Infect Dis Ther (2015) 4:459–487
DOI 10.1007/s40121-015-0076-8

ORIGINAL RESEARCH

A Novel Dynamic Model for Health Economic Analysis of Influenza Vaccination in the Elderly

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Received: April 10, 2015 / Published online: September 9, 2015

ABSTRACT

Introduction: New vaccines are being developed to improve the efficacy of seasonal influenza immunization in elderly persons aged ≥65 years. These products require clinical and economic evaluation to aid policy decisions.

Methods: To address this need, a two-part model has been developed, which we have applied to examine the potential clinical and economic impact of vaccinating elderly persons with adjuvanted trivalent inactivated influenza vaccine (aTIV) relative to conventional trivalent (TIV) and quadrivalent (QIV) vaccines. We compared outcomes in the US population for (1) aTIV in persons aged ≥65 years and QIV in all other age cohorts; (2) QIV in all cohorts; (3) TIV in all cohorts. Low, average, and high intensity seasons with low, average, and high vaccine match scenarios were compared. Probabilistic sensitivity analysis was conducted within each discrete scenario to explore the impact of variation in model inputs on potential outcomes.

Results: Assuming current vaccination coverage rates in the US population with (a) 25% better efficacy of adjuvanted versus non-adjuvanted vaccine against any strain and (b) 35% better efficacy of non-adjuvanted vaccine against matched B versus mismatched B strains, use of aTIV in persons aged ≥65 years and QIV in persons <65 years could reduce influenza cases by 11,166–1,329,200, hospitalizations by 1365–43,674, and deaths by 421–11,320 versus use of QIV in all cohorts. These outcomes are reflected in a corresponding increase in quality-adjusted life-years (QALYs)

Electronic supplementary material The online version of this article (doi:10.1007/s40121-015-0076-8) contains supplementary material, which is available to authorized users.

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of 3003–94,084. If the prevalence of mismatched influenza B was >54.5% of all circulating strains, use of QIV in all cohorts would offset the clinical benefits of aTIV. Elderly aTIV or QIV vaccination was associated with improved outcomes over non-adjuvanted TIV in many of the scenarios, particularly in low match seasons of any intensity. Total cost savings (including direct and indirect healthcare costs plus productivity impacts) with aTIV in the elderly versus QIV in the whole population ranged from $27 million (low intensity, low match) to $934 million (high intensity, high match). Univariate sensitivity analysis of relative vaccine prices in the average intensity, average match scenario indicated that aTIV could be marginally cost saving relative to QIV at the currently published Medicare price for influenza vaccines offering enhanced efficacy in the elderly. Elderly vaccination with aTIV was associated with a higher overall cost compared with TIV in only two scenarios (low intensity with average or high match); the incremental cost/QALY relative to TIV was $9980 in the average match scenario and $28,800 in the high match scenario.

Conclusions: Vaccination of persons aged ≥65 years with aTIV has the potential to provide clinical and economic benefit relative to QIV and TIV. The new model allows the assessment of various alternative strategies for available influenza vaccines.

Funding: Novartis Vaccines.

Keywords: Influenza; Elderly; Vaccine; Trivalent; Quadrivalent; Adjuvant; Vaccination; Economic; Clinical; Outcome

INTRODUCTION

The clinical and economic burden of influenza is significant, particularly in vulnerable populations, such as children, persons with compromised immune function, and the elderly. Notably, the risk of influenza-related complications increases with age [1–3], influenza-associated hospitalizations are most common among elderly aged ≥65 years (especially in those with underlying medical conditions) [4–8], and up to 90% of influenza-attributable mortality is seen in this cohort [9–11].

Significant direct healthcare costs are linked to influenza in persons aged ≥65 years [6]. These costs are driven by substantial numbers of influenza-related hospitalizations, and are increasing as the overall population ages [9]. Moreover, influenza-related hospitalizations in the elderly are associated with significant disability and impairments in activities of daily living. These effects have societal implications as they can be long lasting, and catastrophic disability after influenza hospitalization is a significant problem in this age cohort [12, 13]. Influenza vaccination in the elderly provides substantial benefits [14], and past cost-benefit and cost-effectiveness studies from a number of countries have indicated that this intervention in this age cohort is always cost-effective and is frequently cost saving [15]. Influenza vaccination policy in most developed countries, therefore, targets people aged ≥65 years as part of the effort to reduce the mortality and disability burden in this population [16].

The efficacy of conventional inactivated influenza vaccine [trivalent (TIV) or quadrivalent (QIV)] decreases with advancing age because of reduced production of vaccine-specific antibodies [17]. Attempts to increase immunogenicity have been made with alternatives such as high-dose TIV (60 µg of hemagglutinin (HA)/strain) [18] and an intradermal vaccine [19]. Constant evolution of the influenza strains in circulation further challenges vaccine protection with approximately 35% reduction in efficacy against mismatched versus matched strains [20, 21]. As a result, QIV may offer benefit in seasons where the B lineage selected for TIVs does not match the dominant circulating strain [22]. Notably, however, TIV adjuvanted with the squalene-containing oil-in-water emulsion MF59 (aTIV) increases seroprotection [23, 24] and has been associated with a 25% reduction in risk of hospitalization for influenza or pneumonia versus TIV in the elderly population aged ≥65 years [25]. Moreover, in the elderly, aTIV has been reported to provide better cross-reactivity against mismatched strains than conventional vaccine [26].

As the economic burden of influenza is disproportionately concentrated in the elderly [27], improvements in vaccine immunogenicity and efficacy in this group have economic implications that warrant investigation. Economic modeling is an important and generally accepted method for estimating the economic effects of an intervention [28]. A two-part epidemiologic and economic model was, therefore, developed to assess the clinical and economic impact of vaccination with aTIV in persons aged ≥65 years and QIV in those aged <65 years versus QIV or TIV in all age cohorts.

METHODS

Scenarios of Interest

This analysis compared clinical and economic outcomes over a 1-year period in the United States (US) population for three vaccination strategies: (1) aTIV in those ≥65 years (elderly) and QIV in all other age cohorts; (2) QIV in all cohorts; (3) TIV in all cohorts. We compared outcomes in nine discrete scenarios for low, average, and high intensity (i.e., transmissibility) seasons, factoring in low, average, and high vaccine match against circulating seasonal strains, in a 3 × 3 matrix. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

The average match scenarios (based on the arithmetic means of strain circulation in the US from 1999–2000 through 2013–2014 [29–33]) were 48.3%, 30.4%, 11.0%, and 10.3% for A/H3N2, A/H1N1, B/Victoria, and B/Yamagata, respectively. The low and high match scenarios were based on the 2000/2001 season, during which there was a very high prevalence of influenza B/Yamagata (1.7%, 51.9%, 0%, and 46.4% for A/H3N2, A/H1N1, B/Victoria, and B/Yamagata, respectively).

The TIV and aTIV vaccines contain the dominant circulating B strain (B/Yamagata) in the high match scenarios, but not in the low match scenarios. We also investigated a breakeven scenario for vaccine match, modeled for a low intensity season in which the low attack rate minimizes the clinical impact of vaccine efficacy. We assumed (a) 25% better efficacy of adjuvanted versus non-adjuvanted vaccine against any strain and (b) 35% better efficacy of non-adjuvanted vaccine against matched B versus mismatched B strains.

The Two-Part Model

The model is programmed in Microsoft Excel, and consists of a compartmental, dynamic "epidemiologic module" to estimate the number of influenza cases and a tree-structured "outcomes module" to estimate complications, hospitalizations, deaths, life-years, quality-adjusted life-years (QALYs), and costs associated with influenza cases over a 1-year period (Fig. 1). The model assumes no adverse events of influenza vaccination or treatment, and mutual exclusivity of complications. It also does not consider the impact of strain mutation within a season, and recovered/protected patients remain immune for the duration of the simulation.

Epidemiologic Module

The "epidemiologic module" simulates the transmission of seasonal influenza with a susceptible-infectious-recovered/protected/removed (SIR) model consisting of 6 compartments (Fig. 2). It estimates the dynamic changes over one year with or without vaccination (three unique age-stratified strategies can be defined) in the uninfected, infected with influenza, and the recovered/protected/removed populations. The population size is constant and proportions in the different compartments (or health states) can vary by age cohort i (0–3 years, 4–6, 7–9, 10–19, 21–34, 35–49, 50–64, 65–69, 70+). No patients enter or leave the system over the modeled year, and proportions in each compartment sum to 1. Patients recovered/protected/removed from infection (including patients who die as a result of infection) are fully immune and, therefore, cannot be re-infected or infect others for the remainder of the simulation (effectively removed from the simulation).

As illustrated in Fig. 2, in the proportion of the population that will be vaccinated (Cv_i), some people who receive vaccination are susceptible (S_i) and some are already protected by previous vaccination or influenza exposure (R_i). Among those not yet protected (S_i), vaccination can be successful (the individual enters compartment VR_i) or unsuccessful (enters compartment VS_i). Vaccine efficacy $(1 - P_i)$ determines distributions over the VS_i and VR_i compartments. All persons already protected before vaccination (R_i) will move to compartment VR_i.

The rate at which individuals in age cohort i transition from susceptible S_i to infected/infectious I_i is the force of infection, λ_i. Patients who are not fully protected after

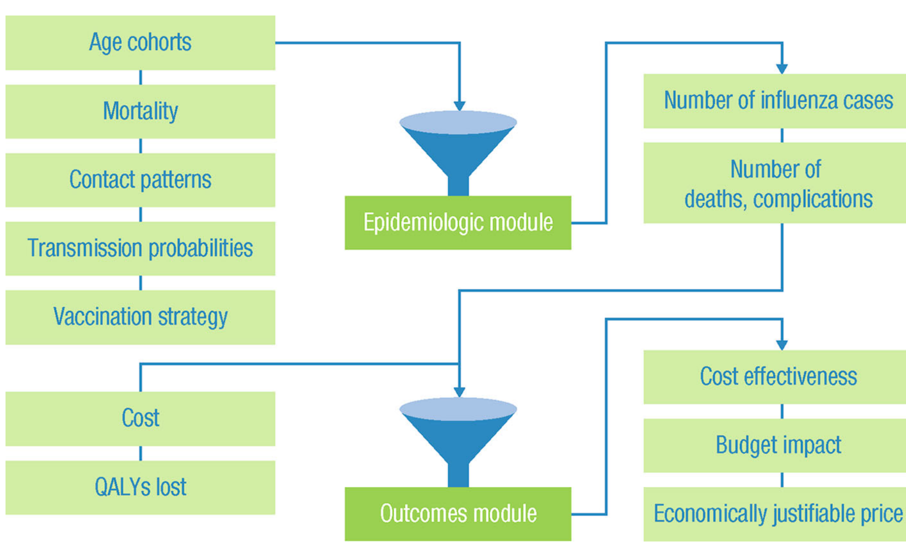

Fig. 1 The two-part epidemiologic and economic model. *QALY* quality-adjusted life-year

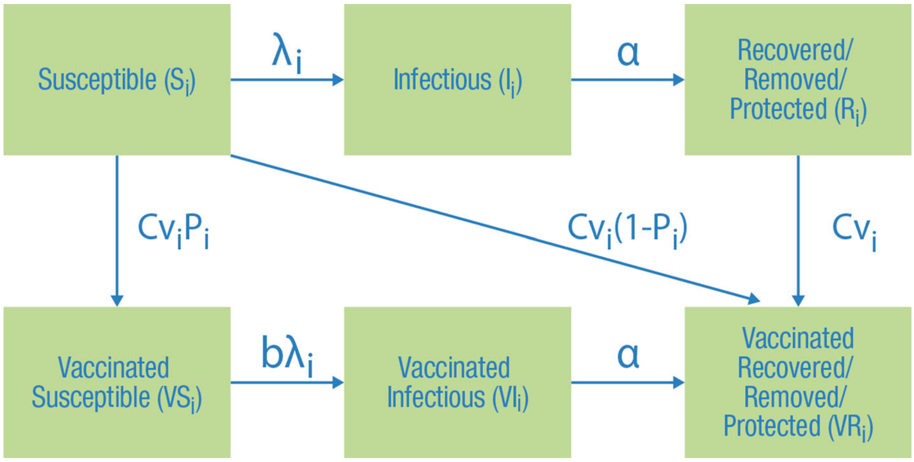

Fig. 2 The susceptible-infectious-recovered (SIR) compartment model for seasonal influenza. $S_i(t)$ = Fraction of susceptible individuals to influenza in age cohort i at time t. $I_i(t)$ = Fraction of infectious individuals in age cohort i at time t. $R_i(t)$ = Fraction of recovered/protected/removed from influenza in age cohort i at time t. $VS_i(t)$ = Fraction of vaccinated but still susceptible for influenza in age cohort i at time t. $VI_i(t)$ = Fraction of influenza cases despite being vaccinated in age cohort i at time t. $VR_i(t)$ = Fraction of vaccinated recovered/protected/removed in age cohort i at time t. Cv_i = Vaccine coverage in age cohort i. P_i = Probability of unsuccessful vaccination in age cohort i. $\lambda_i(t)$ = Force of infection in age cohort i at time t. $b\lambda_i(t)$ = Force of infection in vaccinated cohort in age cohort i at time t; α = Recovery rate

vaccination (VS_i) can be infected, but at a rate lower than or equal to unvaccinated individuals, represented by $b\lambda_i$, where $0 < b \leq 1$. Upon infection with influenza, individuals recover according to rate α and move to R_i (or VR_i); they are immune to further influenza infection for the remainder of the year and, therefore, cannot infect others (i.e., effectively removed from the simulation).

Changes in the proportion of patients over the compartments are defined by the differential equations:

$$\frac{dS_i(t)}{dt} = -S_i(t)\lambda_i(t) - S_i(t)Cv_iP_i - S_i(t)Cv_i(1 - P_i)$$

$$\frac{dVS_i(t)}{dt} = -VS_i(t)b\lambda_i(t) + S_i(t)Cv_iP_i$$

$$\frac{dI_i(t)}{dt} = S_i(t)\lambda_i(t) - I_i(t)\alpha$$

$$\frac{dVI_i(t)}{dt} = VS_i(t)b\lambda_i(t) - VI_i(t)\alpha$$

$$\frac{dR_i(t)}{dt} = I_i(t)\alpha - R_i(t)Cv_i$$

$$\frac{dVR_i(t)}{dt} = VI_i(t)\alpha + S_i(t)Cv_i(1 - P_i) + R_i(t)Cv_i$$

The force of infection $\lambda_i(t)$ is the rate at which susceptible individuals in age cohort i are infected at time t. It is the summation of the rates of infection at time t from all infected/infectious in age cohorts j:

$$\lambda_i(t) = \sum_j \lambda_{ij}(t)$$

where:

$$\lambda_{ij}(t) = \sigma \cdot \gamma_{ij} \cdot \varphi_i \cdot \xi_j \cdot I_j(t) = \beta_{ij} \cdot I_j(t)$$

where:

σ is the transmissibility parameter.

γ_{ij} is the average number of contacts per day between susceptible individuals in age cohort i with infectious individuals in age cohort j.

φ_i is the susceptibility of a susceptible individual in age cohort i.

ζ_j is the infectivity of an infective individual in age cohort j.

$I_j(t)$ is the fraction of infectious individuals in age cohort j at time t.

β_{ij} is the rate of infection of susceptible individuals in age cohort i by infectious individuals in cohort j (referred to as the WAIFW or Who Acquired Infection from Whom matrix; see Electronic Supplementary Material (ESM) for further discussion of derivation and implications for transmission dynamics).

Inputs of the model include age-stratified population [34], an age-stratified contact matrix (γ) representing interactions between individuals in the population leading to spread of the disease ([35], adapted to fit this model's age structure; Table S1), duration of infection ($1/\upsilon$) (assumed gamma distribution with mean of 4 days and standard deviation of 1 day [36–38], strain circulation [29–33], vaccine coverage by age [39], and vaccination efficacy by strategy by level of vaccine match to circulating strains by age [20, 21 25, 40]. The susceptibility φ_i, infectivity ζ_j, and transmission σ parameters are derived through a calibration process described below and in the ESM. Full details of these inputs are shown in Tables S1–S8.

Outcomes Module

The "outcomes module" calculates the outcomes associated with influenza according to a tree structure (Fig. 3; Tables 1, 2, 3 [27, 39, 41–48]). Upon infection with influenza, a person can experience symptoms (first chance node and corresponding split path). If symptoms are present, a patient might seek medical consultation (second chance node). Given medical consultation, antivirals and/or other drugs might be prescribed (third and fourth chance nodes). The conditional probabilities of influenza-related complications can be influenced by the prescription of antivirals and other drugs. We assumed the risk of complications to be the same with and without vaccination (i.e., the risk of complications is entirely dependent on whether an individual is infected with influenza). The probability of hospitalization or death in the presence of a complication is the result of the calibration process described below. The conditional probabilities with their sources are shown in Table S9.

Direct costs (US$) for medical care, including medical consultation, prescriptions for antivirals and other drugs [42], and costs of complications with and without hospitalization [42, 43, 49], were included (Table 1). Indirect costs covered productivity losses based on the severity of complications [27]. QALY reductions for the duration of symptoms of influenza and its complications (Table 2) and QALY losses due to life-years lost due to fatal complications were also included (Table 3). Life-years and QALYs lost were discounted at 3% per annum.

Expected outcomes and costs for each new influenza case were calculated by multiplying the probability of each event as reflected in the final branches of the tree with the corresponding outcomes and costs. In combination with the incidence of influenza over the course of a 1-year period as estimated with the "epidemiologic module", the expected outcomes associated with influenza over this period were obtained.

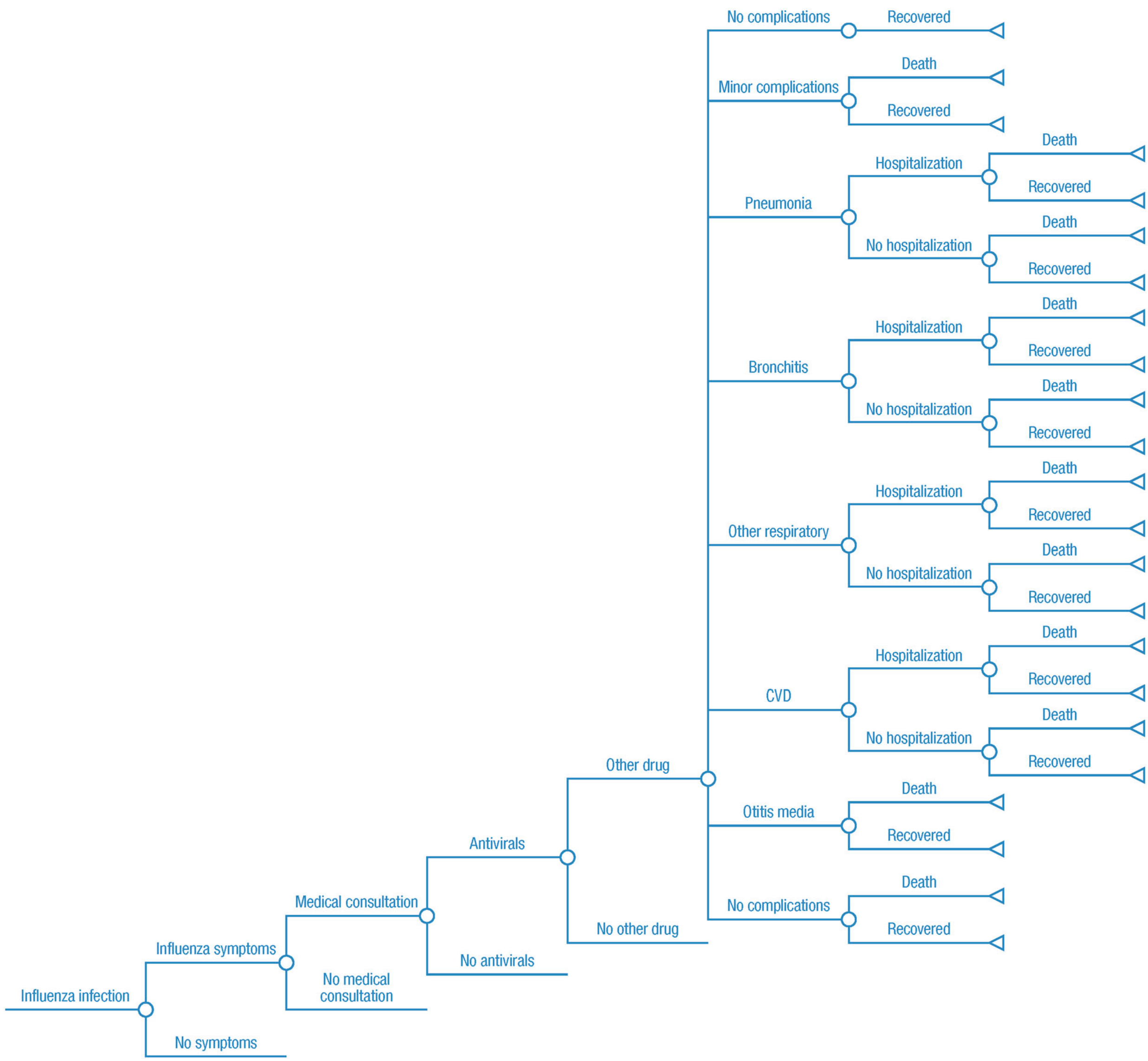

Fig. 3 Outcomes associated with influenza. *CVD* cardiovascular disease

Calibration of the Model

The model was calibrated to the age-stratified number of cases based on age-stratified estimated gross attack rates [27] and estimates of influenza incidence [27, 29, 50] by adjusting a factor for transmissibility (σ) and age-specific factors for susceptibility (φ_i). Conditional probabilities for hospitalization and death by complication according to age were then calibrated to literature-based estimates [27] (see the ESM for further detail).

Estimation of Model Outcomes

For each scenario and vaccination strategy of interest, we conducted a probabilistic analysis (second-order Monte Carlo simulation) by

Table 1 Input data: costs used in the model

Variable	Estimate ($US)	Source
Vaccine acquisition		
TIV	9.45	CDC [39]
aTIV	13.65	Assumption
QIV	13.65	Assumption
Vaccine administration		
All ages	21.00	Prosser [41]
Antiviral cost		
All ages	92.35	Talbird et al. [42]
Medical consultation		
All ages	98.79	Talbird et al. [42]
Complications		
Pneumonia without hospitalization		
All ages	206	Talbird et al. [42]
Pneumonia with hospitalization		
0–19	5513	Talbird et al. [42]
20–64	14,828	
≥65	14,137	
Bronchitis without hospitalization		
All ages	221	Talbird et al. [42]
Bronchitis with hospitalization		
0–19	3906	Talbird et al. [42]
20–64	7449	
≥65	8834	
Other respiratory without hospitalization		
All ages	221	Talbird et al. [42]
Other respiratory with hospitalization		
0–19	3906	Talbird et al. [42]
20–64	7449	
≥65	8834	
CVD without hospitalization		
All ages	2711	American Heart Association [43]
CVD with hospitalization		
All ages	6017	American Heart Association [43]

Table 1 continued

Variable	Estimate ($US)	Source
Otitis media		
All ages	224	Talbird et al. [42]
Lost productivity costs		
Without complications		
0–3	145	Molinari et al. [27]; case not medically attended
4–6	97	
7–19	73	
20–64	68	
65+	145	
Extra loss due to minor complications		
0–3	183	Molinari et al. [27]; weighted average of non-high-risk and high-risk outpatient visit
4–6	209	
7–9	191	
10–19	186	
20–49	167	
50–64	386	
65+	832	
Extra loss due to serious complications (pneumonia, bronchitis, CVD)		
0–3	1333	Molinari et al. [27]; weighted average of non-high-risk and high-risk outpatient visit
4–6	1576	
7–9	1520	
10–19	1603	
20–49	1934	
50–64	2411	
65+	2256	
Otitis media		
All ages	0	Assumed no additional days lost

aTIV adjuvanted trivalent inactivated influenza vaccine, *CDC* Centers For Disease Control And Prevention, *CVD* cardiovascular disease, *QIV* Quadrivalent inactivated influenza vaccine, *TIV* trivalent inactivated influenza vaccine

which variation in the model input parameters (summarized with probability density functions) was propagated through the model to obtain distributions for the following outcomes of interest: number of influenza cases, complications, deaths, life-years lost,

Table 2 Input data: QALY loss with influenza and impact of events

Variable	Estimate	Low	High	Distribution	Source/comments
Minor complications	0.00000	0.00000	0.00000	Gamma	Assumption
Pneumonia	0.01041	0.00674	0.01487	Gamma	Lee et al. [44]
Bronchitis	0.00904	0.00585	0.01291	Gamma	Lee et al. [44]
Other respiratory	0.00904	0.00585	0.01291	Gamma	Lee et al. [44]
CVD	0.10000	0.06471	0.14284	Gamma	Dyer et al. [45]
Otitis media	0.01382	0.00894	0.01974	Gamma	Prosser et al. [46]

CVD cardiovascular disease, *QALY* quality-adjusted life-year

Table 3 Input data: life expectancy and QALY loss due to death

Age	Discounted life-years lost when dying	Discounted QALYs lost when dying				Source/comments
	Estimate	Estimate	Low	High	Distribution	
0–3	30.8	27.7	25.0	30.5	Normal	EQ-5D assumed 0.9 over rest of life
4–6	30.5	27.5	24.8	30.2	Normal	EQ-5D assumed 0.9 over rest of life
7–9	30.2	27.2	24.5	29.8	Normal	EQ-5D assumed 0.9 over rest of life
10–19	29.3	26.4	23.8	29.0	Normal	EQ-5D assumed 0.9 over rest of life
20–34	27.2	24.5	22.1	26.9	Normal	EQ-5D assumed 0.9 over rest of life
35–49	23.5	21.1	19.1	23.2	Normal	EQ-5D assumed 0.9 over rest of life
50–64	18.3	15.8	14.2	17.3	Normal	Fryback et al. [47] adjusted average for remaining life-years
65–69	14.2	12.0	10.9	13.2	Normal	Fryback et al. [47] adjusted average for remaining life-years
70+	7.1	5.9	5.4	6.5	Normal	Fryback et al. [47] adjusted average for remaining life-years

Source: life expectancy: [48]
CDC Centers for Disease Control and Prevention, *QALY* Quality-adjusted life-year

QALYs lost, and costs. The distributions for these outcomes were summarized with the mean ("probabilistic mean"), low (2.5th percentile), and high (97.5th percentile) estimates.

The model output was further used to estimate budget impacts and cost-effectiveness of the competing interventions.

RESULTS

The model outputs for the low, average, and high intensity modeled seasons with low, average, and high vaccine match are summarized in Tables 4, 5, 6 and Figs. 4 and 5. Assuming (a) 25% better efficacy of adjuvanted versus non-adjuvanted vaccine against any strain and (b) 35% better efficacy of non-adjuvanted vaccine against matched B versus mismatched B strains, clinical benefits of aTIV vaccination in the population ≥65 years and QIV in the population <65 years suggested by the model (versus vaccination of the whole population with QIV) included reductions in influenza cases of 11,166–1,329,200 (low estimate reflects probabilistic mean in low intensity, low match scenario; high estimate reflects probabilistic mean in high intensity, high match scenario), 1365–43,674 fewer hospitalizations, and 421–11,320 fewer deaths (Table 4). These clinical outcomes were reflected in gains of 3003–94,084 QALYs. As illustrated in Fig. 4, elderly vaccination with aTIV or QIV was associated with improved outcomes over non-adjuvanted TIV in many of the scenarios, particularly in low match seasons of any intensity. Moreover, in all scenarios, elderly vaccination with aTIV was shown by the model to be at least as effective as QIV in reducing cases and other clinical outcome rates (Fig. 4; Tables 4, 5). The number of influenza cases (95% Credible Interval [CrI]) when vaccinating all age cohorts with TIV ranged from 5.6 million (0.0–35.7) in the low intensity, high match scenario to 45.9 million (1.4–71.4) in the high intensity, low match scenario. Total costs (95% CrI) when vaccinating all age cohorts with TIV ranged from $6.2 billion (3.8–16.4) in the low intensity, high match scenario to $19.8 billion (4.9–29.4) in the high intensity, low match scenario.

The breakeven analysis, which modeled a low intensity season in which the difference between elderly aTIV and QIV in number of cases was as close to zero as possible, showed that the prevalence of circulating mismatched strains would have to exceed 54.5% for QIV to offset the benefits of aTIV.

The potential impact of aTIV versus QIV vaccination in the elderly on costs was split evenly between direct savings ranging from $15 million (low intensity, low match) to $475 million (high intensity, high match) and indirect savings from $12 million to $459 million (Fig. 5; Table 6). Elderly aTIV vaccination was associated with increased overall cost over TIV in only two scenarios (low intensity with average or high match) but still represented good value for money with an incremental cost/QALY relative to TIV of $9980 in the average match scenario and $28,800 in the high match scenario. In both these scenarios, however, elderly aTIV dominated QIV with lower cost (−$171,071; −$222,553) and higher QALYs (14,676; 17,136). Univariate sensitivity analysis of relative vaccine prices in the average intensity, average match scenario indicated that aTIV could be marginally cost saving relative to QIV at current Medicare prices for influenza vaccines (Fig. 6 [51–53]).

Inspection of variability of results across scenarios showed that the outputs were most sensitive to vaccine match, followed by season intensity. The probabilistic nature of the model was illustrated by the probabilistic mean, low, and high estimates for each outcome within each discrete scenario, reflecting variation of inputs in observational studies and surveillance data.

DISCUSSION

We demonstrate that vaccination of persons aged ≥65 years with aTIV has the potential to provide clinical and economic benefit relative to QIV and TIV. The dynamic model described herein can be used to inform policy decisions regarding seasonal influenza vaccination. Similar dynamic compartmental models have

Table 4 Probabilistic means of clinical model outputs for all scenarios, together with absolute and percentage differences between the aTIV ≥ 65 QIV < 65 and QIV groups

	Probabilistic means (95% CrI)				
	Low intensity			Average intensity	
	Low match	Average match	High match	Low match	Average match
No. of influenza cases					
aTIV ≥ 65 QIV < 65	6,027,660 (78,909; 36,311,558)	5,777,353 (75,423; 38,843,395)	5,261,063 (75,878; 33,685,356)	21,578,258 (123,112; 59,447,194)	19,316,966 (126,949; 55,496,404)
QIV	6,038,826 (78,925; 36,766,189)	6,157,580 (76,309; 39,373,704)	5,623,605 (76,992; 36,418,579)	21,741,326 (122,355; 58,978,203)	19,986,583 (127,646; 57,253,746)
TIV	9,223,607 (84,893; 45,308,781)	6,646,200 (76,373; 40,819,092)	5,567,761 (78,157; 35,703,665)	28,003,833 (147,513; 65,918,137)	21,369,092 (129,967; 58,358,976)
Difference[a]	−11,166 (−15; −454,631)	−380,227 (−886; −530,310)	−362,542 (−1114; −2,733,223)	−163,069 (757; 468,991)	−669,617 (−697; −1,757,342)
% difference	−0.2% (0%; −1.2%)	−6.2% (−1.2%; −1.3%)	−6.4% (−1.4%; −7.5%)	−0.8% (0.6%; 0.8%)	−3.4% (−0.5%; −3.1%)
No. of hospitalized cases					
aTIV ≥ 65 QIV < 65	74,540 (732; 478,659)	68,658 (731; 488,150)	61,649 (717; 422,060)	270,480 (1400; 887,920)	234,462 (1386; 783,668)
QIV	75,905 (737; 504,229)	76,027 (753; 529,411)	70,303 (729; 477,838)	275,925 (1417; 892,722)	254,636 (1456; 861,123)
TIV	119,250 (838; 638,887)	83,191 (761; 553,680)	69,182 (737; 474,702)	364,768 (1746; 1,065,454)	272,990 (1512; 870,456)
Difference[a]	−1365 (−5; −25,570)	−7369 (−22; −41,261)	−8654 (−12; −55,778)	−5445 (−17; −4802)	−20,174 (−70; −77,455)
% difference	−1.8% (−0.6%; −5.1%)	−9.7% (−2.9%; −7.8%)	−12.3% (−1.7%; −11.7%)	−2.0% (−1.2%; −0.5%)	−7.9% (−4.8%; 9.0%)
No. of deaths					
aTIV ≥ 65 QIV < 65	11,111 (128; 69,130)	9972 (123; 68,219)	8612 (117; 58,637)	41,558 (207; 125,706)	34,556 (218; 108,141
QIV	11,532 (134; 70,644)	11,661 (129; 79,266)	10,638 (123; 70,694)	43,098 (210; 127,822)	39,650 (232; 125,079)
TIV	18,554 (145; 93,987)	12,898 (129; 81,952)	10,403 (122; 71,827)	58,292 (258; 153,658)	42,631 (238; 125,801)
Difference[a]	−421 (−5; −1515)	−1689 (−6; −11,047)	−2026 (−5; −12,057)	−1540 (−3; −2116)	−5094 (−14; −16,939)
% difference	−3.7% (−4.0%; −2.1%)	−14.5% (−4.7%; −13.9%)	−19.0% (−4.3%; −17.1%)	−3.6% (−1.3%; −1.7%)	−12.8% (−6.1%; −13.5%)

	Probabilistic means (95% CrI)			
	Average intensity	High intensity		
	High match	Low match	Average match	High match
No. of influenza cases				
aTIV ≥ 65 QIV < 65	21,745,069 (135,227; 57,835,457)	38,432,664 (456,246; 64,711,422)	38,509,481 (342,987; 68,646,356)	37,884,145 (485,622; 66,618,131)
QIV	22,616,695 (136,917; 59,223,921)	38,792,998 (458,714; 65,017,135)	39,367,544 (329,147; 70,314,941)	39,213,345 (591,599; 68,087,578)
TIV	22,528,976 (137,585; 57,974,422)	45,945,792 (1,428,394; 71,443,604)	41,066,246 (397,398; 71,657,334)	39,161,286 (457,098; 67,290,103)
Difference[a]	−871,626 (−1,60; −1,388,463)	−360,335 (−2468; −305,713)	−858,063 (13,839; −1,668,585)	−1,329,200 (−105,978; −1,469,448)
% difference	−3.9% (−1.2%; −2.3%)	−0.9% (−0.5%; −0.5%)	−2.2% (4.2%; −2.4%)	−3.4% (−17.9%; −2.2%)

Table 4 continued

	Probabilistic means (95% CrI)			
	Average intensity	**High intensity**		
	High match	**Low match**	**Average match**	**High match**
No. of hospitalized cases				
aTIV ≥ 65 QIV < 65	265,663 (1394; 843,838)	484,446 (6399; 1,016,720)	467,724 (3770; 1,067,724)	457,235 (5820; 1,030,868)
QIV	291,576 (1496; 925,050)	496,117 (6064; 1,044,831)	500,958 (4026; 1,146,636)	500,909 (6419; 1,100,235)
TIV	290,282 (1467; 910,043)	601,994 (17,940; 1,177,357)	526,056 (4632; 1,197,190)	499,814 (5722; 1,122,835)
Difference[a]	−25,914 (−102; −81,212)	−11,671 (335; −28,111)	−33,234 (−256; −78,912)	−43,674 (−599; −69,367)
% difference	−8.9% (−6.8%; −8.8%)	−2.4% (5.5%; −2.7%)	−6.6% (−6.4%; −6.9%)	−8.7% (−9.3%; −6.3%)
No. of deaths				
aTIV ≥ 65 QIV < 65	39,103 (195; 118,692)	75,847 (834; 142,897)	70,199 (512; 144,230)	67,877 (821; 139,586)
QIV	45,781 (222; 136,438)	78,792 (854; 148,743)	79,315 (603; 157,884)	79,197 (949; 159,363)
TIV	45,515 (223; 134,019)	97,605 (2707; 172,222)	83,680 (641; 168,366)	78,954 (856; 161,318)
Difference[a]	−6678 (−27; −17,747)	−2945 (−19; −5847)	−9116 (−92; −13,654)	−11,320 (−128; −19,777)
% difference	−14.6% (−12.1%; −13.0%)	−3.7% (−2.3%; −3.9%)	−11.5% (−15.2%; −8.6%)	−14.3% (−13.5%; −12.4%)

aTIV adjuvanted TIV, *CrI* Credible interval, *QIV* quadrivalent inactivated seasonal influenza vaccine, *TIV* trivalent inactivated seasonal influenza vaccine

[a] aTIV ≥ 65 QIV < 65 vs. QIV

Table 5 Probabilistic means of life-year model outputs for all scenarios, together with absolute and percentage differences between the aTIV ≥ 65 QIV < 65 and QIV groups

	Probabilistic means (95% CrI)				
	Low intensity			Average intensity	
	Low match	Average match	High match	Low match	Average match
Life-years lost					
aTIV ≥ 65 QIV < 65	119,855 (1453; 754,342)	108,682 (1399; 736,809)	94,467 (1319; 657,418)	449,394 (2386; 1,340,734)	377,962 (2440; 1,148,208)
QIV	123,419 (1498; 763,164)	125,035 (1411; 852,997)	113,796 (1395; 776,478)	463,373 (2398; 1,383,146)	426,823 (2518; 1,309,509)
TIV	196,872 (1616; 1,004,312)	137,566 (1452; 909,825)	111,621 (1396; 771,007)	621,855 (2877; 1,630,082)	458,629 (2601; 1,342,590)
Difference[a]	−3564 (−45; −8822)	−16,354 (−11; −116,189)	−19,329 (−76; −119,060)	−13,979 (−13; −42,412)	−48,860 (−78; −161,301)
% difference	−2.9% (−3.0%; −1.2%)	−13.1% (−0.8%; −13.6%)	−17.0% (−5.4%; −15.3%)	−3.0% (−0.5%; −3.1%)	−11.45% (−3.1%; −12.3%)
QALYs lost					
aTIV ≥ 65 QIV < 65	117,725 (1468; 750,989)	107,623 (1373; 733,587)	94,487 (1322; 647,505)	438,909 (2388; 1,285,147)	372,051 (2412; 1,132,941)
QIV	120,729 (1485; 743,748)	122,300 (1436; 845,124)	111,623 (1385; 763,855)	450,997 (2369; 1,323,062)	414,739 (2498; 1,225,306)
TIV	191,326 (1594; 979,054)	134,239 (1420; 848,383)	109,669 (1391; 742,570)	601,487 (2832; 1,571,490)	445,309 (2621; 1,267,852)
Difference[a]	−3,003 (−17; 7241)	−14,676 (−63; −111,537)	−17,136 (−62; −116,350)	−12,088 (19; −37,916)	−42,688 (−86; −92,365)
% difference	−2.5% (−1.1%; 1.0%)	−12.0% (−4.4%; −13.2%)	−15.4% (−4.5%; −15.2%)	−2.7% (−0.8%; −2.9%)	−10.3% (−3.5%; −7.5%)

	Probabilistic means (95% CrI)			
	Average intensity	High intensity		
	High match	Low match	Average match	High match
Life-years lost				
aTIV ≥ 65 QIV < 65	430,921 (2180; 1,270,924)	820,806 (8712; 1,539,347)	769,512 (5592; 1,504,797)	746,076 (8396; 1,478,850)
QIV	494,200 (2303; 1,373,854)	849,283 (9001; 1,585,870)	855,562 (6176; 1,693,696)	854,594 (9581; 1,656,636)
TIV	491,324 (2400; 1,387,800)	1,044,395 (28,369; 1,807,352)	900,522 (6859; 1,731,406)	852,086 (8770; 1,674,012)

Table 5 continued

	Probabilistic means (95% CrI)			
	Average intensity	High intensity		
	High match	Low match	Average match	High match
Difference[a]	−63,279 (−123; −102,930)	−28,477 (−288; −46,523)	−86,050 (−583; −188,899)	−108,518 (−1185; −177,786)
% difference	−12.8% (−5.3%; −7.5%)	−3.4% (−3.2%; −2.9%)	−10.1% (−9.4%; −11.2%)	−12.7% (−12.4%; −10.7%)
QALYs lost				
aTIV ≥ 65 QIV < 65	425,351 (2139; 1,244,395)	799,416 (9050; 1,514,181)	756,731 (5738; 1,481,470)	735,083 (8837; 1,411,542)
QIV	480,757 (2305; 1,376,679)	824,106 (9078; 1,526,880)	830,698 (6341; 1,630,491)	829,167 (9502; 1,578,863)
TIV	478,110 (2371; 1,343,693)	1,008,153 (28,582; 1,729,806)	872,887 (7000; 1,661,897)	826,870 (8940; 1,572,709)
Difference[a]	−55,406 (−165; −132,284)	−24,690 (−28; −12,699)	−73,966 (−603; −149,021)	−94,084 (−665; −167,320)
% difference	−11.5% (−7.2%; −9.6%)	−3.0% (−0.3%; −0.8%)	−8.9% (−9.5%; −9.1%)	−11.3% (−7.0%; −10.6%)

aTIV adjuvanted TIV, *CrI* credible interval, *QALY* quality-adjusted life-year, *QIV* quadrivalent inactivated seasonal influenza vaccine, *TIV* trivalent inactivated seasonal influenza vaccine

[a] aTIV ≥ 65 QIV < 65 vs. QIV

Table 6 Probabilistic means of cost model outputs for all scenarios, together with absolute and percentage differences between the aTIV ≥ 65 QIV < 65 and QIV groups

	Probabilistic means (95% CrI)				
	Low intensity			Average intensity	
	Low match	Average match	High match	Low match	Average match
Total direct cost ($)					
aTIV ≥ 65 QIV < 65	5,862,744,268 (4,979,922,003; 10,166,329,974)	5,796,738,194 (4,994,456,377; 10,204,589,456)	5,698,162,740 (4,292,767,662; 9,643,329,431)	8,042,255,362 (5,017,513,611; 13,684,333,296)	7,637,145,164 (5,030,839,595; 12,801,170,782)
QIV	5,878,055,661 (4,982,789,561; 10,145,399,899)	5,878,094,283 (5,001,678,875; 10,603,198,208)	5,822,014,487 (4,294,639,371; 10,273,676,447)	8,101,747,787 (5,015,458,077; 13,751,296,307)	7,859,208,792 (5,025,722,591; 13,373,063,888)
TIV	5,739,239,448 (4,378,561,262; 10,856,173,435)	5,342,177,037 (4,391,573,217; 10,286,682,937)	5,175,843,264 (3,709,083,469; 9,818,803,927)	8,460,800,122 (4,421,920,239; 14,362,290,693)	7,448,134,136 (4,420,810,998; 12,886,597,651)
Difference[a]	−15,311,393 (−2,867,558; 20,930,076)	−81,356,090 (−7,222,498; −398,608,752)	−123,851,747 (−1,871,709; −630,347,016)	−59,492,425 (2,055,534; −66,963,011)	−222,063,629 (5,117,004; −571,893,106)
% difference	−0.3% (−0.1%; 0.2%)	−1.4% (−0.1%; −3.8%)	−2.1% (0%; −6.1%)	−0.7% (0%; −0.5%)	−2.8% (−0.5%; −3.1%)
Indirect cost ($)					
aTIV ≥ 65 QIV < 65	1,110,302,032 (13,854,187; 6,784,356,482)	1,032,491,013 (13,489,616; 6,797,683,492)	935,607,459 (13,392,215; 6,020,317,629)	3,970,902,930 (23,200,992; 11,022,832,351)	3,493,632,292 (21,642,149; 10,008,866,236)
QIV	1,121,879,432 (13,857,192; 6,894,131,583)	1,122,205,497 (13,412,778; 7,266,508,478)	1,034,308,658 (13,623,912; 6,824,717,033)	4,029,749,632 (23,517,142; 11,121,157,288)	3,710,329,636 (22,568,815; 10,539,753,244)
TIV	1,742,858,530 (14,947,014; 8,509,014,244)	1,221,436,489 (13,965,662; 7,659,444,819)	1,021,275,371 (13,674,913; 6,658,587,239)	5,264,980,704 (27,958,457; 12,760,578,793)	3,972,405,432 (22,813,591; 10,773,920,531)

Table 6 continued

	Probabilistic means (95% CrI)				
	Low intensity			Average intensity	
	Low match	Average match	High match	Low match	Average match
Difference[a]	−11,577,400 (−3005; −109,775,101)	−89,714,484 (76,838; −468,824,986	−98,701,199 (−231,697; −804,399,404)	−58,846,702 (−316,150; −98,324,937)	−216,697,344 (−926,666; −530,887,008)
% difference	−1.0% (0; −1.6%)	−8.0% (0.6%; −6.5%)	−9.5% (−1.7%; −11.8%)	−1.5% (−1.3%; −0.9%)	−5.8% (−4.1%; −5.0%)
Total direct + indirect cost ($)					
aTIV ≥ 65 QIV < 65	6,973,046,301 (5,003,286,410; 16,935,685,977)	6,829,229,207 (5,014,149,292; 17,041,186,131)	6,633,770,199 (4,335,127,694; 15,573,397,118)	12,013,158,292 (5,051,828,358; 24,754,660,792)	11,130,777,456 5,059,015,169; 22,495,970,672)
QIV	6,999,935,094 (5,012,016,015; 16,969,916,361)	7,000,299,780 (5,025,257,724; 17,873,288,303)	6,856,323,145 (4,335,505,451; 16,786,551,891)	12,131,497,418 (5,051,677,478; 24,808,699,146)	11,569,538,428 (5,059,573,085; 23,847,488,759)
TIV	7,482,097,978 (4,413,863,390; 19,288,387,147)	6,563,613,526 (4,415,528,049; 17,916,981,003)	6,197,118,635 (3,781,220,870; 16,424,107,679)	13,725,780,826 (4,457,920,325; 26,960,720,664)	11,420,539,567 (4,454,804,797; 23,556,900,364)
Difference[a]	−26,888,793 (−8,729,605; −34,230,384)	−171,070,573 (−11,108,432; −832,102,172)	−222,552,946 (−377,757; −1,213,154,773)	−118,339,127 (150,880; −54,038,354)	−438,760,972
% difference	−0.4% (−0.2%; −0.2%)	−2.4% (−0.2%; −4.7%)	−3.2% (0%; −7.2%)	−1.0% (0%; −0.2%)	−3.8% (0%; −5.7%)

	Probabilistic means (95% CrI)			
	Average intensity	High intensity		
	High match	Low match	Average match	High match
Total direct cost ($)				
aTIV ≥ 65 QIV < 65	7,986,717,334 (4,477,887,289; 13,311,825,736)	10,451,882,571 (5,131,545,727; 14,743,859,812)	10,280,324,161 (5,090,903,332; 15,151,961,976)	10,166,916,234 (5,094,458,505; 14,819,582,203)

Table 6 continued

	Probabilistic means (95% CrI)			
	Average intensity	High intensity		
	High match	Low match	Average match	High match
QIV	8,265,153,875 (4,568,855,041; 14,250,701,310)	10,577,579,955 (5,114,923,273; 14,940,387,210)	10,643,914,304 (5,087,375,982; 15,671,318,987)	10,642,258,998 (5,124,313,065; 15,497,524,847)
TIV	7,621,849,879 (3,829,515,363; 13,262,097,930)	11,129,946,026 (4,624,382,452; 15,498,063,020)	10,304,309,619, (4,490,331,834; 15,587,278,564)	10,018,298,331 (4,499,448,132; 14,906,251,468)
Difference[a]	−278,436,541 (−90,967,751; −938,875,574)	−125,697,384 (16,622,455; −196,527,398)	−363,590,142 (3,527,350; −519,357,010)	−475,342,764 (−29,854,560; −677,942,645)
% difference	−3.4% (−2.0%; −6.6%)	−1.2% (0.3%; −1.3%)	−3.4% (0.1%; −3.3%)	−4.5% (−0.6%; −4.4%)
Indirect cost ($)				
aTIV ≥ 65 QIV < 65	3,973,558,988 (22,931,245; 10,755,438,916)	7,084,181,963 (86,711,992; 12,413,064,115)	6,977,144,522 (64,687,791; 13,166,770,234)	6,847,245,982 (96,087,031; 12,647,790,170)
QIV	4,251,961,937 (23,716,365; 11,446,478,381)	7,206,819,673 (91,200,807; 12,682,056,752)	7,314,457,858 (56,299,005; 13,684,890,330)	7,306,436,705 (94,599,232; 13,393,293,148)
TIV	4,235,281,989 (23,738,955; 11,275,778,442)	8,652,279,149 (261,563,517; 13,974,858,650)	7,656,940,347 (71,689,988; 14,130,577,268)	7,290,869,681 (85,840,012; 13,337,119,616)
Difference[a]	−278,402,949 (−785,449; −691,039,465)	−122,637,710 (−4,488,815; −268,992,637)	−337,313,335 (8,388,786; −518,120,096)	−459,190,723 (1,487,799; −745,502,978)
% difference	−6.5% (−3.3%; −6.0%)	−1.7% (−4.9%; −2.1%)	−4.6% (14.9%; −3.8%)	−6.3% (1.6%; −5.6%)
Total direct + indirect cost ($)				
aTIV ≥ 65 QIV < 65	11,960,276,322 (4,576,925,878; 24,229,988,647)	17,536,064,533 (5,226,804,809; 27,034,351,861)	17,257,468,684 (5,156,471,377; 28,168,163,497)	17,014,162,216 (5,187,077,012; 27,323,581,109)
QIV	12,517,115,812 (4,670,390,664; 25,768,606,570)	17,784,399,628 (5,200,635,357; 27,440,685,930)	17,958,372,161 (5,138,305,995; 29,275,883,763)	17,948,695,702 (5,232,732,541; 28,800,572,607)
TIV	11,857,131,868 (3,928,358,136; 24,373,203,580)	19,782,225,175 (4,885,909,124; 29,392,587,997)	17,961,249,966 (4,545,947,757; 29,714,206,125)	17,309,168,012 (4,570,594,151; 28,079,994,755)

Table 6 continued

	Probabilistic means (95% CrI)			
	Average intensity	High intensity		
	High match	Low match	Average match	High match
Difference[a]	−556,839,490 (−93,464,786; −1,538,617,923)	−248,335,094 (26,169,452; −406,334,069)	−700,903,477 (18,165,382; −1,107,720,266)	−934,533,487 (−45,655,530; −1,476,991,498)
% difference	−4.4% (−2.0%; −6.0%)	−1.4% (0.5%; −1.5%)	−3.9% (0.4%; −3.8%)	−5.2% (−0.9%; −5.1%)

aTIV adjuvanted TIV, *CrI* credible interval, *QIV* quadrivalent inactivated seasonal influenza vaccine, *TIV* trivalent inactivated seasonal influenza vaccine

[a] aTIV ≥ 65 QIV < 65 vs. QIV

been described previously [54–57]. Importantly, they enable herd immunity benefits of vaccination, which are not adequately addressed by static models, to be captured. The use of dynamic models such as that described here to inform policy making in persons aged ≥65 years is particularly pertinent because significant healthcare costs are linked to influenza in this population [6]. Note that the present analysis was based on the results of previous studies and other information from the literature, and did not involve the collection of any new data from human or animal subjects.

In the US, a very broad routine annual vaccination recommendation is in place (all persons aged ≥6 months with no contraindications) [58]. Moreover, the US Centers for Disease Control and Prevention (CDC) does not currently recommend any one influenza vaccine product over another in the elderly (i.e., no preference is expressed at present for QIV, high-dose, or adjuvanted vaccine over conventional TIV) [58]. As a result of recent studies indicating increased vaccine effectiveness of high-dose influenza vaccine in the over-65 population [59, 60], there is sentiment towards using the high-dose vaccine in that population, despite the current lack of a preferential recommendation for its use. Additionally, as QIV supplies continue to increase within the US, there appears to be increasing support for its use in the general population, again despite the lack of a preferential recommendation for such use by the CDC. Both the QIV and high-dose TIV vaccines are covered by insurance in the US. Of note, the high-dose TIV is covered by the Medicare Part B program despite its higher cost; this is significant, as the majority of the over-65 population in the US is covered by this public payer [61].

The effectiveness of current vaccination recommendations in the elderly is under debate, as conventional vaccines are reported to provide suboptimal protection in this group [7]. High-dose TIV uptake in the elderly is expected to increase in the US and other countries in the near future, but there remains a need for additional vaccines offering enhanced immunogenicity in this population [62].

Adjuvantation of inactivated vaccines (e.g., with oil-in water adjuvants) has the potential to address unmet influenza vaccination needs in the elderly [16, 62], and has been reported to provide better cross-reactivity against mismatched strains than conventional vaccines in the elderly in several studies [26, 63–65]. The potential for improved outcomes with adjuvanted vaccine was apparent from the model, which showed probabilistic mean reductions in clinical outputs and overall costs relative to QIV even in modeled low match seasons. The breakeven analysis carried out after the main simulations suggested that QIV would only offer incremental benefit over aTIV in the elderly if the proportion of mismatched strains in circulation was as high as 54.5% or above, a level which has not been observed in the US over the last 15 years.

Of note, high-dose TIV has been associated with a 24.2% increase in efficacy against laboratory-confirmed influenza [59] and a 22% increase in effectiveness for preventing probable influenza infections and hospitalizations in persons aged ≥65 years [60]. This suggests that economic comparisons of high-dose TIV with other inactivated influenza vaccine options using the model would be of considerable interest and could be the subject of a future analysis. For now, and on the basis of the data and assumptions built into the present model and the above observations with high-dose

Fig. 4 Graphic summary of the main clinical and life-year ▶ outputs of the model. All values are probabilistic means (see Tables 4 and 5 for 95% credible intervals for probabilistically modeled values). *aTIV* adjuvanted TIV, *QALY* quality-adjusted life-year, *QIV* quadrivalent inactivated seasonal influenza vaccine, *TIV* trivalent inactivated seasonal influenza vaccine

vaccine, we would expect such an analysis to yield results comparable to those obtained here with aTIV in subjects aged ≥65 years. Such a hypothesis would require future confirmation, however.

As reported above, the potential impact of aTIV versus QIV on costs was split evenly between direct and indirect savings. Direct cost savings were derived from reduced hospitalizations among the elderly, who experience increased serious influenza complication rates over younger populations [27]. Indirect cost savings accrued mainly from the impact on younger working relatives/associates, who are likely to experience work interruptions due to the need for visitation and care giving, with accompanying losses of productivity [27]. Sensitivity analysis of vaccine prices in the average intensity, average match scenario indicated that aTIV could be marginally cost saving relative to QIV at current Medicare prices.

The importance of indirect protection of older persons through herd immunity effects is illustrated by experience of influenza outbreaks in residential institutions [5]. As mentioned earlier, the structure of the SIR model on which the analysis was based accounts for herd immunity effects, through which the elderly benefit from decreased transmission of influenza among the broader population as a result of vaccination [16].

The data used to populate the model were subject to a number of limitations. Mannino et al.'s study [25] demonstrating the 25%


(a) Cases
aTIV ≥65y; QIV <65y
QIV all
TIV all
High intensity, high match
High intensity, average match
High intensity, low match
Average intensity, high match
Average intensity, average match
Average intensity, low match
Low intensity, high match
Low intensity, average match
Low intensity, low match
37,884
39,213
39,161
38,509
39,368
41,066
38,433
38,793
45,946
21,745
22,617
22,529
19,317
19,987
21,369
21,578
21,741
28,004
5,261
5,624
5,568
5,777
6,158
6,646
6,028
6,039
9,224
0
10,000
20,000
30,000
40,000
50,000
No. of cases (thousands)
(b) Hospitalizations
aTIV ≥65y; QIV <65y
QIV all
TIV all
High intensity, high match
High intensity, average match
High intensity, low match
Average intensity, high match
Average intensity, average match
Average intensity, low match
Low intensity, high match
Low intensity, average match
Low intensity, low match
457,235
500,909
499,814
467,724
500,958
526,056
484,446
496,117
601,994
265,663
291,576
290,282
234,462
254,636
272,990
270,480
275,925
364,768
61,649
70,303
69,182
68,658
76,027
83,191
74,540
75,905
119,250
0
100,000
200,000
300,000
400,000
500,000
600,000
700,000
No. of hospitalizations

Fig. 4 continued

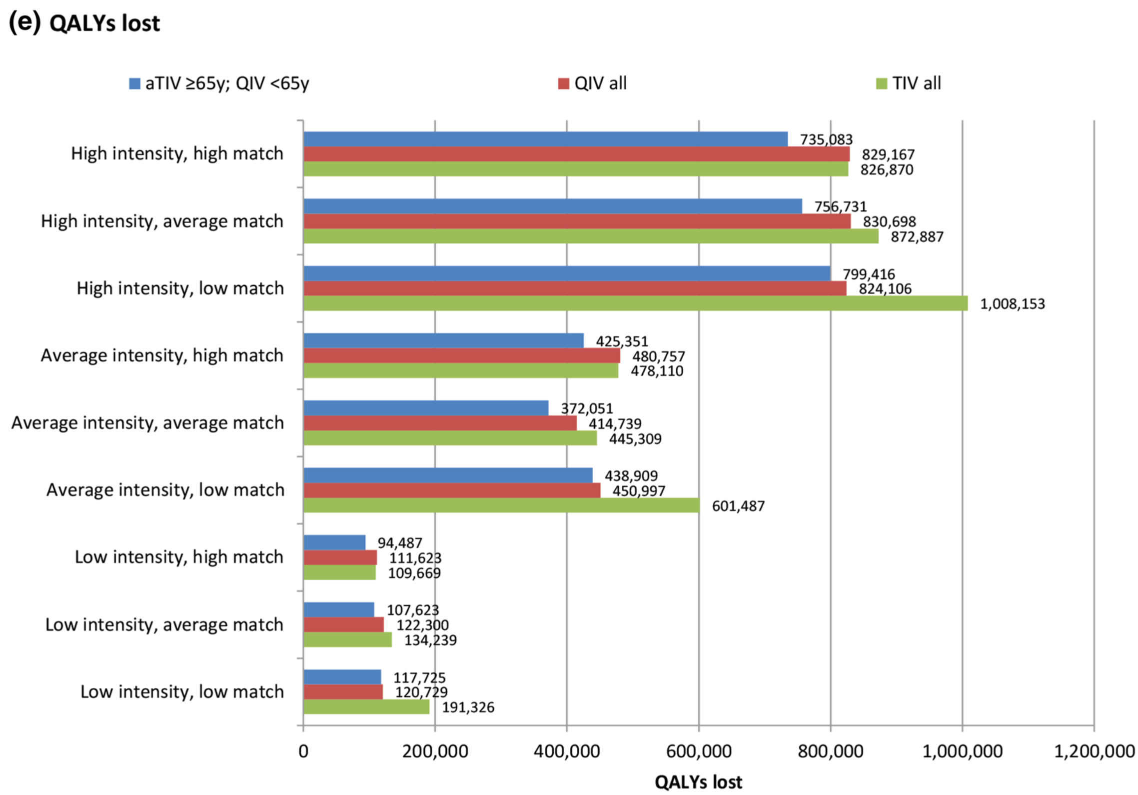

Fig. 4 continued

reduction in risk of hospitalization for influenza or pneumonia versus TIV in adults aged ≥65 years was observational only, did not assess aTIV's impact on the reduction of influenza cases, and did not compare aTIV directly with QIV [25]. There was no stratification other than age in the model, with no account taken of chronic disease status or residential/contact status. The model does not account for adverse effects of influenza vaccination. In addition, costs were treated deterministically in the model even though significant variation occurs in clinical practice. Despite these limitations, the findings are in line with what would be expected for a vaccine offering enhanced immunogenicity that has a potentially positive effect on clinical outcomes and costs relative to conventional vaccines, given the known economic burden of influenza [66] and the public health and economic benefits of vaccination [66, 67].

CONCLUSION

We have developed a dynamic model to assist vaccination policy decisions directing choices between different formulations of seasonal influenza vaccine. The US scenario modeled suggests that vaccination of persons aged ≥65 years with aTIV has the potential to provide clinical and economic benefit relative to QIV and TIV. We recommend further investigation of the clinical and economic impact of aTIV relative to other vaccine formulations in the elderly.

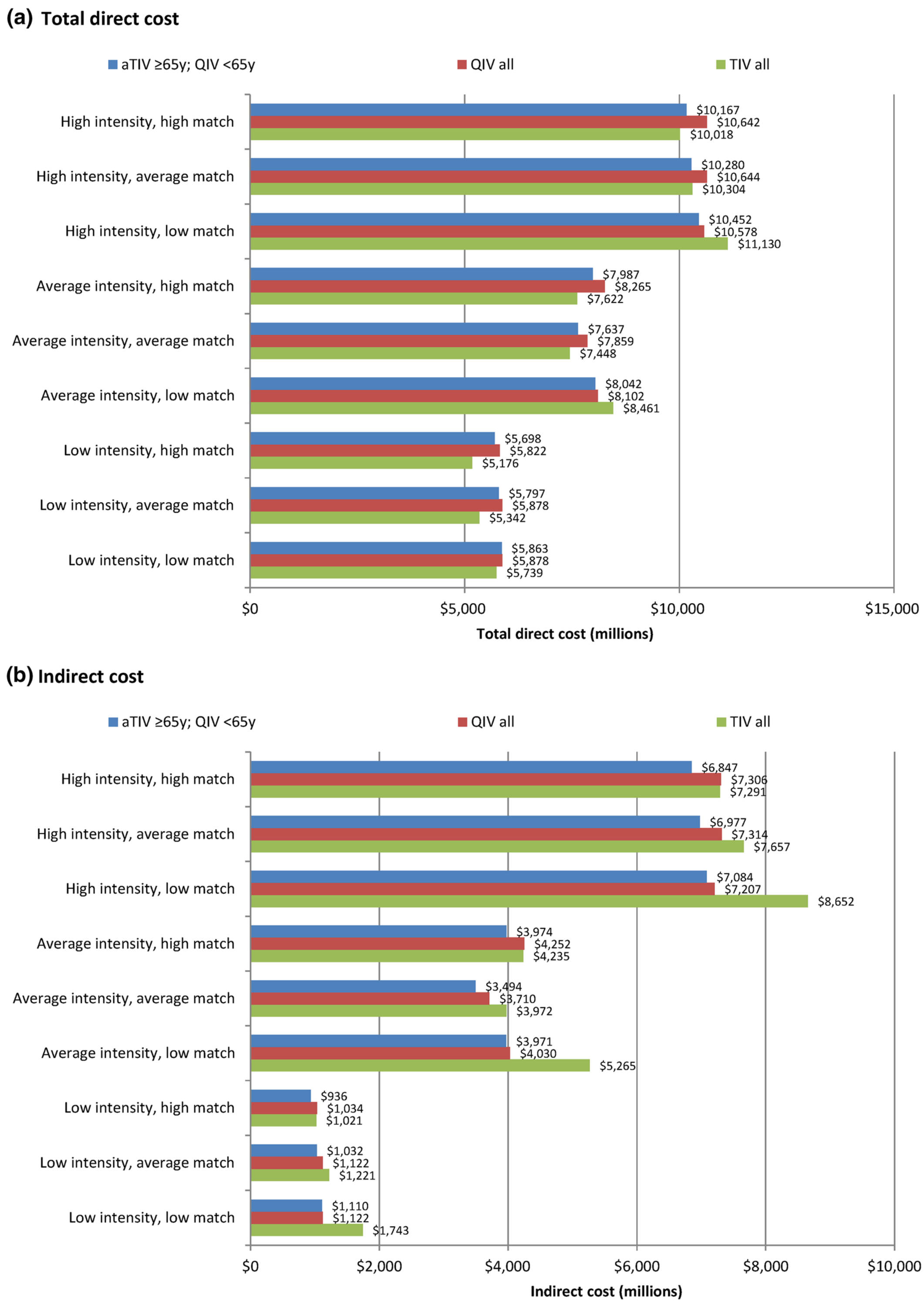

Fig. 5 Graphic summary of the main cost outputs of the model. All values are probabilistic means (see Table 6 for 95% credible intervals for probabilistically modeled values). *aTIV* adjuvanted TIV, *QIV* quadrivalent inactivated seasonal influenza vaccine, *TIV* trivalent inactivated seasonal influenza vaccine

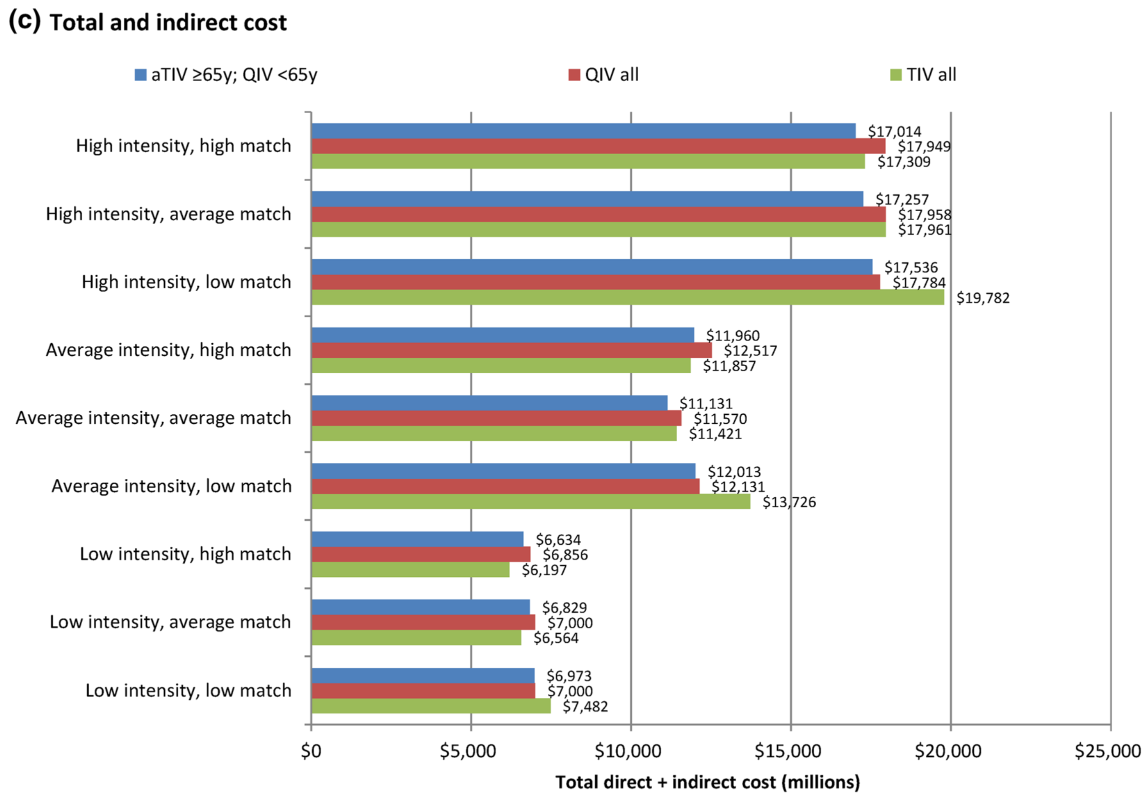

Fig. 5 continued

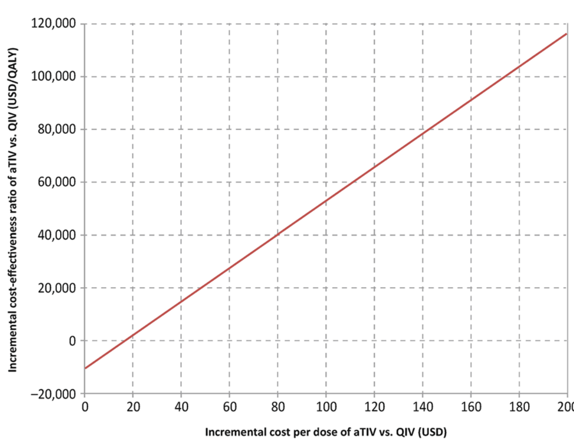

Fig. 6 Univariate sensitivity analysis of relative vaccine prices in the average intensity, average match scenario. *aTIV* adjuvanted trivalent inactivated influenza vaccine, *QALY* quality-adjusted life-year, *QIV* quadrivalent inactivated influenza vaccine

ACKNOWLEDGMENTS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. Medical Writing support for the development of this manuscript was provided by Christopher Dunn and Scott Malkin at Gardiner-Caldwell Communications, Macclesfield, UK. Funding for this support was provided by Novartis Vaccines. Modeling support for the analyses described in this manuscript was provided by

MAPI Values, Boston, MA, USA. Funding for this support was provided by Novartis Vaccines.

Conflict of interest. Mark Mullikin, Norbert Farkas, and Eckhardt Petri declare that they are current or former employees of Novartis Vaccines. Jeroen P. Jansen and Marc Van Ranst have no conflict of interest. Litjen Tan has served on scientific advisory boards for Pfizer, Merck, Novartis, Temptime Corp., and TruMedSystems within the past year. All honoraria for these services were donated directly to the Immunization Action Coalition.

Compliance with ethics guidelines. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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