THE VALUE OF QUADRIVALENT INFLUENZA VACCINES: AN EVIDENCE BASED REVIEW

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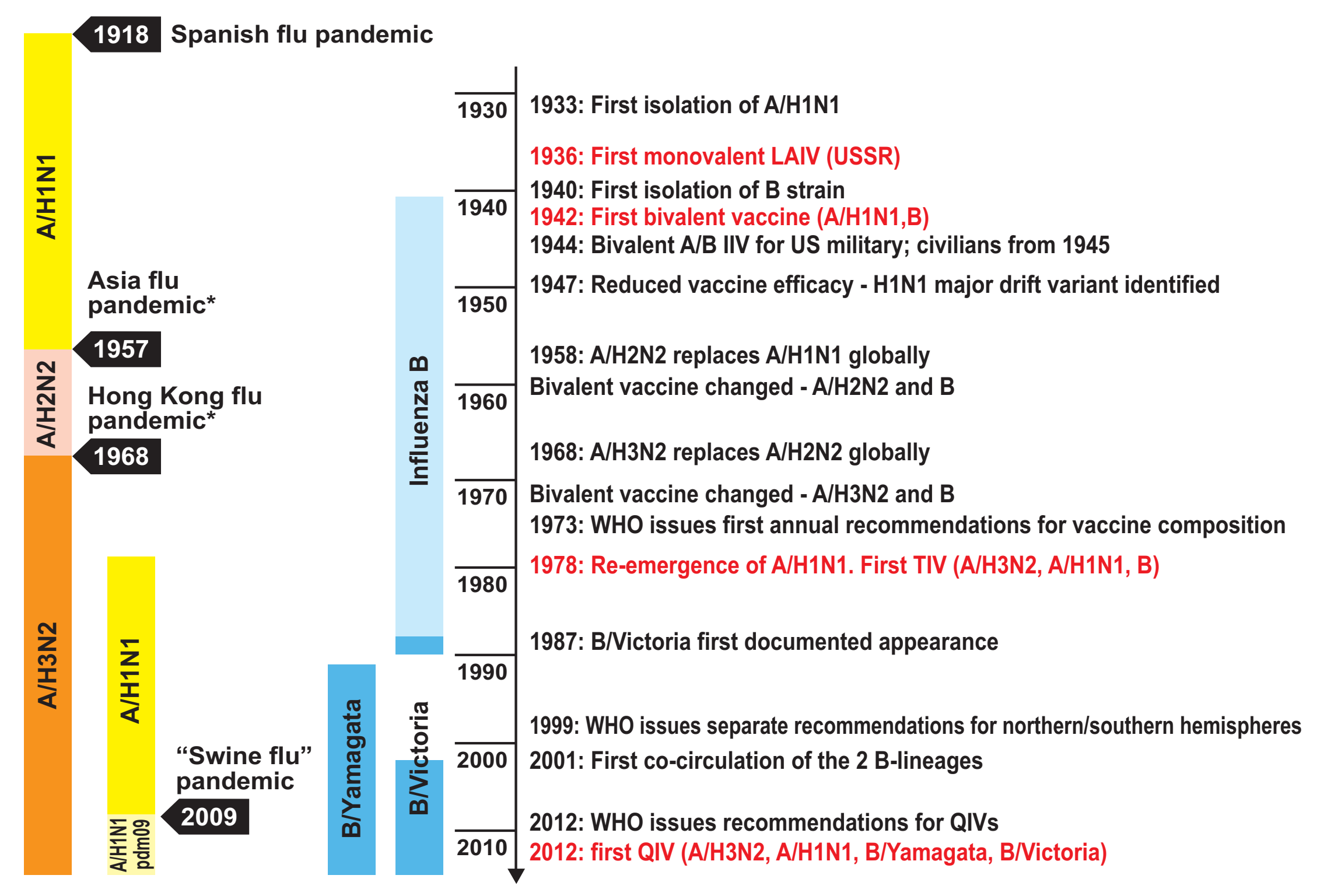
INTRODUCTION

The development of influenza vaccines

- The composition of influenza vaccines is constantly evolving reflecting the rapid genomic and antigenic changes of the circulating influenza viruses (**Figure 1**).
- The first trivalent influenza vaccines (TIVs) containing two influenza A subtypes (A/H3N2, A/H1N1) and one influenza B virus were produced in 1978[1].
- Since 2001, viruses belonging to two antigenically distinct influenza B lineages (B/Victoria and B/Yamagata) have co-circulated[2].
- Because the two influenza B lineages are co-circulating, new quadrivalent influenza vaccines (QIVs) containing two representatives strains of each influenza A and B virus types were developed.
- The degree of similarity or difference between the circulating viruses, and the strains included in the vaccines is referred to as vaccine match or mismatch, and impacts the vaccine's effectiveness.
- TIVs contain only one of the two influenza B lineages: the one predicted as more likely to circulate globally in a given influenza season[1].
- However, the two influenza B lineages frequently co-circulate; consequently, mismatch regularly occurs with TIVs[1].

Figure 1. The evolution of influenza viruses and vaccine development



Sources: Hammoun et al.[1] and McCullers et al.[14].

*Asian influenza pandemic caused by the shifted A/H2N2 strain and Hong Kong influenza pandemic caused by the shifted A/H3N2 strain: both examples of A-strain through reassortment (sharing) of genetic material.

LAIV, live-attenuated trivalent influenza vaccine; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine; WHO, World Health Organization

- Between 2010 and 2013, the influenza B lineage selected for inclusion in the annual TIV did not match the predominant circulating lineage in approximately 25% of influenza seasons in 26 countries[3].
- A mismatch yields suboptimal protection against influenza B infections and increases influenza public health burden[4,5]. The number of influenza B cases and the associated morbidity and mortality may be reduced with QIVs that contain representative strains of both influenza B lineages[6,7].

Currently available QIVs and country recommendations

- QIVs are currently produced using egg- or cell- cultures, and more recently with the use of recombinant technologies.
- An increasing number of countries currently recommend QIV, either permissively (TIV or QIV) or preferentially (TIV available but QIV preferred) (**Table 1**).
- Health authorities are sometimes hesitant to adopt preferential recommendations because they might be concerned whether QIV production and timely supply can meet their population's increasing vaccination needs.

Table 1. Current recommendations for influenza vaccination use

Country / Authority (Year)	Age/group indicated for QIVs
Permissive recommendations for QIVs	
WHO (2012)	Pregnant women, Children <5 y, Health care workers, Elderly > 65 y, Chronic conditions
Germany (2013)	Pregnant women, Children <5 y, Health care workers, Elderly > 65 y, Chronic conditions
US (2013)	Children ≥ 6 m, Adults
Hong Kong (2013)	Children ≥ 3 y, Adults
Canada (2014)	≥ 6 m
Italy (2014)	Children ≥ 3 y, Adults
France (2014)	Children ≥ 3 y, Adults
Belgium (2015)	≥2 y
Brazil (2014)	≥60 y
Prefential recommendations for QIVs	
UK (2013)	Children 2–7 y, Children at risk 2–18 y
Germany (2014)	All long-distance travelers
Brazil (2015)	Elderly
Australia (2015)	≥ 6 m

m, months; QIV, quadrivalent influenza vaccine; UK, United Kingdom; US, United States; WHO, World Health Organization; y, years

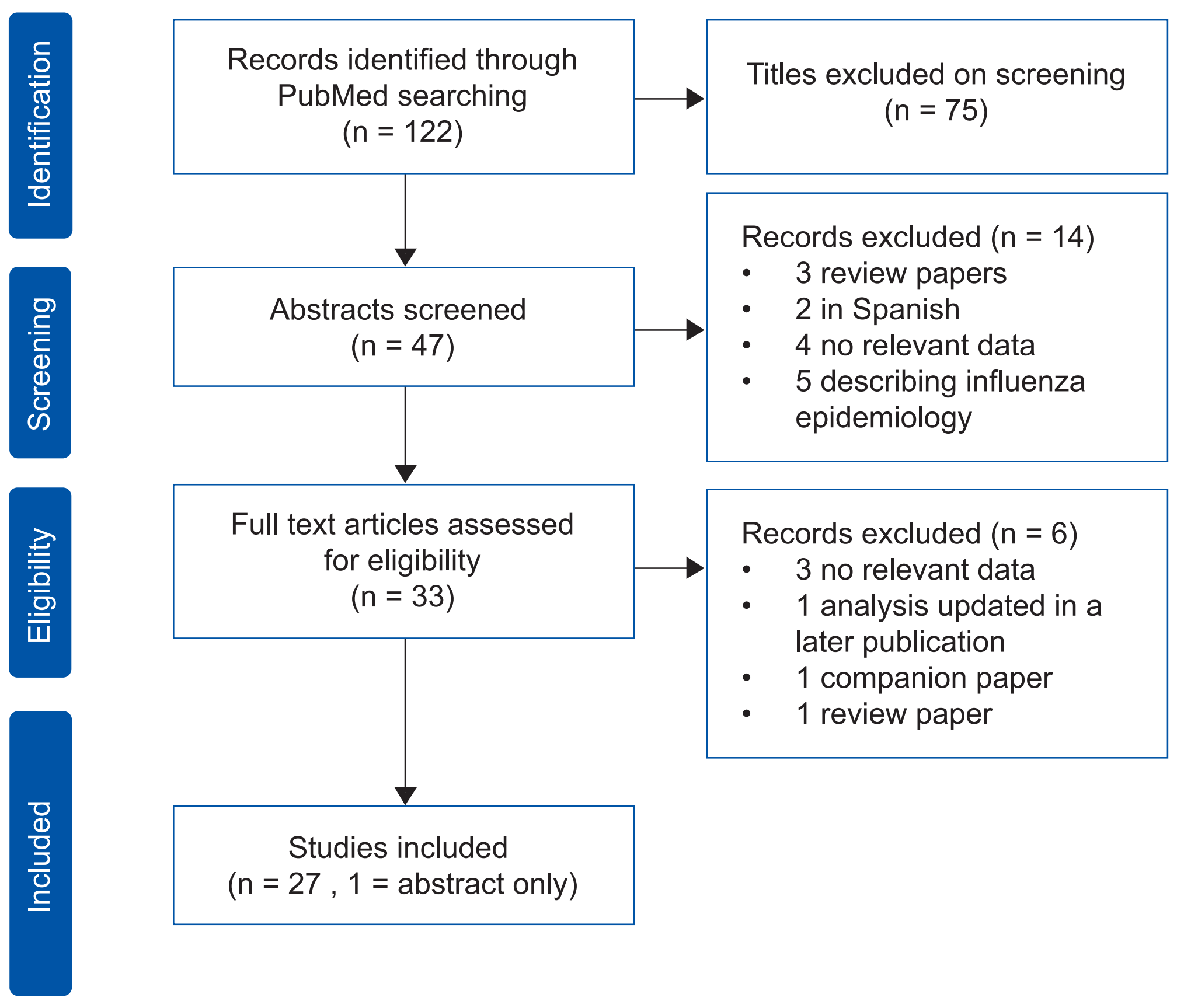
OBJECTIVE

- We reviewed the development of currently licensed QIVs and provide an overview of their societal value by focusing on the preventable disease burden. We searched and report modelling studies estimating the potential impact of QIVs compared to TIVs in terms of clinical outcomes and associated complications averted.

METHODS

- Using the search string provided in **Figure 2**, we systematically queried the PubMed database for papers formally comparing the added value of QIV versus TIV in terms of burden of illness, hospitalisations and deaths averted.
- We selected articles through a three-step selection procedure: 1) screening of title and abstract, 2) screening of full-text article, and 3) screening during the data-extraction phase.

*Figure 2. Results of the literature search**



Identification

Records identified through PubMed searching
(n = 122)

Titles excluded on screening
(n = 75)

Screening

Abstracts screened
(n = 47)

Records excluded (n = 14)
- 3 review papers
- 2 in Spanish
- 4 no relevant data
- 5 describing influenza epidemiology

Eligibility

Full text articles assessed for eligibility
(n = 33)

Records excluded (n = 6)
- 3 no relevant data
- 1 analysis updated in a later publication
- 1 companion paper
- 1 review paper

Included

Studies included
(n = 27 , 1 = abstract only)

*Search string: "(Quadrivalent OR tetravalent) (influenza vaccine OR flu vaccine) (cost OR burden OR epidemiology OR death OR mortality OR illness OR hospitalization OR hospitalization)" No limits applied.

RESULTS

- We retrieved 27 eligible studies from 14 countries: from Europe (10 studies), the United States (US) and Canada (10 studies), Asia-Pacific and Western Pacific (6 studies), and Africa (one study).
- The studies used multiple modelling methods to estimate the potential added value of QIV over TIV in various vaccination scenarios.
- Estimates were dependent upon the choice of baseline assumptions, e.g. assumed degree of cross-protection by TIVs, and level of mismatch in a given season.
- Static models produced lower differences compared to the dynamic models that accounted for herd-protection or disease transmission effects.

European studies

All models have estimated that the use of QIV would have averted a significant number of influenza cases, hospitalisations, and deaths. **Table 2** summarises the main results of these models, and additional findings are presented below:

- Data from France, Germany, Italy, Spain, and the United Kingdom were used in a static model. This model estimated that replacement of TIV with QIV during 2002–2013 (pandemic season excluded) would have prevented approximately one million additional influenza cases, as well as high numbers of hospitalisations and deaths (**Table 2**).
- Extrapolation of these data to the 27 member countries of the European Union also showed that QIV would have prevented high numbers of influenza cases, hospitalisations, and deaths (**Table 2**).
- In Belgium, a dynamic model extended the current immunisation strategy from individuals at risk to include children aged 2–17 years. Assuming 50% coverage of QIV among 2–17 years old, QIV would have averted almost three million influenza cases, as well as a significant number of hospitalisations, and deaths (**Table 2**)[8].

North America, Asia-Pacific, Western Pacific, and Africa

All models have also estimated that the use of QIV would have averted a significant number of influenza cases, hospitalisations, and deaths. **Table 3** summarises the main results of these models, and additional findings are presented below:

- In the US, retrospective studies reported that: 42% of the 2001–2009 annual office visits in <65 year olds, 30% of the 1997–2009 annual hospitalisations in all ages, and 51%–95 of all influenza-associated deaths in four of 12 seasons, were attributable to influenza B[9,10]. QIVs would have averted 15.8% more influenza B cases in 2000–2013, and would reduce influenza B cases in 2014–2034 by 27.2%[11].
- In Hong Kong, vaccination of ≥65 year-olds with QIV between 2001 and 2009 is estimated to have prevented 191.3 influenza illnesses per 100,000 population in elderly, with the highest reduction in those aged ≥80 years (reduction of 451.4 illness per 100,000 population)[12].
- In Australia, the highest impact of QIV was in young children and in older adults. In adults aged ≥65 years old, QIVs were estimated to prevent an additional 10.1 hospitalisations and 2.1 deaths per 100,000 person-years[13].

Table 2. Summary of QIV modeling data in different European countries

Country	Model type	Vaccinated population	Influenza vaccine coverage (%)	Illness averted by QIVs compared with TIVs Total cases	Total hospitalisations	Total Deaths
5 countries: France, Germany, Italy, Spain, UK[15]	Static	6 m–2 y	6.1–19.2	28,877	140	0
		2–17 y	4.1–14.0	219,163	348	7
		18–49 y high risk	30.9–52.0	83,635	389	79
		18–49 y low risk	6.5–12.0	133,656	110	0
		50–64 y high risk	30.9–52.0	89,908	1,801	325
		50–64 y low risk	14.9–25.3	86,216	515	0
		65+ y	48.6–69.2	393,270	21,151	9,391
		All ages		1,034,727	24,453	9,799
	Extrapolated to 27-EU	All ages		1,624,533	37,317	14,866
UK[16]	Dynamic	All ages	17.6–71.1**	88,755 annually	1050 annually	230 annually
UK[17]	Static	≥ 65 y & risk groups	34.07–100**	1.4 million 183,844	41,780 4,871	19,906 2,142
Germany[18]	Dynamic	0–15 y	26.8–33.4*	79,000 annually	–	–
		16–60 y		223,000 annually	–	–
		≥ 61 y		93,000 annually	–	–
		All ages		395,000 annually	–	–
Germany[19]	Dynamic	All ages	–	276,505 annually	5,609 annually	262 annually
Finland[20]	Dynamic	All ages	10–75**	40,500 annually	360 annually	54 annually
Belgium[8]	Dynamic	2–17 y	50	2,953,995	16,968	1,455
Spain[21]	Static	≥ 65 y, at risk ≥ 3 y	0–72.47**	18,565 in the first year	407 in the first year	181 in the first year
Italy[22]	Static	All ages at risk & ≥ 65 y	9% QIV, 31.02 total	2,632	100	–
France[23]	Static	All ages	–	6,214 consultations	614	372

*Coverage across seasons **coverage across age ranges

EU, European Union; m, month; QIV, quadrivalent influenza vaccine; US, United States; UK, United Kingdom; y, years

Table 3. Summary of QIV modeling data in North America, Asia-Pacific, Western-Pacific, Africa

Country, model type, age group	Influenza vaccine coverage (%)	Illness averted by QIVs compared with TIVs Total cases	Total hospitalisations	Total Deaths
North America				
US, Static, All ages[24]	18–30*,	2.7 million (range 2,200–970,000)	21,440 (range 14–8,200)	1,371 (range 1–485)
US, Static, All ages[25]	21.3–66.6**	30,251	3,512	722
US, Static, ≥ 65 y[26]	67	36,701	1,345	211
US, Static, ≥ 65 y[27]	64.7	39,136	1,648	458
US, Dynamic, All ages[28]	25–60**	1.9 million annually	–	1,396 annually
US, Dynamic, All ages[29]	46.2	1.3 million	18,354	2,981
US, Dynamic, All ages[30]	Weekly age based from CDC	6.3 million (average 482,000 annually)	–	–
US, Dynamic, All ages[11]	Weekly age based from CDC	16 million	137,645	16,199
Canada, Dynamic, All ages[16]	16.1–64.4*	135,538 annually	1,876 annually	328 annually
Canada, Static, All ages[31]	27–81**	2,516 annually	27 annually	5 annually
Asia-Pacific and Western Pacific				
Hong Kong, Static, All ages[12]	11.0–39.1**	91/100,000	1.8/100,000	0.046/100,000
Hong Kong, Static, All ages[32,33]	39.1	25.6/100,000	–	–
Australia, Static, All ages[34]	2–20 (selected range)	0.1/100,000 (3.8% reduction)	2/100,000 (2.2% reduction)	0.1/100,000 (2.1% reduction)
Australia, Static, All ages[13]	36.2–74.6	68,271 (1.0% reduction)	3,522 (2.4% reduction)	683 (3.7% reduction)
Thailand, Static, All ages[35]	3–12*	21,974	698	7
Taiwan, Static, All ages[36]	0–39.49**	529,874	8,126	3,590
Africa				
South Africa, Static, All ages[34]	2–20 (selected range)	0.3/100,000	4.8/100,000	2.0/100,00

*Coverage across seasons **coverage across age ranges

CDC, Centers for Disease Control and Prevention; QIV, quadrivalent influenza vaccine; y, years

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CONCLUSIONS

- **On average, influenza B causes globally up to one-third of influenza infections each season.**
- **Accumulated evidence demonstrates that influenza B accounts for a significant portion of the overall burden of influenza, generating a significant increase in the number of medical visits to healthcare services annually.**
- **B-mismatched seasons are accompanied by a higher influenza-related public health burden than well-matched seasons.**
- **The broader adoption of QIVs is expected to contribute to a significant reduction in the burden of influenza, also providing real-life evidence supporting influenza vaccine recommendations and thus informing further the policy maker decisions.**

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Conflict of interests

Philip O. Buck, Anar Andani and Rafik Bekkat-Berkani are employees of the GSK group of companies. Gaël Dos Santos, Rafik Bekkat-Berkani and Philip O. Buck hold shares in the GSK group of companies. Gaël Dos Santos reports he was employed by Business & Decision Life Sciences (on behalf of GSK) at the time of the study and is now employee of the GSK group of companies.

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