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CURRENT OPINION

Influenza Vaccine Effectiveness and Progress Towards a Universal Influenza Vaccine

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Abstract

At various times in recent decades, surges have occurred in optimism about the potential for universal influenza vaccines that provide strong, broad, and long-lasting protection and could substantially reduce the disease burden associated with seasonal influenza epidemics as well as the threat posed by pandemic influenza. Each year more than 500 million doses of seasonal influenza vaccine are administered around the world, with most doses being egg-grown inactivated subunit or split-virion vaccines. These vaccines tend to have moderate effectiveness against medically attended influenza for influenza A(H1N1) and influenza B, and somewhat lower for influenza A(H3N2) where differences between vaccine strains and circulating strains can occur more frequently due to antigenic drift and egg adaptations in the vaccine strains. Several enhanced influenza vaccine platforms have been developed including cell-grown antigen, the inclusion of adjuvants, or higher antigen doses, to improve immunogenicity and protection. During the COVID-19 pandemic there was unprecedented speed in development and roll-out of relatively new vaccine platforms, including mRNA vaccines and viral vector vaccines. These new platforms present opportunities to improve protection for influenza beyond existing products. Other approaches continue to be explored. Incremental improvements in influenza vaccine performance should be achievable in the short to medium term.

Key Points

There are encouraging incremental improvements in existing influenza vaccines.

Universal influenza vaccines remain a long-term goal of influenza vaccine research.

Vaccine approaches that focus on conserved viral components have the potential to provide broader and more durable protection and therefore merit more attention.

1 Introduction

Universal influenza vaccines represent a "holy grail" for influenza research [1, 2]. In the following sections, we review the historical developments in influenza vaccines, and evaluations of their current effectiveness. We examine laboratory measures of influenza vaccine performance, and their correlation with protection. Finally, we review recent developments in vaccine technologies, including advances made during the COVID-19 pandemic, and discuss the implications for universal influenza vaccines.

2 Influenza Vaccine Development

Following the 1918 influenza pandemic (the "Spanish flu"), the post-pandemic A(H1N1) influenza strain was the only circulating strain [3]. The first experimental influenza vaccines were developed in the late 1930s [4], during which Thomas Francis Jr. and Jonas Salk, who later developed the polio vaccine, created an inactivated (killed) influenza A vaccine [5, 6]. This early inactivated whole virus vaccine was tested in the military during World War II [6]. By 1945, the first bivalent influenza vaccine, including influenza B,

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was licensed for use in the USA [7]. In 1947 the failure of an influenza vaccine, which had been effective in 1943/44 and 1944/45, led to improved understanding of antigenic drift in circulating influenza viruses and the importance of updating vaccine strains [8]. The WHO established the Global Influenza Surveillance and Response System (GISRS) in 1952 to monitor influenza activity and identify circulating strains [9]. This network of laboratories and research centers plays a crucial role in the annual selection of influenza strains for the vaccine. In the 1960s two new formulations of inactivated influenza vaccines were created and tested: split and subunit vaccines. Split vaccines contain whole viruses that have been disrupted by a detergent or ether. Subunit vaccines are further purified to remove internal genes, retaining the hemagglutinin and neuraminidase surface proteins. In the late 1960s, split vaccines were approved for use in the USA after clinical trials showed that they were less reactogenic than the inactivated whole virus vaccines [10].

The earliest vaccines developed for influenza were actually live attenuated vaccines, not inactivated vaccines, developed in the 1930s by passaging virus in mice and ferrets [11], although live attenuated vaccines were not licensed for commercial use until 2003 in the USA [7]. Live attenuated influenza vaccines have been used since the 1950s in Russia [12].

As with many other vaccines, standard influenza vaccines contain no adjuvants. However, in recent years, several approaches have been developed to improve influenza vaccines, and one approach is to include an adjuvant to stimulate a stronger immune response to the influenza antigen. The MF59-adjuvanted vaccine has been licensed for use in older adults since 1997 [13], and a monovalent AS03-adjuvanted A(H1N1)pdm09 vaccine was administered to more than 4 million children during the 2009/10 influenza pandemic [14], and to millions of adults, with more than 30 million persons in receipt of the vaccine (Pandemrix®) in Europe alone [15]. Another approach is to increase the antigen content, and a "high-dose" vaccine with four times as much antigen has been approved for use in older adults since 2009 [16]. More recent approaches include using cell-grown or recombinant strains to improve vaccine match [17, 18]. These enhanced influenza vaccines are able to provide improved protection against influenza in older adults [19].

3 An overview of approaches to estimating seasonal influenza vaccine effectiveness (VE)

The appropriate evaluation of effects of health interventions relies on well-designed and properly conducted large randomized controlled trials to balance measured and unmeasured characteristics between intervention and control groups to be able to establish that any observed effects are due to the intervention (causality) [20]. While randomized controlled trials may be feasible for investigations of potential effects of newly developed health interventions and in comparison of active interventions, once the benefits of an intervention are established and the intervention has been approved for use, the appropriateness, and therefore feasibility of trials with a placebo-control group becomes more difficult particularly in the context of universal recommendation from the WHO that all individuals aged ≥6 months should receive an annual influenza vaccination. New influenza vaccines may need to be trialed against existing vaccines, rather than against placebo groups. As such, post-licensure evaluations of effects of a health intervention such as the influenza vaccine are typically via observational (non-randomized) studies of VE. These are often done in settings with established influenza surveillance and vaccination programs. A range of study designs have been used to estimate influenza VE.

Seasonal influenza VE is assessed against varied health outcomes that are broadly based on influenza virus infection and severity (whether asymptomatic, mild/moderately symptomatic, or severe with hospitalization and/or mortality) that may be preventable by vaccination. The outcome against which influenza VE is assessed mostly depends on the outcome that is evaluable with the least bias and that is of importance to public health management and policy decision-making in a population [21]. Ideally, considerations should be made for laboratory-confirmation of influenza virus infection using a gold standard laboratory test such as the reverse transcriptase polymerase chain reaction (rt-PCR) [22]. Non-specific outcomes which may be due to other respiratory pathogens against which the influenza vaccine would not be expected to confer protection; for example, influenza-like illness (ILI) or acute respiratory infection (ARI) clinical syndrome, pneumonia, and all-cause mortality are no longer studied because of potential biases [23]. Irrespective of the outcome of interest, the WHO suggests three study types for estimating seasonal influenza VE [21]. These are the traditional cohort and case-control study types, and a special study type, the test-negative design (TND), which has similarities to a case-control study. In addition, but only in specific circumstances, a fourth study type, the screening method, could also be utilized.

In the cohort study, a clearly defined cohort is identified and separated into two groups based on influenza vaccination status, and then, within each group, those with an outcome of interest are identified and a confounder-adjusted risk ratio of the outcome is estimated by comparing the risk of outcome in the vaccinated relative to the unvaccinated groups. Vaccine effectiveness is then estimated as one minus the estimated adjusted relative risk, multiplied

by 100 %. On the other hand, in a case-control study, individuals with an outcome of interest (cases) are first identified and the odds of influenza vaccination amongst them is determined and compared with the odds of vaccination in a control group of individuals from the same population who do not have the outcome. The confounder-adjusted ratio of the odds (odds ratio [OR]) is calculated, and VE is then estimated as one minus the estimated adjusted OR multiplied by 100 %. While the cohort study is generally more intuitive and the results simpler and easier to interpret/communicate [21], the case-control study tends to be more cost effective and easier to implement [24–26] and, unlike the cohort study, the precision of VE estimates is less affected by the number of participants, and rarity of an outcome [21]. However, appropriate selection of the control group in a case-control study can be challenging, and selection bias can seriously affect the validity of VE estimates [27].

While a retrospective cohort study is relatively fast and inexpensive, a prospective cohort study takes longer, is more expensive, and can require a large number of participants to detect a statistically significant effect of a vaccine [21, 28]. Further, participants in a prospective cohort study are recruited with their vaccination status (vaccinated and unvaccinated) determined from the beginning of a season and participants are then followed up for an outcome [29], whereas most cohort studies of influenza VE are retrospective with both vaccination and outcome statuses determined at study commencement [30–34]. Determination of vaccination status independent of outcome (blinded determination) in a retrospective cohort study is often difficult to achieve, thus, presenting increased potential for misclassification bias [35, 36]. On the other hand, a case-control study can only be conducted retrospectively with grouping of participants based on already known outcome status (cases and controls) before vaccination status is also determined retrospectively. One of the major problems with this study type is identification of persons who represent the exposure distribution in the same population from which the individuals with a study outcome (cases) are derived (appropriate controls), in order to limit selection bias [37]. Another potential issue with this study type is misclassification of vaccination status, especially when ascertainment of vaccination status is unblinded to an outcome and could therefore easily relate to outcome status; thus, the potential for differential misclassification by outcome status [36]. Even so, for both cohort and case-control study types, outcome definition may differ between studies, and this may present difficulties in comparing estimates of VE; for example, the outcome in some studies may be ILI, and in others, symptomatic laboratory-confirmed influenza. Even with laboratory confirmation, laboratory tests may differ between studies, which further complicates comparisons of VE estimates between studies.

To address some of these issues, particularly with identification of appropriate controls for cases, in 2005, Skowronski and colleagues from British Columbia, Canada described the first implementation of the TND for influenza VE [38], although earlier evaluations of other vaccines such as the pneumococcal vaccine, had been based on a methodologically similar approach [39–41]. Since then, the TND has been embedded in influenza surveillance programs in other locations for influenza VE estimations [42, 43], and is also being utilized in evaluations of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines [44, 45], due to its simplicity (ease of implementation), adaptability, and low cost compared with the cohort or case-control study types [46].

In the TND study of influenza VE, individuals presenting to a clinic or hospital are enrolled if they meet a clearly defined symptom set. A respiratory specimen is collected and tested for influenza, and those testing positive for influenza are regarded as cases and those whose specimens test negative are the controls [42, 47, 48]. Ideally, confirmatory testing should be by using RT-PCR or another highly sensitive and specific test [49, 50]. Influenza vaccination status of both the cases and controls are determined from medical records and/or self-report, with the use of medical records or a vaccine registry preferable to limit recall and social desirability biases associated with self-reported vaccination [51, 52]. The odds of vaccination among the cases and the controls are determined and the confounder-adjusted ratio of the odds is calculated. Vaccine effectiveness is then estimated as one minus the estimated adjusted OR, multiplied by 100%.

The major criteria for participation in a TND study of influenza VE is a person seeking medical attention for ILI or ARI. As such, all participants are health care seekers for the same symptom set, although the assumption is that participants' illnesses are of similar severity. When viewed from a case-control perspective, considering the similarity of the TND with the case-control study type, the TND satisfies the major principle that underpins the validity of a case-control study since cases and controls derive from the same group of health care-seeking individuals in the population [43, 53, 54]. This is an inherent strength in the TND as similarity between cases and controls is optimized, thus minimizing selection bias and mitigating confounding by health care-seeking behavior [47]. Nevertheless, confounding by health care-seeking behavior may persist if substantial variation in symptom severity results in differential health care-seeking behavior with respect to influenza vaccination status [55]. Other approaches have also been suggested to optimize the performance of the TND, including the use of alternative control group(s) [56], and double negative controls for detecting confounding [57].

Apart from the cohort and case-control study types, and the TND study, which is currently the most commonly used

study design for VE evaluation, the screening method has also been suggested for evaluation of VE [58, 59]. Although of a lower methodological quality, and therefore, VE estimates from it may not be as reliable compared with the cohort, case-control, and TND study types, this method has previously been used for evaluations of the *Haemophilus influenzae* type b [60], pneumococcal [61], mumps [62], and pertussis [63] vaccines. In the screening method, three parameters are required for VE estimation: the number of cases and influenza vaccine uptake proportion amongst them, and the influenza vaccine uptake proportion in the population from which the cases are derived [61]. Influenza vaccination among cases and the reference population are then compared, and VE is estimated by subtracting vaccination proportion among cases from vaccination proportion in the reference population and then divided by the vaccination proportion in the reference population multiplied by one minus vaccination proportion among cases, and the result multiplied by 100%. This can be expressed as [(PVP – PVC)/(PVP ×(1 – PVC))] × 100%, where PVP = vaccination proportion in the reference population, and PVC = vaccination proportion among cases [58, 64]. As the name implies, the screening method is a first-step evaluation (a screen) of VE that is helpful in monitoring of VE over time assuming any biases remain constant, and in determining if further and more extensive evaluations are required [64]. It is a less resource-intensive and a rapid method of VE estimation, mostly utilized for quick decision-making and forecasting [59, 64].

That said, irrespective of study type for VE estimation, potential confounders such as age, sex, chronic medical conditions and other high-risk conditions, calendar time, and prior seasonal influenza vaccination and infection must be addressed considering that all of these approaches are prone to confounding [48, 65]. Even so, irrespective of the study type, residual confounding would most certainly remain due to poorly measured, unmeasured, and unknown and therefore unadjusted confounders [47].

4 Effectiveness of Current Influenza Vaccines

A host of factors influence influenza VE, including differences in circulating influenza virus strains by season and geographical region (Northern vs Southern hemisphere), differences in population demography, and different levels of population immunity against influenza from previous influenza vaccinations and infections [66]. In addition, immune responses to vaccination differ across individuals [67, 68], and it has been suggested that repeated vaccination likely affects immune response, and therefore, may attenuate VE [69, 70]. As such, VE evaluations only provide place-, season-, time-, and population-specific estimates of effectiveness. Even so, VE estimations should be vaccine-specific (live-attenuated/inactivated and number of virus strains), influenza type/subtype-specific, i.e., against A(H1N1), A(H3N2), and influenza B, and setting-specific, for example, outpatient and in-patient settings. As previously mentioned, VE estimations are typically made against specific health outcomes that are preventable by influenza vaccination. Vaccine effectiveness estimates may also vary by study characteristics (methods of estimation) [71, 72]. Herein, we summarize the findings from recent evidence reviews of estimates of VE of current influenza vaccines against laboratory-confirmed influenza virus infection with medically attended acute respiratory illness, focusing on estimates from TND studies.

While there are several published evidence reviews of influenza VE, most pooled evidence from any study type had varied intervention comparisons, populations, and outcomes. Within the past decade, a few published systematic reviews with meta-analysis of evidence from TND studies demonstrated variable effectiveness of the current influenza vaccines between influenza virus types/subtypes, and across geographical regions, age groups, and levels of influenza vaccine antigenic similarity with circulating influenza virus strains [66, 73–75].

A recent most comprehensive review of the published papers showed that generally VE was moderate in the Southern hemisphere and low in the Northern hemisphere based on VE estimates in outpatient settings from after the 2009/10 influenza pandemic to the 2019/20 influenza season: 54% (48–59%) and 37% (32–42%), respectively [66]. Vaccine effectiveness against influenza virus types/subtypes was slightly higher in the Southern hemisphere compared with the Northern hemisphere: 64% (53–72%) versus 56% (51–60%) for A(H1N1)pdm09, 42% (31–51) versus 22% (15–29%) for A(H3N2), and 56% (45–64%) versus 42% (34–49%) for influenza B, although estimates against A(H1N1)pdm09 and influenza B in the Northern hemisphere were considerably higher and moderate when compared with the overall estimate from the Northern hemisphere [66]. These findings were similar to the findings based on seasonal influenza VE estimates from before the 2009/10 pandemic up to the 2014/15 influenza season, including an estimated VE of 67% (29–85) for the A(H1N1) that was in circulation before the pandemic [73]. Vaccine effectiveness tended to be highest against A(H1N1)pdm09, higher against influenza B, and lowest against A(H3N2) in both the Southern and Northern hemispheres and across continents [66, 73]. Vaccine effectiveness was significantly higher when vaccines were antigenically more similar compared with less similar to the circulating virus strains: 49% (45–53%) versus 9% (−28–8%) for all influenza, 36% (31–41%) versus 1% (−15–14%%) for A(H3N2), and 51%% (47–55%%) versus

20%% (−9–41%%) for influenza B [66]. There were no identified antigenically dissimilar vaccines against A(H1N1) pdm09, although VE was reportedly higher for antigenically similar versus partially similar vaccines and estimates against almost all influenza types/subtypes declined with older age in the Northern hemisphere [66].

Several enhanced seasonal influenza vaccines were developed in the past decade and these vaccines have been approved for use in many jurisdictions. They include the high-dose inactivated vaccine by Sanofi Pasteur; the MF59-adjuvanted vaccine by Seqirus; the cell-based inactivated vaccine by Seqirus; and the recombinant HA vaccine by Sanofi Pasteur [76, 77]. Each of these was found to have improved performance over standard inactivated vaccines in trials and in immunogenicity assessments [18, 19, 78–81]. However, there is a paucity of published real-world evaluations of effectiveness of these vaccines compared with no vaccination against laboratory-confirmed influenza, as published evaluations tended to compare them mostly with the traditional influenza vaccines [77]. There have been a few published systematic reviews of efficacy/effectiveness and/or safety of some of the enhanced vaccines [17, 82–84]. Based on a recent comprehensive systematic review that compared the enhanced vaccines with the traditional vaccines in subjects aged ≥18 years irrespective of health status and clinical setting (whether outpatient or in-patient), VE for the high-dose vaccines against laboratory-confirmed influenza outcomes irrespective of influenza strain ranged from −9% (−158–54%) to 19% (−27–48%) [77]. For the MF59-adjuvanted vaccine, seasonal influenza VE against laboratory-confirmed influenza irrespective of influenza strain ranged between −30% (−146–31%) and 88% (51–100%) [77]. For the cell-based vaccine, VE against laboratory-confirmed influenza was −5.8% (−36.1–17.7%) for influenza A, and 21.4% (−7.3–42.4%) for influenza B [77]. For the recombinant vaccine, VE against laboratory-confirmed influenza outcomes irrespective of virus strain ranged between 3% (−31–28%) and 19% (−27–48%) [77]. Overall, the enhanced vaccines generally provide a small to moderate improvement in protection compared to standard inactivated vaccines.

5 Comparison of Influenza Vaccine Effectiveness Estimates with Clinical Trial Immunogenicity Results

Whereas influenza VE estimates provide a retrospective assessment of how well a vaccine has performed, vaccine immunogenicity data can be used to predict the future performance of a vaccine. Influenza vaccines are designed to elicit immunity predominantly against the hemagglutinin surface protein, which plays a critical role in allowing the virus to bind to host cells. The hemagglutination inhibition (HAI) assay measures the level of antibodies in a serum sample that can prevent cell binding, reflecting the level of immunity to influenza [85]. Regulatory authorities use HAI data to evaluate influenza vaccine performance, and new inactivated influenza vaccines can be licensed based on immunogenicity criteria, with the HAI assay, rather than efficacy data [86]. The HAI assay is an established "correlate of protection" for influenza vaccines, because it has been shown consistently that achieving higher antibody levels on the HAI assay after receipt of influenza vaccination is correlated with having a greater level of protection against influenza virus infection [87].

While antibody levels measured by the HAI assay capture the majority of protection conferred by influenza vaccines [88], some individuals with high antibody levels measured by the HAI assay can still be infected, while other individuals with low levels seem to be protected [89]. It is likely that other immune mechanisms are responsible for some of the protection conferred by inactivated influenza vaccines [90, 91]. This could include cell-mediated immune processes [92], or antibodies to other parts of the virus [93]. Antibodies can also mediate antibody-dependent cellular cytotoxicity, which occurs when antibodies generated after vaccination bind to viral antigens presented on the surface of infected cells. This binding marks these cells for recognition by natural killer cells and other immune cells, leading to the destruction of the infected cells.

Cellular immunity plays a particularly important role in the protection provided by live attenuated vaccines [94], and some newer vaccine platforms [95]. The CD8+ cytotoxic T lymphocytes stimulated by vaccination can recognize and kill infected cells, reducing viral replication and limiting the spread of the virus within the host, attenuating disease severity. These cellular responses should also provide broader protection since they target conserved viral proteins [96]. The CD4+ helper T cells help to activate B cells to produce antibodies and assist in the development and function of cytotoxic T lymphocytes. They also produce cytokines that enhance the immune response, leading to more effective clearance of an infection. Enhanced influenza vaccines have demonstrated improved cellular responses and antibody-dependent cellular cytotoxicity than standard-dose vaccines [97].

Influenza vaccines, particularly those administered intranasally, induce mucosal immunity, which is the first line of defense against respiratory viruses like the influenza virus [98]. A key component of this mucosal immune response is the production of IgA antibodies, which are secreted onto the mucosal surfaces of the respiratory tract [99]. These IgA antibodies can prevent influenza virus from attaching to and entering epithelial cells, effectively stopping the infection before it can take hold. Parenteral inactivated influenza

vaccines tend not to stimulate a substantial mucosal antibody response [100].

For enhanced influenza vaccines, it is presumed that antibody levels measured by the HAI assay also correlate with protection against infection, but it has not been established whether the relative importance of HAI is the same. For example, if an individual receives a boost in their HAI titer from 10 to 80 following standard inactivated vaccine, would the level of protection be the same as if their HAI titer was boosted from 10 to 80 by a high-dose vaccine or an adjuvanted vaccine? Perhaps the enhanced vaccines might be able to confer a greater degree of broader protection via other immune mechanisms such as cellular immunity, in addition to the level of protection conferred by boosting the HAI titer from 10 to 80. It has been recognized that enhanced vaccines stimulate generally higher antibody levels than standard influenza vaccines, and provide improved protection, but it has not been shown whether their improved protection is entirely due to the improvement in HAI titers or whether there are additional benefits via other immune mechanisms. A correlate of protection has not been established for live attenuated influenza vaccines [101]. All of these areas are important directions for future research [102].

6 Current Progress on the Development of a Universal Influenza Vaccine

In 2018 the US National Institute of Allergy and Infectious Diseases outlined a plan for development of a universal influenza vaccine [103]. Their stated objectives were to develop a vaccine that could provide at least 75% protection against symptomatic influenza, provide protection lasting more than one year, and be suitable for all age groups [103]. So far, no candidate influenza vaccine has achieved even one of these stated goals. One approach described in this strategy was via improving our understanding of immune correlates of protection, i.e., the protective immune mechanisms triggered by natural influenza virus infection or vaccination [92, 102, 104]. As explained above, the HAI titer is an established correlate of protection for influenza vaccines, but additional correlates might suggest additional vaccine targets. For example, the correlation of anti-neuraminidase antibody with protection [105], suggests that inclusion of a higher amount of neuraminidase in influenza vaccines might improve their performance [106].

Another important fundamental area of research is how previous exposures, whether infections or vaccinations, influence immune responses to new exposures. This is often termed "imprinting" [107, 108]. Optimizing the early-life imprint, for example, by vaccinating infants with a cell-grown vaccine, might improve immunity in the longer term [109]. Repeated administration of influenza vaccines can result in reduced immune responses [70, 110], and identifying the mechanisms underlying this phenomenon could also aid universal vaccine development.

During the COVID-19 pandemic, development of SARS-CoV-2 vaccines occurred at an unprecedented pace. Global roll-out of approved vaccines began within a year of the start of the pandemic, following expedited clinical trials. Several platforms were used for SARS-CoV-2 vaccines, including mRNA vaccines, viral vector vaccines, and inactivated vaccines. This was the first time mRNA and viral vector vaccines had been used on such a large scale. Placebo-controlled Phase III trials reported very high levels of protection against symptomatic infection, against a low level of population immunity and specifically a low level of immunity in placebo recipients. As time progressed, SARS-CoV-2 variants emerged, and population immunity increased, resulting in reduced VE for SARS-CoV-2 vaccines [111]. Booster doses of SARS-CoV-2 vaccines are now recommended annually, with regular strain updates similar to influenza vaccines.

Vaccine platforms used in the COVID-19 pandemic may also be applied for influenza vaccines. Moderna and Sanofi Pasteur are developing influenza mRNA vaccines [112–114]. Preliminary indications are that these vaccines may stimulate stronger cellular responses but provide relatively similar levels of clinical protection to other enhanced influenza vaccines, but with increased reactogenicity, limiting potential value. Further improvements of influenza mRNA vaccines could include identifying formulations with reduced reactogenicity or including additional viral antigens such as neuraminidase to improve immunogenicity and protection. One interesting idea is to add numerous strains into an mRNA vaccine, aiming to provide much broader protection against potential future strains [115]. Several viral vector influenza vaccines have also been tested [116–118], with the VXA-A1.1 vaccine currently in Phase II [119].

Prior to the COVID-19 pandemic, a promising approach for universal influenza vaccination involved stimulating antibodies against conserved regions of the hemagglutinin protein. This could be achieved by vaccinating with chimeric strains of seasonal influenza viruses in which the immunodominant head region of the hemagglutinin is replaced with a non-human hemagglutinin, while the stalk of the hemagglutinin is retained [120–122]. This approach boosts antibodies to a conserved region of the virus that has been linked with protection [123]. These vaccines remain in clinical trials.

Vaccine approaches that focus on conserved viral components such as nucleoprotein (NP) merit increased attention due to their potential to provide broader and more durable protection [124]. Unlike the surface proteins targeted by most current vaccines, which are prone to rapid mutation and variability among viral strains, the nucleoprotein and

other internal viral proteins are highly conserved across different strains of a virus [125]. This means that vaccines targeting NP can potentially offer cross-protection against multiple strains, including those that may not be well covered by existing vaccines. The protection conferred by such vaccines is likely to be largely mediated by the cellular immune response, particularly through the activation of CD4 and CD8 T cells [126]. As a consequence, these vaccines might not be expected to prevent initial infection but should significantly modify the course of the disease by limiting viral replication and reducing the impact of infection. Focusing on conserved viral components like the nucleoprotein could also provide more resilience against viral mutations and the emergence of new variants [125].

Another promising direction is to improve live attenuated influenza vaccines [101]. SARS-CoV-2 vaccines sprayed into the nose or inhaled via the mouth are being investigated in clinical trials, including adenovirus-vector vaccines [127]. Similar approaches could be investigated for influenza vaccines [128]. Another option to provide incremental improvements in current influenza vaccines would be to combine two or more of the enhanced approaches described earlier; for example, adding adjuvants to a cell-grown vaccine, or using a higher cell-grown antigen dose. New adjuvants are also being explored [129]. Intradermal administration of influenza vaccines can improve immunogenicity but this approach has not gained traction [130]. Finally, investigating the use of other viral components such as nucleoprotein could provide broader protection [131].

7 Conclusions

Universal influenza vaccines remain a long-term goal of influenza vaccine research. At present, several approaches being explored will likely provide incremental benefits over existing vaccines, such as adding adjuvants to cell-based vaccines, and using mRNA technology or other new platforms. It currently appears unlikely that in the next decade we will be able to introduce a truly universal vaccine, which would provide a higher level of protection against symptomatic influenza across multiple years [103]. Nevertheless, incremental improvements in existing vaccines – developed via universal influenza vaccine research – will surely reduce global influenza deaths and hospitalizations.

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Data availability Not applicable.

Declarations

Potential Conflicts of Interest B.J.C. has been a consultant for AstraZeneca, Fosun Pharma, GlaxoSmithKline, Haleon, Moderna, Novavax, Pfizer, Roche, and Sanofi Pasteur. G.N.O. reports no potential conflicts of interest.

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