulatory and policy changes, and the fact that we advocate continuous HTA, this article reports an update of our previous findings.

Methods

The original HTA on the use of aTIV in the Italian elderly[3] was inspired by the EUnetHTA core model.[5] It addressed several domains: the health problem (epidemiology and burden of disease); characteristics, immunogenicity/effectiveness and safety of available vaccines; economic evaluation of available alternatives; and organizational and ethical implications of influenza vaccination. The study population was that of the elderly, defined as subjects aged $\geq$65 years, who are among the targets of annual influenza immunization.[2] The full methodology and results of the first HTA report are reported elsewhere.[3] Here, we present an update of the original evaluation.

The health problem domain was addressed by implementing different approaches. Specifically, all available national surveillance systems were identified through the national influenza network InfluNet[6] and comprehensively assessed. The epidemiology of influenza in Italy was characterized by analyzing Influenza-Like

Illness (ILI) attack rates and data on virological surveillance. Whenever possible, elderly specific data were extracted; the atypical pandemic period (2009/10) was excluded from the analysis.

An analysis of the disease burden in terms of complications, hospitalizations and mortality was then performed. First, routinely collected administrative and surveillance data[6,7] were retrieved and analyzed. Second, a scoping review was performed by using the following combination of MeSH and free-text terms in PubMed: 'influenza', 'elderly', 'older', 'senior', 'burden', 'complic*', 'hospital*', 'death*', 'Ital*'. The search was widened to European (first choice) and international evidence (by excluding the search term 'Ital*') in order to collect the data necessary to populate the CEA and budget impact analysis (BIA) model. The subsequent decision on which values to use was expert-driven.

As aTIV vaccination was the intervention of interest, a full systematic review of the immunogenicity, efficacy/effectiveness, safety and reactogenicity of this vaccine was carried out. Specifically, the following aspects were comprehensively assessed: absolute and relative immunogenicity, efficacy/effectiveness and safety. The full methodology is reported in Supplementary Material S1. We did not perform a full systematic review of the available comparators, as this was deemed unnecessary and resource-consuming; indeed, the first TIVs have been in use for several decades and an updated (last update 2018) systematic Cochrane review on the matter is already available.[8] We therefore constructed an overview of existing systematic reviews and meta-analyses dealing with the immunogenicity, efficacy, effectiveness and safety of TIVs and QIVs in the elderly by applying the following search strategy: (('influenza'[Title/Abstract] AND vaccine*[Title/Abstract] AND 'systematic review'[Title/Abstract])) AND ('elderly'[Title/Abstract] OR ('older'[Title/Abstract] AND adult*[Title/Abstract])). The search was performed in PubMed, Embase and Cochrane Library.

The CEA considered all the vaccine types available to the Italian elderly in the 2018/19 season, namely TIV, aTIV and QIV. The CEA was performed in accordance with the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement;[9] full methodology details can be found in Supplementary Material S2. Briefly, a static decisional-tree model was adopted for the whole cohort of Italian elderly. The study was conducted from the third payer's perspective within the time-frame of a single average influenza season. The BIA evaluated the sustainability of the preferential use of aTIV for all subjects aged ≥75 years (as per recent guidelines)[2] in comparison with the observed 2018/19 market shares of single vaccines.

Regarding organizational implications, an analysis of Italian vaccination recommendations, VC and procedures of vaccine distribution were analyzed. Concerning the strategies implemented in order to pursue VC targets, we examined the latest update (2018) of the Cochrane review[10] on interventions to increase influenza vaccination rates among the community-dwelling elderly and performed a rapid literature overview on PubMed by using the following search terms: 'vaccin*', 'influenza', 'recommend*', 'distribut*', 'organ*', 'strateg*', 'procedur*'.

Ethical analysis was performed by means of the so-called 'triangular model', a well-recognized regulatory approach.[11] This model places the human being at the centre of the ethical reflection and of the judgement of lawfulness/unlawfulness. The analytical scheme is divided into three phases: (i) collection and analysis of data on the technology (cognitive phase); (ii) evaluation of how the technology relates to the person's integral good (evaluation phase) in terms of risk/benefit ratio; quality of life; respect for patients' autonomy; obtainment of informed consent; and possibility of ensuring equal access; (iii) elaboration of the final ethical opinion, with identification of any ethical problem that decision-makers should take into account (prescriptive phase).

Results

Health problem

In Italy, ILI epidemics occur annually, their incidence and duration varying widely in terms of both seasons and age-classes

(Supplementary Material S3). ILI epidemics generally start 1–3 weeks later in the elderly than in the general population. The average 18-season (from 1999/00 to 2017/18) ILI peak incidence was about half as high in the elderly as in the general population (4.6 vs. 9.6‰). Over this 18-season period, the average detection rate of type A viruses in the general population was markedly higher than that of type B (76 vs. 24%), with influenza type B predominating over type A in only four (22%) of the 18 seasons. Most type A detections belonged to the H3N2 subtype (Supplementary Material S4). It also emerged that, unfortunately, the national surveillance network does not routinely report the (sub)type distribution by age-class. To address this issue, we recently conducted a systematic review[12] of the comparative distribution of A and B viruses in the elderly, but were able to identify only one study from Italy.[13] In that study,[13] most virus B detections (94.8%) were concentrated in the <65-year age-group, while only 5.2% of detections involved subjects aged ≥65 years.

The literature on the burden of influenza in Italy is rather limited; some relevant data, such as the probability of developing complications and being hospitalized, are missing. Sessa et al.[14] described 6057 patients who were followed up by their general practitioners (GPs) for ILI in the 1998/99 season, 35.1% of whom (and 57.8% of the 709 patients aged ≥65 years) developed ≥1 complication, particularly upper respiratory tract infections (42.0%) and bronchitis (42.0%). About 0.4% (1.2% of patients with complications) were hospitalized. However, the results of this Italian study differ substantially from what has been reported in the international literature and supported by national experts. For instance, in a widely cited large-scale (n = 141 293 ILI patients) six-season UK study,[15] the probability of developing ≥1 complication was about three times lower (10.9%), with high-risk elderly subjects displaying greater probability than their low-risk counterparts (12.6 vs. 9.7%). This difference between the two studies was probably due to the single-season time-frame and relatively small sample size of the Italian study.

Regarding data on influenza-attributed hospitalization, no elderly-specific Italian data were found. According to experts' opinion, one of the most comprehensive sources of such data is the US inFLUenza hospitalization SURVeillance NETwork.[16] The cumulative hospitalization rate in the elderly varied from a minimum of 30.2 per 100 000 in 2011/12 to a maximum of 438.1 in 2017/18. However, these figures may be underestimated by about five times, owing to under-detection due to underutilization of influenza testing and its sensitivity pattern in the elderly.[17]

According to death certificates, on average about 90% of influenza deaths in Italy occur in the elderly,[7] and there is a positive relationship between the age of elderly sub-cohorts and mortality (figure 1). However, death certificates underestimate the real number of deaths for several reasons, mainly because they do not consider deaths due to influenza complications (e.g. pneumonia or worsening heart failure, which are often reported as the initial cause of death). Rizzo et al.[18] overcame this problem by estimating excess deaths due to pneumonia and influenza [14.1 (range 0–38) per 100 000] and all causes [98.9 (range 0–107) per 100 000] in Italy across 32 influenza seasons.

Influenza vaccines available in the 2018/19 season

Table 1 reports the main characteristics of influenza vaccines available in the 2018/19 season.

Previously published systematic reviews and meta-analyses[8,19–23] generally highlighted suboptimal immunogenicity, efficacy and effectiveness of TIVs in the elderly. In particular, a large meta-analysis by Goodwin et al.[19] revealed that the elderly had significantly lower odds of being seroconverted against all (sub)types than young adults. In the Cochrane review[8] the absolute efficacy of TIVs against laboratory-confirmed influenza (LCI) was 58% (95% CI: 34–73%), while re-assessment[21] of these findings provided an
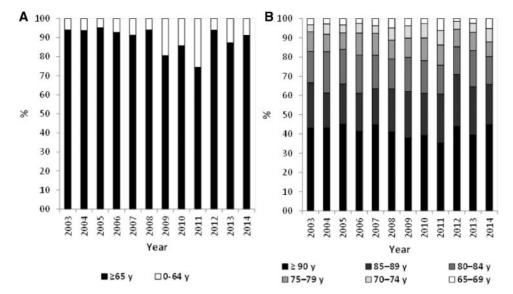
Figure 1 Influenza-attributable deaths (death certificates) in the elderly (≥65 years) and non-elderly (<65 years) Italian population (A) and within the elderly population (B)

Table 1 Influenza vaccines available in Italy in 2018/19 season[2]

Characteristics		TIV	QIV	aTIV
Component	A(H1N1)pdm09	+	+	+
	A(H3N2)	+	+	+
	B(Yam)	−	+	−
	B(Vic)	+	+	+
	Adjuvant	−	−	MF59®
Age indication		≥6 months	≥6 months	≥65 years
Notes		In children (0.5–9 years) and adolescents (10–17 years) use of QIV should be preferred, given the high impact of influenza B and potential lineage mismatch. If QIV is not available, TIV must be used. In at-risk adults (18–64 years) and healthcare workers, QIV should also be preferred. Pregnant women, who are at higher risk from influenza A(H1N1)pdm09, could receive either TIV or QIV		TIV, aTIV and QIV are recommended for people aged ≥65 years. However, given the high impact of influenza A(H3N2) in subjects aged ≥75 years and evidence of the greater effectiveness of aTIV in this population, aTIV should provide higher protection than either TIV or QIV

estimate of 49% (95% CI: 33–62%). Regarding the ability of TIVs to protect against hospitalization- and mortality-related proxy outcomes, estimates are inconsistent.[8]

For what concerns QIV, an immunogenicity meta-analysis by Moa et al.[24] showed that QIV was non-inferior to TIV with regard to shared strains, but superior for the fourth B strain, which was not included in TIV. However, a recent meta-regression by Beyer et al.[20] underlined that pre-seasonal immunity is the main driver of the impact of B-lineage mismatch on TIV vaccine effectiveness (VE); thus, QIV would have a significant advantage over TIV in younger age-classes, while in the elderly the benefit would be rather limited.[20] No absolute efficacy/effectiveness data on QIV could be established.

Table 2 reports the main characteristics of aTIV; the full results of the systematic review are presented in Supplementary Material S1. Briefly, in the elderly, aTIV was found to be more immunogenic than TIV versus both homologous and drifted strains and generally more effective than both TIV and QIV, its absolute VE being relatively high regardless of the influenza-related outcome.

From the safety standpoint, all available vaccines may be deemed acceptable. When compared with unadjuvanted vaccines, aTIV may cause more solicited adverse events (especially local); these, however, were judged acceptable from the risk-benefit viewpoint (table 3; Supplementary Material S1).

Economic evaluation of aTIV

Head-to-head comparison of TIV and aTIV showed that the latter was highly cost-effective. In contrast, QIV was dominated by aTIV (table 3). Probabilistic sensitivity analysis showed that, compared with TIV, aTIV was cost-saving/-effective (ICER < €30 000/QALY) in 76.4% of simulations.

In comparison with the observed (2018/19 season) market situation, a strategy in which aTIV is preferentially given to all ≥75-years old would be associated with 9699, 1 014, 311 and 12 influenza episodes, complications, hospitalizations and deaths less, respectively. This alternative strategy would also save about €0.53 million in vaccination campaigns, resulting in total budget savings of over €1.67 million (table 3).

The complete results of the CEA and BIA are shown in Supplementary Material S2.

Organizational and ethical implications of the use of aTIV

In Italy, annual influenza vaccination is available free-of-charge to the elderly and to subjects at risk or of particular social value; the main organizational challenge is achieving VC goals. Despite the Italian MoH recommendations (minimum and optimal VC of 75 and 95%, respectively),[2] VC in the elderly population remains rather

Table 2 The main characteristics, immunogenicity, effectiveness and safety of the adjuvanted trivalent influenza vaccine[a]

Characteristics	Description
General	Influenza vaccine, surface antigen, inactivated, adjuvanted with MF59C.1® (aTIV) is indicated for active immunization against influenza in the elderly (≥65 years), especially for those with an increased risk of associated complications. One 0.5 ml dose of the vaccine is composed of: • influenza virus surface antigens (haemagglutinin and neuraminidase) of strains belonging to A(H1N1), A(H3N2) and B (15mcg of haemagglutinin of each strain) recommended by the World Health Organization; • MF59C.1® adjuvant is composed of: 9.75 mg squalene, 1.175 mg polysorbate 80, 1.175 mg sorbitan trioleate, 0.66 mg sodium citrate, 0.04 mg citric acid, water for injections; • It may contain traces of eggs, such as ovalbumin or chicken proteins, kanamycin and neomycin sulphate, formaldehyde, cetyltrimethylammonium bromide and barium sulphate, which are used during the manufacturing process.
Immunogenicity	When compared with non-vaccination, aTIV is highly immunogenic against A(H1N1), A(H3N2) and B vaccine-like strains, regardless the serological outcome (e.g. geometric mean titre and geometric mean ratio, seroconversion and seroprotection rates). Analogously, the absolute immunogenicity against drifted/heterologous strains is generally high, especially against those belonging to A(H3N2). Compared with unadjuvanted TIVs (relative immunogenicity) aTIV has generally been found more immunogenic against vaccine-like A(H1N1), A(H3N2) and B strains. Indeed, several meta-analyses have shown a statistical superiority of aTIV, independently from the (sub)type considered. aTIV has also proved clearly superior to TIV against drifted A(H3N2) strains in both haemagglutinin inhibition and microneutralization tests.
Effectiveness	The absolute effectiveness of aTIV has proved relatively high, with some variability of estimates, depending on influenza-related outcome, being 58% (95% CI 5–82%) against LCI [72% (95 CI 2–93%) when considering only community-dwelling elderly], 87% (95% CI 35–97%) against hospitalizations for acute coronary syndrome and 93% (95% CI 52–99%) against hospitalizations for cerebrovascular events. Regarding hospitalizations for pneumonia/influenza, the absolute effectiveness of aTIV was 48% (95% CI 20–66%), 69% (95% CI 29–66%) and 49% (95% CI 30–60%) in influenza seasons 2002/03, 2004/05 and 2011/12, respectively. Moreover, it was as high as 94% (95% CI 47–100%) against ILI among the institutionalized elderly. When compared with unadjuvanted TIVs (relative effectiveness), aTIV was found to be 63% (95% CI 4–86%), 25% (95% CI 2–43%) and 34% (95% CI 18–47%) more effective against LCI, hospitalizations for pneumonia/influenza and influenza-like illness, respectively. aTIV was recently shown to be 3.3% ($P < 0.05$) more effective than QIV in preventing influenza hospital encounters in US Medicare beneficiaries (≥65 years, $n > 13$ million) in the 2017/18 season.
Safety	According to the summary of product characteristics, very common (≥1/10) undesirable effects include tenderness, injection site pain, fatigue, myalgia, headache; common (≥1/100–<1/10) effects are redness, swelling, ecchymosis, induration, nausea, diarrhoea, vomiting, sweating, arthralgia, fever, malaise and shivering. Most of these are mild or moderate and resolve spontaneously within 1–2 days. In randomized clinical trials (solicited adverse events) aTIV was generally found more reactogenic than unadjuvanted TIVs, especially for what concerns local events. In contrast, in an integrated analysis of 64 clinical trials, unsolicited adverse events were less common with aTIV than with TIVs.
Co-administration with other vaccines	aTIV can be safely co-administered with both 23-valent pneumococcal polysaccharide and 13-valent pneumococcal conjugate vaccines, without significant immunologic inference.

a: The full set of references is available in Supplementary Material S1.

Table 3 Base-case results of the cost-effectiveness and budget impact analyses of the influenza vaccines available to the Italian elderly in the 2018/19 season

CEA

Strategy	Total costs, €	Δ Total costs, €	Effectiveness, QALY	Δ Effectiveness, QALY×10⁴	ICER, €/QALY
TIV	10.92	–	8.960839	–	–
aTIV	11.35	0.43	8.960935	0.96	4527
QIV	14.21	2.86	8.960864	Negative	Dominated

BIA

Scenario	Vaccination costs, €	Δ Vaccination costs, €	Event costs, €	Δ Event costs, €	Total costs, €	Δ Total costs, €
Current[a]	83 571 644	−532 596	15 723 809	−1 139 182	99 295 453	−1 671 778
Alternative[b]	83 039 048		14 584 627		97 623 675	

a: Elderly specific market shares, as per Regional allotments for 2018/19 influenza season.
b: A scenario in which all subjects aged ≥75 years receive aTIV, while those aged 65–74 years receive QIV, as per Ministerial Circular[2].

low (about 53%), with huge interregional differences.[25] Furthermore, procedures of vaccine distribution and administration vary among Regions.[2]

In order to achieve the recommended VC, new strategic and organizational measures are needed. These must involve the whole health-planning chain, from decision-makers to GPs, who play a key role in linking patients' health needs with adequate public health surveillance and protection.

Effective strategies, already described in previous studies, could also be promoted in Italy. These include new approaches to vaccination campaigns, especially in target groups like the elderly,[2,26] the creation of regional lists of elderly patients based on disease codes of

exemption from payment, in order to identify high-risk subjects to be actively called,[2] and promoting vaccination in hospital.[27,28] The Cochrane review on interventions to increase influenza VC in the community-dwelling elderly[10] identified three main pillars that can be effective: increasing community demand (e.g. reminders, recalls, counselling), enhancing vaccination access (e.g. alternative places of vaccination) and provider/system-based interventions (e.g. GPs' gratification). Similar interventions have been judged to be transferable to the Italian setting.

With regard to ethical issues, the data reveal that the risk/benefit ratio of influenza vaccination in the elderly is positive. Several studies have shown that aTIV has a higher level of immunogenicity

and effectiveness in the elderly and a safety profile similar to that of unadjuvanted vaccines. The reduction of morbidity and the possible preservation of self-sufficiency could have considerable impact on the subject's quality of life. Respect for the patient's autonomy requires that informed consent be obtained. For this reason, it is important to organize personalized consultations before vaccine administration and to evaluate the patient's ability to understand the information provided and to express his/her consent. Finally, in the interests of the common good, access to vaccination should be ensured for the entire target population. Decision-makers must bear in mind all of the above-mentioned aspects and also organize adequate pharmacovigilance.

Discussion

This HTA update highlighted some important aspects for the decision-making process regarding influenza vaccination in the elderly. We underlined that influenza is highly age-dependent; while its incidence is higher among younger age-classes, influenza-related hospitalizations and deaths mostly involve the elderly. Available vaccines are effective, safe and ethically acceptable. In the elderly, aTIV seems to be the most effective vaccine and appeared to be the best choice. This is in line with the recent statement by the Public Health England and Joint Committee on Vaccination and Immunization[29] on the preferential use of aTIV in ≥65-years olds. However, decision-makers should also consider how to implement preventive interventions effectively promoting activities aimed at reaching target populations and increasing VC.

With respect to resource allocation, economic evidence on influenza vaccination in the elderly is still insufficient. A 2017 systematic review[30] of economic evaluations of influenza vaccination in the elderly identified only eight items, most of which suggested the cost-effectiveness of vaccination vs. non-vaccination. Analogously, a systematic review of Italian HTA and economic studies[31] found that vaccinating the elderly against influenza yields a positive benefit/cost ratio in comparison with non-vaccination. The added value of our work is that it analyzed different vaccine types. A paper[32] specifically compared aTIV with TIV and QIV in the USA and concluded that using aTIV in the elderly could yield greater clinical and economic benefits. In contrast, previous Italian CEAs of aTIV[33,34] compared aTIV only with TIV and non-vaccination. In any case, for what concerns the comparison of aTIV vs. TIV, our results are comparable to previous Italian findings[33,34] in that aTIV proved cost-effective. On the other hand, in previous research, aTIV was also found dominant over TIV. This can probably be explained by the fact that previous research used ILI as an influenza-related proxy, while the present CEA used LCI, which is more conservative.

However, the limited comparative effectiveness data may be an issue in interpreting our results and some uncertainty persists, in particular with respect to the comparison between aTIV and QIV. In fact, our analysis was primarily based on the evidence[20] that QIV does not bring a significant advantage to the elderly. This seems to be confirmed by a recent multi-season analysis[35] showing a substantial cross-lineage protection of trivalent vaccines and by a US study[36] where the absolute VE of TIV and QIV were 38 and 18% in 2016/17 season. Considering that the price and relative VE are the main drivers of economic outcomes, a re-evaluation should be done once the price of either vaccine is dropped and/or new comparative effectiveness data are available.

According to MacKean et al.,[37] Health Technology Reassessment is 'a structured, evidence-based assessment of the clinical, social, ethical and economic effects of a technology currently used in the healthcare system, to inform optimal use of that technology in comparison to its alternatives'. This study fits this definition and is one of the first Italian attempts to meet the urgent need for continuity in the HTA process.

Two principal shortcomings could impact the overall interpretation of results. First, it was not deemed feasible to conduct systematic reviews in all the HTA domains. Alternative methods, including umbrella and scoping reviews and the appraisal of existing systematic reviews, were adopted in order to mitigate this shortcoming. Second, the pool of Italy and elderly specific original research on several influenza domains was very limited and, therefore, international findings were borrowed to feed the economic models.

Nevertheless, this update sheds lights on the appropriateness of the use of technologies as the only way to optimize and strengthen the value of public health interventions.[38] This research is fostering the development of recommendations on vaccination policies based on different inputs, with a view to improving the use of existing vaccines.[39]

In this regard, there is a need to enhance existing surveillance systems, to perform robust large-scale population-based studies to track the natural history of influenza among Italians and to further investigate social, cultural and economic factors playing a role in patients' attitudes and behaviours in order to deliver additional, up-to-date information to guide future choices concerning resources allocation.

Supplementary data

Supplementary data are available at *EURPUB* online.

Funding

Key points

- As health technology assessment (HTA) is a continuous process, seasonal influenza vaccines should be re-assessed each year as soon as new relevant data become available or regulatory or policy changes occur.
- Influenza vaccination is recommended in the elderly. Three different vaccine types are available in Italy for the 2018/19 season. However, fiscal federalism makes their use heterogeneous across the country and necessitates evidence of the appropriateness of their use.
- This HTA update revealed that the adjuvanted trivalent influenza vaccine could be adopted in the Italian elderly in preference to unadjuvanted trivalent and quadrivalent vaccines, and that adherence to the latest MoH recommendations on its use in all subjects aged ≥75 years could save money.

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