Influenza – the need to stay ahead of the virus

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As illustrated in a series of publications in the current and previous issue of *Eurosurveillance* [1-3], the ongoing influenza epidemics in Europe and North America are dominated by influenza A(H3N2) viruses. The majority of these appear to vary antigenically from the current northern hemisphere vaccine strain A/Texas/50/2012(H3N2) and more closely related to the vaccine strain A/Switzerland/9715293/2013(H3N2) recommended for the 2014/15 season of the southern hemisphere. In line with the observed antigenic mismatch between circulating and vaccine A(H3N2) viruses, preliminary estimates of influenza vaccine effectiveness (IVE) from Canada in the general population [3] and in hospitalised patients [4] and from the general population in the United Kingdom (UK) [5] complement previous data for the United States (US) [6]. All point to an overall substantially reduced vaccine effectiveness with point estimates of −8%, −16.8%, 3.4%, and 22%, respectively, as compared to seasons with a good match between circulating viruses and vaccine strains. This situation highlights the difficulties to accurately and timely anticipate antigenic changes of influenza viruses for inclusion of the proper antigenic (drift) variants in the vaccine.

Recommendations for the influenza vaccine composition are issued twice a year by the World Health Organization (WHO), in February and September, for the northern and southern hemisphere influenza seasons, respectively [7]. Recommendations are based on surveillance data and analysis of the virus characteristics provided by the National Influenza Centres from the WHO Global Influenza Surveillance and Response System (GISRS). For the four categories of seasonal influenza viruses, i.e. two influenza A virus subtypes A(H3N2) and A(H1N1)pdm09 and two influenza B lineage, B-Yamagata and B-Victoria viruses, data taken into account comprise epidemiological data as well as virological data in order to evaluate the genetic evolution of the viruses, their antigenic characteristics and susceptibility to antivirals, as well as their geographical distribution and impact. These are complemented by serological data aimed at evaluating the ability of post-vaccination sera from the previous season to neutralise the most recently circulating viruses with particular focus on potential drift variants [8]. The serological study in Finland in vaccinated healthcare workers by Haveri et al. in this issue points to a reduced cross-protection towards currently circulating drifted influenza A(H3N2) viruses [2].

Despite expansion of the GISRS network especially following the 2009 influenza A(H1N1) pandemic and continuous improved surveillance worldwide [9], predicting six months ahead of time which influenza variants will be predominating the next season remains a challenge. To achieve this, a better understanding of the link between genetic and antigenic evolution of the virus is required. Recent studies have provided information on key residues of the haemagglutinin that contribute to major antigenic changes for the influenza A(H3N2) and A(H1N1)pdm09 viruses [10,11]. Substitutions for at least one of these key residues (aa 159) were observed for the drifted A(H3N2) viruses from the current influenza season. However, in order to stay ahead of the virus, new means to better predict which genetic group of viruses will most likely become predominant are needed. This might be achieved through analysis of the evolutionary trajectories of the virus sequences taking into account minority variants that can be detected through Next Generation Sequencing. The feasibility on a large scale and benefits for the definition of the vaccine composition of an approach combining improved prediction of genetic variants likely to emerge and their impact on virus antigenicity, will require more research.

In spite of the challenges to define the vaccine composition, when excepting the 2009 pandemic, mismatches for viruses circulating in Europe occurred only once for A(H1N1) viruses and three times for A(H3N2) viruses in the past 12 years (Table).

In addition, for type B viruses, a mismatch occurred three times, in two instances related to the inclusion of the wrong influenza B lineage in the composition of the trivalent vaccine. Making global predictions for

Antigenic match with vaccine strains of influenza viruses circulating in Europe from 2003/04 to 2014/15

Season (northern hemisphere)	Vaccine composition (northern hemisphere)			Circulating viruses[a]		
	A(H1N1)	A(H3N2)	Type B (lineage)	A(H1N1)	A(H3N2)	Type B lineage
2003/04	A/New Caledonia/20/99	A/Moscow/10/995	B/Hong Kong/330/2001 (VIC)		H3N2	
2004/05	A/New Caledonia/20/99	A/Fujian/411/02	B/Shanghai/361/02 (VIC)		H3N2	
2005/06	A/New Caledonia/20/99	A/California/7/2004	B/Shanghai/361/02 (VIC)	H1N1		VIC
2006/07	A/New Caledonia/20/99	A/Wisconsin/67/2005	B/Malaysia/2506/2004 (VIC)		H3N2	
2007/08	A/Solomon Islands/3/2006	A/Wisconsin/67/2005	B/Malaysia/2506/2004 (VIC)	H1N1		YAM
2008/09	A/Brisbane/59/2007	A/Brisbane/10/2007	B/Florida/4/2006 (YAM)		H3N2	VIC
2009/10	A/Brisbane/59/2007	A/Brisbane/10/2007	B/Brisbane/60/2008 (VIC)	H1N1pdm09		
2010/11	A/California/7/2009 (pdm)	A/Perth/16/2009	B/Brisbane/60/2008 (VIC)	H1N1pdm09		VIC
2011/12	A/California/7/2009 (pdm)	A/Perth/16/2009	B/Brisbane/60/2008 (VIC)		H3N2	
2012/13	A/California/7/2009 (pdm)	A/Victoria/361/2011	B/Wisconsin/1/2010 (YAM)	H1N1pdm09	H3N2[b]	YAM
2013/14	A/California/7/2009 (pdm)	A/Texas/50/2012	B/Massachusets/2/2012 (YAM)	H1N1pdm09	H3N2	
2014/15	A/California/7/2009 (pdm)	A/Texas/50/2012	B/Massachusets/2/2012 (YAM)		H3N2	

pdm: pandemic; VIC: Victoria; YAM: Yamagata.

[a] Only viruses accounting for more than 10% of the circulating viruses are mentioned ; mismatches are highlighted in grey.

[b] Mismatch related to antigenic changes of the vaccine strain upon growth in eggs.

influenza B viruses has proven particularly challenging as different influenza B lineages may predominate or co-circulate in different regions. Availability of tetravalent vaccines containing influenza B strains from both the B-Yamagata and B-Victoria lineage in addition to the two A(H3N2) and A(H1N1)pdm09 strains provides a solution but will not prevent a mismatch due to the emergence of a drift variant. Mismatch may also be related to antigenic changes of the vaccine strain upon growth in eggs as seen for the A(H3N2) strain during the 2012/13 season [12].

Mismatches concerning the A(H3N2) component of the vaccine impacted most on public health as A(H3N2) viruses are known to confer more severe illness with potential for complications especially in the elderly, a population that is also one of the main targets for vaccination. The extent to which a mismatch results in reduced IVE, however, is variable [13]. Vaccine effectiveness depends on the immunogenicity of the vaccine itself. This may vary with the type of vaccine (e.g. inactivated, presence of adjuvant, live attenuated), and for each vaccine strain. It also depends on the quality of the elicited immune response that is known to vary between individuals especially with age.

The role of pre-existing immunity that results from previous infection or vaccination also needs to be considered. In this respect, more serological data to inform, before the beginning of the season, about the antibody levels in the population against the various influenza viruses, including potential drift variants would be desirable. Finally, IVE depends on the extent of the mismatch between the vaccine strain and the circulating virus and the predominance of the drift variants among circulating viruses needs to be taken into account. This highlights the importance of quality surveillance that integrates virological and epidemiological data. Predicting the actual impact of a given mismatch on IVE is thus very challenging. It requires integration of virological, serological and epidemiological data that are not always available and knowledge for the establishment of correlations is lacking. For instance, the impact of repeat vaccination that has sometimes shown to have a negative effect on IVE as reported from Canada by Skowronski et al. [3] remains a complex and unresolved issue that requires further investigation [14].

In the absence of methodologies to predict the impact of a mismatch on IVE, real time epidemiological evaluation of IVE is the preferred option in order to guide appropriate responses to suboptimal vaccine effectiveness. Recent years have seen marked improvements in the capacity of generating early in-season epidemiological measures of IVE, despite the many pitfalls attached to such studies [15,16]. The first issue relates to the case definition. Indeed, a clinical outcome such as influenza-like illness (ILI) lacks specificity and may lead to underestimation of IVE. Therefore, laboratory confirmation of ILI, as done in the Canadian and the UK studies published last week and in the current *Eurosurveillance* issue, is increasingly considered as a standard. The second issue is bias. As all observational studies, IVE studies are prone to bias. Both negative and positive confounding can alter the quality of IVE, requiring the documentation of a minimum set of variables to be included as covariates in models.

The increasing use of the test–negative case–control design, whereby controls are individuals consulting for ILI and testing negative for influenza, allows reducing the potential bias linked to differential healthcare seeking behaviours according to vaccination status. The third issue relates to the power of the studies. Even in countries with a well-established General Practice (GP)-based sentinel surveillance system, it is difficult to conduct large scale studies allowing precise early estimates, especially for subgroup analysis. This is especially true for measurement of IVE in elderly patients as such patients, although the main target of seasonal influenza vaccination, are difficult to recruit in sufficient numbers at GP offices.

The European Centre for Disease Prevention and Control (ECDC)-funded Influenza Monitoring Vaccine Effectiveness (I-MOVE) network set up in 2007, including 22 partners from 17 European Union/European Economic Area (EU/EEA) countries with Epiconcept as the coordinating hub, has proven its ability to generate early reliable IVE estimates, taking into account the issues above [17]. To do so, I-Move partners have agreed on high quality standardised protocols allowing the pooling of the data at European level. Such an initiative, together with similar ones from other parts of the world e.g. in North America , South America, Australia [15] paves the way for providing IVE data to complement virological data, as basis for the decision-making process for the next season vaccine composition, at the WHO annual February meeting [18].

The new requirement from the European Medicines Agency (EMA) asking influenza vaccines market authorisation holders to provide annual brand-specific effectiveness data should bring more resources into the IVE studies [19]. This should result in more powered studies but requires, as a prerequisite, the set up of new mechanisms for public-private partnership in the sensitive area of monitoring and evaluation of immunisation programmes and related vaccines, that are acceptable to both sides. Several initiatives, including the Innovative Medicines Initiative (IMI) Advance project, are currently working on this issue [20]. More powered IVE studies conducted specifically in elderly should also be undertaken in the near future through the I-MOVE + project currently under preparation.

However, despite those recent or soon to be expected improvements, unsolved challenges persist, in case of a mismatch. IVE estimates cannot always be obtained before the start of the epidemic in countries hit first and breakdown by virus (sub-)type or lineage is not always possible in case of mixed circulation of influenza viruses. Furthermore, it should be emphasised that extrapolation of IVE determined in a given context to other regions or settings is not always possible. Indeed, as mentioned above, differences in type of vaccine use, target populations for vaccination, pre-existing immunity resulting from previous circulation of influenza viruses, as well as the level of predominance of the drifted variants among circulating viruses will have an impact on IVE. However, the availability of interim assessments of IVE from other parts of the world and also from a European country, as presented in this issue for the UK, at a time where the influenza epidemic is still rising in most European countries, has proven useful in allowing national authorities, in line with the ECDC risk assessment, to issue recommendations for both health professionals and the lay public [5,21]. These mainly concern the strengthening of infection control measures and the early use of influenza antiviral medication for persons at higher risk for serious complications, either as post-exposure prophylaxis or treatment.

Although in the case of a mismatch reduced vaccine effectiveness can be anticipated towards the drifted variant, vaccination should still be recommended also for the ongoing season. Indeed, it will still provide protection towards the other viruses that match the vaccine strain. Despite the fact that in the older and more vulnerable population, IVE was very low as reported from Canada by McNeil et al. [4] in hospitalised adults presenting with acute respiratory illness, overall some cross-protection towards the drifted variant can be anticipated, in the sense that even if it does not prevent infection per se it could contribute to reduce disease severity leading to complications or even death [21,22].

Evidently, instead of a better measurement of low effectiveness a better vaccine is needed. This would mean, a more effective vaccine for all age groups, affording broad cross-protection within each sub-type or lineage of seasonal influenza viruses, thus allowing to avoid the need for annual vaccination and update of the vaccine composition. Of course, a universal vaccine covering all influenza A virus subtypes and protecting from potential pandemic strains would be ideal [23].

Conflicts of interest

Authors' contributions

SW and DLB jointly drafted the manuscript and both approved the final version.

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