Quadrivalent influenza vaccine: a new opportunity to reduce the influenza burden

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Keywords

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Summary

Influenza illness is caused by influenza A and influenza B strains. Although influenza A viruses are perceived to carry greater risk because they account for the majority of influenza cases in most seasons and have been responsible for influenza pandemics, influenza B viruses also impose a substantial public health burden, particularly among children and at-risk subjects.
Furthermore, since the 2001-2002 influenza season, both influenza B lineages, B/Victoria-like viruses and B/Yamagata-like viruses have co-circulated in Europe.
The conventional trivalent influenza vaccines have shown a limited ability to induce effective protection when major or minor mismatches between the influenza B vaccine component and circulating strains occur. For this reason, the inclusion of a second B strain in influenza vaccines may help to overcome the well-known difficulties of predicting the circulating B lineage and choosing the influenza B vaccine component.
Two quadrivalent influenza vaccines, a live-attenuated quadrivalent influenza vaccine (Q/LAIV) and a split inactivated quadrivalent influenza vaccine (I/QIV), were first licensed in the US in 2012. Since their introduction, models simulating the inclusion of QIV in influenza immunization programs have demonstrated the substantial health benefits, in terms of reducing the number of influenza cases, their complications and mortality.
In the near future, evaluations from simulation models should be confirmed by effectiveness studies in the field, and more cost-effectiveness analyses should be conducted in order to verify the expected benefits.

Introduction

Influenza is an acute viral illness of the respiratory tract, and constitutes a substantial public health burden in terms of morbidity, mortality and related costs. About 3-5 million cases of severe illness occur each year worldwide, resulting in about 250,000 to 500,000 deaths per year, high hospitalization and mortality rates, and considerable loss of productivity [1-3].
From a microbiologic point of view, type A and type B Influenza viruses differ markedly in terms of their hosts and epidemiology. Influenza A viruses have other animal reservoirs, in addition to humans, and display high antigenic variability, which mainly involves their surface glycoproteins: hemagglutinin (HA) and neuroaminidase (NA). Antigenic shift and antigenic drift are the two well-known mechanisms responsible for major and minor variations; antigenic shift is the main cause of the appearance of new influenza A strains with pandemic potential. Antigenic drift determines annual seasonal influenza epidemics [4].
Influenza B viruses, for which humans are the sole host of epidemiological relevance, do not undergo antigenic shift, but they can undergo antigenic drift. Since at least 1983, two parallel evolutionary B pathways with little antigenic cross-reactivity have been recognized, thus allowing two distinct genetic lineages to be identified: the B/Victoria/2/1987 (Victoria) and B/Yamagata/16/1988 (Yamagata) strains [5-6]. Since 2002, the two distinct influenza B lineages have frequently co-circulated, with one of the two predominating over the other in each season [7]. For example, in ten consecutive influenza seasons in Italy – from 2003-2004 to 2012-2013 – variations in the prevalence of circulating B lineages were reported: in 2007/2008 and 2012/2013, B viruses accounted for 47.7% and 58%, respectively, of viruses isolated, while in other seasons B viruses co-circulated with virus A, although with a lower prevalence [8].
Vaccination is the most effective means of reducing the number of influenza cases and related complications. Annual influenza immunization is, in particular, recommended in elderly subjects, children aged six months or more, pregnant women and individuals with chronic conditions, such as respiratory/heart/liver diseases, diabetes, or a weakened immune system. Indeed, these categories are at heightened risk of influenza-related complications and mortality [9].
In Italy, the National Ministry of Health annually publishes influenza prevention recommendations, specifying the groups to whom vaccination is offered free of charge. In addition, the Ministry sets a minimum target of vaccination coverage of 75% and an optimal target of 95% [10].

Tab. I. Influenza vaccination strains and viruses circulating in the northern hemisphere in the seasons from 1995/96 to 2015/2016.

Season	Influenza vaccination strains, Northern Hemisphere			Virus circulating in Europe and US		
	A/H1N1	A/H3N2	B	A/H1N1	A/H3N2	B
1995/96	Texas/91	Johan/94	Beijing/93	Texas/91	Johan/94	Beijing/93
1996/97	Bayern/95	Wuhan/95	Beijing/93	Bayern/95	Wuhan/95	Beijing/93
1997/98	Bayern/95	Wuhan/95	Beijing/93	Bayern/95	Syd/97	Harbin/94
1998/99	Beijing/95	Syd/97	Beijing/93	Bay/95+Beij/95	Syd/97	Beijing/93
1999/00	Beijing/95	Syd/97	Beijing/93	NewCal/99	Syd/97	Beijing/93
2000/01	NewCal/99	Pan/99	Yaman/98	Bay/95+NC/99	Syd/97	Sichuan/99
2001/02	NewCal/99	Pan/99	Sich/99 (Y)	NewCal/99	Pan/99	Sic/99+HK01
2002/03	NewCal/99	Pan/99	HK/01 (V)	NewCal/99	Fuj/02(Pan/99)	Sic/99+HK01
2003/04	NewCal/99	Pan/99	HK/01 (V)	NewCal/99	Fuj/02	Jiangs/03
2004/05	NewCal/99	Wyom/03	Jiangs/03 (Y)	NewCal/99	Calif/04	J/03+Mal/04
2005/06	NewCal/99	Calif/04	Jiangs/03 (Y)	NewCal/99	Cal/04+Wis/05	J/03+Mal/04
2006/07	NewCal/99	Wiscons/05	Malays/04 (V)	NC/99+Sal/06	Wisc/05	J/03+Mal/04
2007/08	Salom Is/06	Wiscons/05	Malays/04 (V)	Sal/06+Bris/07	Wisc/05+Bris/07	Bri/07+Mal/04
2008/09	Bris/07	Bris/07	Florida/06 (Y)	Bris/07	Bris/07	Florida/06+Brisb/08
2009/10	Bris/07	Bris/07	Bris/08 (V)	-	Bris/07	Bris/08 (V)
2009/10	Calif/09			Calif/09		
2010/11	Calif/09	Perth/09	Bris/08 (V)	Calif/09	Perth/09	Bris/08 (V)
2011/12	Calif/09	Perth/09	Bris/08 (V)	Calif/09	Vict/11+Brisb/11	Bris/08+Wisc/10
2012/13	Calif/09	Vict/11	Wiscons/10 (Y)	Calif/09	Vict/11+Texas/12	Bris/08 (V)+Mass/12 (Y)
2013/14	Calif/09	Vict/11	Mass/12 (Y)	Calif/09	Texas/12	Bris/08 (V)+Mass/12 (Y)
2014/15	Calif/09	Texas/12	Mass/12 (Y)	Calif/09	Switzerl/13 +Texas/12	Phuk/13(Y)+Mass/12(Y)
2015/16	Calif/09	Switzerl/13	Phuk/13(Y)	Calif/09	Hong Kong/14	Bris/08 (V)+Phuk/13 (Y)

Legend: in yellow: minor mismatches; in red: major mismatches; in green: new influenza A strains with pandemic potential.

The World Health Organization (WHO) annually recommends vaccine composition on the basis of global virological surveillance. Annual trivalent influenza vaccines (TIVs) contain two influenza A strains (H1N1 and H3N2) and only one influenza B virus. The effectiveness of TIVs therefore depends on the degree of matching between the vaccine strain and circulating viral strains.

In the last two decades, four major and at least eight minor mismatches between vaccine and circulating B viruses have occurred in the northern hemisphere, thus impairing the performances of TIVs (Tab. I) [6]. Specifically, Ambrose CS and colleagues observed that, in Europe, a B-mismatch between vaccine and circulating strains occurred in 5 of 10 seasons between 2001 and 2011 [7]. The effect of antigenic mismatching between vaccine and circulating strains on vaccine effectiveness has emerged from observational and experimental studies [6, 11-14]. A recent meta-analysis by the Centers for Disease Control and Prevention (CDC) and the Marshfield Foundation reported that trivalent subunit or split influenza vaccines displayed good effectiveness in preventing lab-confirmed influenza illness when matching was good, but that vaccine effectiveness decreased when a drifted strain dominated the epidemiological picture [15]. Therefore, inaccurate prediction of the predominant influenza B lineage leaves many vaccinated individuals with suboptimal protection against influenza B disease caused by the influenza B lineage not included in the licensed trivalent vaccine [11].

To minimize the impact of B-mismatch on vaccine effectiveness, in February 2009 the Food and Drug Administration (FDA), for the first time, considered the inclusion of an additional influenza B strain in the antigenic composition of seasonal influenza vaccines [16]. Subsequently, in February 2012, the WHO recommended the production of quadrivalent influenza vaccines (QIVs) for seasonal immunization. In 2012, the European Medicines Agency (EMA) also highlighted the need for a quadrivalent vaccine that could overcome the lack of protection against the influenza B lineage not present in the trivalent vaccine. Finally, in February 2013, the WHO issued its first guidelines recommending that both expected B-strains be included in the vaccine composition [17-18].

In recent years, scientific research has addressed this need, and two quadrivalent influenza vaccines (QIVs) have been developed: a live-attenuated quadrivalent influenza vaccine (Q/LAIV) and a split inactivated quadrivalent influenza vaccine (I/QIV) [19].

Main evidence from pre- and post-marketing evaluations of licensed quadrivalent influenza vaccines

The immunogenicity, safety and tolerability of quadrivalent influenza vaccines have been evaluated in children, adults and the elderly in several clinical trials.

Live-attenuated quadrivalent influenza vaccine (Q/LAIV)

Q/LAIV has mainly been tested in children. A phase-III, randomized, double-blind study performed on 2,312 children aged 2-17 years demonstrated that the immunogenicity of an investigational Q/LAIV was non-inferior to that of two licensed T/LAIVs, one containing a B strain from the Yamagata lineage and the other containing a strain from the Victoria lineage. Moreover, this Q/LAIV proved safe and well tolerated [20].
Since 2014/2015, Q/LAIV has been used in a universal pediatric vaccination programme in the United Kingdom (UK). In this real-life scenario, the vaccine was seen to provide significant protection against drifted circulating influenza B viruses [21].

Inactivated quadrivalent influenza vaccine (I/QIV)

Children and adolescents

With respect to I/QIV, a phase II study was conducted in two groups of children aged 18-47 months: the first group was constituted by children who had received two doses of TIV in the previous season and who received one dose of TIV or I/QIV in the study season; the second group was composed of unprimed children who received two doses of I/QIV or TIV 28 days apart during the study season. In comparison with the TIV, the I/QIV displayed superior immunogenicity towards the alternative-lineage B strain, without impairing the immune responses to shared strains. Moreover, the two vaccines proved similar in terms of reactogenicity and safety [22]. These results were confirmed in a randomized phase III study conducted by Domachowske JB and colleagues in healthy children aged 3-17 years [23]. Langley and colleagues also investigated the immunogenicity and safety of a I/QIV candidate versus TIVs, in a phase-III randomized controlled trial involving 3,094 children aged 3-17 years. The I/QIV was non-inferior to the TIVs in terms of immunogenicity towards the shared strains (A/H3N2 and A/H1N1), and, in comparison with TIV controls, elicited superior responses to the added B strains. Solicited reactions, unsolicited adverse events and serious adverse events were similar in the I/QIV and pooled TIV groups [24].

Adults and elderly

The promising results obtaining with I/QIV in children were also confirmed in clinical trials performed in adult populations.
In a phase-III clinical trial comparing I/QIV with TIV/Victoria and TIV/Yamagata vaccines, 4,659 adult volunteers received one vaccine dose. Overall, the I/QIV was highly immunogenic and, on day 21, displayed greater immunogenicity towards the additional B strain than TIV, without interfering with the antibody responses to the three shared antigens [25]. The I/QIV candidate was also tested in 1,565 adults aged ≥ 18 years in a phase III, randomized, active-controlled, multicenter trial during the 2011/2012 influenza season. For all four vaccine strains, antibody responses to the I/QIV were non-inferior to those elicited by the TIV for matched strains. For both B strains, antibody responses to the I/QIV were non-inferior to the response to the TIV for the matched strains, and were superior to the responses elicited by the TIVs that lacked the corresponding B strain. The I/QIV also confirmed its acceptable safety profile in an adult population [26].
The safety of I/QIV was investigated through a routine surveillance system in Western Australia in 2015 in a sample of 1,685 healthcare workers (HCWs). The results indicated little difference between the reactogenicity of I/QIV and that of TIV; the percentage of HCWs reporting pain or swelling at the injection site was slightly higher among those who had received I/QIV than those who had received TIV (6.9% *vs* 4.2%, respectively; $p = 0.02$) [27].
The safety of I/QIVs was verified in a review of data from the Vaccine Adverse Event Reporting System (VAERS) in the US from 7/1/2013 to 5/31/2015. The most frequent non-fatal serious adverse events were: injection site reactions, such as pain and erythema, constitutional symptoms, Guillain-Barré syndrome, seizures, and anaphylaxis, though these were rare or very rare. Adverse events reported to the VAERS following I/QIVs were similar to those following TIVs [28].
On the basis of this evidence, the two quadrivalent influenza vaccines have recently been licensed in many countries, and have been gradually replacing TIVs in the immunization programs of these countries.

Expected benefits of the quadrivalent influenza vaccines

As mentioned above, two different influenza B strains may co-circulate during an influenza season. Therefore, adding a second B strain to influenza vaccines increases the likelihood of achieving adequate protection against influenza B disease. Some recent studies have evaluated the expected benefits of including QIVs in national immunization programs. For instance, Eichner et al. compared the effects of QIVs and TIVs on influenza incidence by using an individual simulation model in which the concomitant transmission of four influenza strains, maternal protection, boosting of existing immunity, loss of immunity and cross-immunizing events between the B lineages over 50 years were considered as variables. Their study found that QIV administration could prevent 11.2% of all influenza B infections which still occur with TIV, thus reducing the influenza burden on the community [29].
The public health impact of QIVs in the United States was analyzed in a model by Crépey and colleagues in a dynamic retrospective framework with real-life vaccine mismatch.
Assuming 70% cross-protection of the efficacy of a matching vaccine, the model predicted that QIV would have prevented, on average, about 16% more B lineage

cases than TIV over the period 2000-2013 [30]. The elderly (≥ 65 years) and adults aged 50-64 years were seen to benefit most from QIV, with 21% and 18% reductions, respectively, in B lineage cases [30].
Van Bellinghen et al. conducted a lifetime economic evaluation of QIVs in comparison with TIVs in elderly people and clinical risk groups in the UK. Using a multi-cohort Markov model, they estimated that quadrivalent influenza vaccination could further reduce the disease burden of influenza. The QIVs would be expected to result in substantial health benefits, reducing the number of symptomatic influenza cases, medical visits, complications, hospitalizations for complications and deaths, in comparison with TIVs [31]. In the UK, another study by Meier et al. applied a lifetime, multi-cohort static Markov model involving seven age-groups, and obtained analogous findings [32].
Thommes EW and colleagues used an age-stratified, dynamic four-strain transmission model which incorporated strain interaction, transmission-rate seasonality and age-specific mixing in the population, in order to demonstrate the cost-effectiveness of quadrivalent influenza vaccines in Canada and the United Kingdom. The results of this analysis revealed that switching from trivalent to quadrivalent vaccines would be a cost-effective means of further reducing the burden of influenza in both countries [33].
You JH and colleagues simulated the outcomes of QIV vs. TIV in 6 age-groups: 0-4 years, 5-9 years, 10-14 years, 15-64 years, 65-79 years and ≥ 80 years. Direct cost alone, direct and indirect costs, and loss of quality-adjusted life-years (QALYs) due to TIV-unmatched influenza B infection were simulated for each study arm. In the base-case analysis, QIV was more effective than TIV in all age-groups, and proved to be cost-effective from the societal perspective in all age-groups, except for those aged 15-64 years. From the healthcare provider's perspective, QIV seemed to be cost-effective in very young (6 months – 9 years) and older (≥ 80 years) age-groups [34].
In Italy, a lifetime, multi-cohort, static Markov model was constructed, and was run in one-year cycles for a lifetime (Maximum age: 100 years). The analysis demonstrated that QIV would be cost-effective compared with TIV. Specifically, QIV would be expected to reduce the number of influenza cases (by about 1,413.887), complications (by about 169,638), hospitalizations for complications (by about 41,862) and influenza deaths (by about 20,905). The incremental cost-effectiveness ratio (ICER) was € 18,883/QALY for the base case [8].

Conclusions

Influenza B viruses have a considerable public health burden, particularly among children and at-risk subjects. The belief that influenza B illness is less severe than influenza A leads to underestimation of its real impact. However, the type B influenza virus causes 20% to 25% of influenza infections worldwide. Since the mid-1980s, surveillance data have shown frequent co-circulation of both influenza B lineages, B/Victoria-like and B/Yamagata-like, during influenza seasons. The conventional TIVs, containing only a single B strain, showed limited ability to induce effective protection when major or minor mismatches between the influenza B vaccine component and the circulating strains occurred, thus substantially reducing the clinical effectiveness of the trivalent influenza vaccine [35].
The availability of QIVs may contribute to overcoming the well-known difficulties of predicting the circulating B lineage and choosing the right influenza B vaccine component in trivalent influenza vaccines (TIVs) [36].
In recent years, two QIVs, an inactivated vaccine and a live-attenuated vaccine, have been developed and licensed for human use on the basis of the good safety, tolerability and immunogenicity profiles demonstrated during the entire pre-marketing research process [37]. In some countries, such as Canada, national guidelines now recommend QIVs in preference to trivalent vaccines for use in children and young people [38].
Available models simulating the inclusion of QIVs in influenza immunization programs support the benefits of this new preventive tool in terms of reductions in symptomatic influenza cases and related complications. Indeed, QIVs could reduce both direct costs in term of medical visits, hospitalizations and antibiotic prescriptions, and indirect costs related to working days lost by affected people and their caregivers.
However, some issues need to be addressed in the near future. In particular, estimations from simulation models should be confirmed by effectiveness studies in the field and more cost-effectiveness analyses should be conducted in order to verify the expected advantages in different epidemiological scenarios.

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