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New Wisdom to Defy an Old Enemy: Summary from a scientific symposium at the 4th Influenza Vaccines for the World (IVW) 2012 Congress, 11 October, Valencia, Spain

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ABSTRACT

Both seasonal and pandemic influenza cause considerable morbidity and mortality globally. In addition, the ongoing threat of new, unpredictable influenza pandemics from emerging variant strains cannot be underestimated. Recently bioCSL (previously known as CSL Biotherapies) sponsored a symposium 'New Wisdom to Defy an Old Enemy' at the 4th Influenza Vaccines for the World Congress in Valencia, Spain. This symposium brought together a renowned faculty of experts to discuss lessons from past experience, novel influenza vaccine developments, and new methods to increase vaccine acceptance and coverage.

Specific topics reviewed and discussed included new vaccine development efforts focused on improving efficacy via alternative administration routes, dose modifications, improved adjuvants, and the use of master donor viruses. Improved safety was also discussed, particularly the new finding of an excess of febrile reactions isolated to children who received the 2010 Southern Hemisphere (SH) trivalent inactivated influenza vaccine (TIV). Significant work has been done to both identify the cause and minimize the risk of febrile reactions in children.

Other novel prophylactic and therapeutic advances were discussed including immunotherapy. Standard IVIg and hIVIg have been used in ferret studies and human case reports with promising results. New adjuvants, such as ISCOMATRIX™ adjuvant, were noted to provide single-dose, prolonged protection with seasonal vaccine after lethal H5N1 virus challenge in a ferret model of human influenza disease. The data suggest that adjuvanted seasonal influenza vaccines may provide broader protection than unadjuvanted vaccines. The use of an antigen-formulated vaccine to induce broad protection between pandemics that could bridge the gap between pandemic declaration and the production of a homologous vaccine was also discussed.

Abbreviations: $AlPO_4$, aluminum phosphate; APC, antigen-presenting cell; AUC, area under the curve; BPL, Beta-Propiolactone; CI, confidence interval; FDA, US Food and Drug Administration; HAI, hemagglutination inhibition; hIVIg, hyperimmune intravenous immunoglobulin; HPV, human papillomavirus; IIV, inactivated influenza vaccine; IRF1, interferon regulatory factor 1; IVIg, intravenous immunoglobulin; IVW, Influenza Vaccines for the World; LAIV, live attenuated influenza vaccine; MPHs, monovalent pool harvests; MTHFR, methylenetetrahydrofolate reductase; PCR, polymerase chain reaction; SH, Southern Hemisphere; SLAM, signaling lymphocyte activation molecule; SNP, single-nucleotide polymorphism; TDOC, taurodeoxycholate; TGA, Therapeutic Goods Administration; TIV, trivalent influenza vaccine; VAERS, Vaccine Adverse Event Reporting System; WA, Western Australia.

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Finally, despite the availability of effective vaccines, most current efforts to increase influenza vaccine coverage rates to higher levels (i.e., above 70–80%) have been ineffective in highly developed countries where the vaccine is used, hindered by the public's skepticism towards vaccines in general. New educational and social media methods to increase vaccine acceptance and coverage were discussed. While the first priority should be the development of improved influenza vaccines, a particular focus on the aging global population is critical. It is also important to draw lessons from other academic disciplines that can help to inform vaccine education programs, policy, and communication. By tailoring communications and patient education using an understanding of cognitive bias and the model of preferred cognitive styles, the likelihood of effecting desirable health decisions can be maximized, leading to improved vaccine coverage and control of influenza and other vaccine-preventable diseases.

1. Introduction

Experience over the past century has demonstrated that the threat of new influenza pandemics from emerging variant strains is persistent and poses a serious threat to public health [1]. The timing and characteristics of pandemics are highly unpredictable, with different age groups affected depending on the influenza strain and history of previous exposures [2]. In recent years, new variant influenza strains have caused clinical illness in humans through bird-to-human or pig-to-human transmission [2–5]. Although none of these variants has yet been associated with large-scale human-to-human transmission, their existence highlights the need for high-quality virologic surveillance in poultry and pigs, and in persons working with these animals, as well as in the general population.

Current influenza vaccines have an excellent safety profile [6]; however, they are, on average, only moderately effective [7]. New vaccines that exhibit higher levels of protection and require less frequent administration are needed. Current vaccine development is focused on improving immunogenicity and efficacy via alternative administration routes, higher antigen doses, improved adjuvants, and the use of alternative master donor viruses for live, attenuated vaccines [8,9]. Strategies in which different vaccine approaches are used in specific sub-populations, or individualized vaccinology [10], may help to optimize the balance between benefit and risk. The developing fields of systems biology [11], vaccinomics, and predictive vaccinology may aid in the prediction of an individual's response to a vaccine, both in terms of efficacy and adverse events, and will allow an increasingly individualized vaccine approach [10].

A particular area of vaccine development for bioCSL is to minimize the risks of febrile reactions in the pediatric population, because their 2010 Southern Hemisphere (SH) Trivalent Influenza Vaccine (TIV) was associated with increased reports of fever-related convulsions in younger children compared to previous seasons [12]. A comprehensive 2-year investigation, monitored by the Therapeutic Goods Administration (TGA) and the US Food and Drug Administration (FDA), has revealed preliminary conclusions as to the likely contributing factors. Information to date suggests that bioCSL's standard method of manufacture retains more virus components than those of other manufacturers, and that the particular characteristics of the 2010 virus components contributed to an excessive immune response in some young children, triggering increased fever and fever-related convulsions. Confirmation of the contributing component(s) and the development of surrogate assays will assist in altering the formulation of bioCSL's inactivated influenza vaccines (IIVs) to minimize the future incidence of febrile reactions in the pediatric population.

Among other novel research ideas, passive immunotherapy is an emerging method for preventing and treating influenza and may become an effective therapy for both seasonal and pandemic settings. A number of human and animal studies have reported the prophylactic and therapeutic efficacy of convalescent serum/plasma, IVIg, and hyperimmune products in cases of influenza infections resistant to antiviral therapy, and rescue therapy during pandemics [13–18]. These products contain cross-reactive or strain-specific antibodies and immunomodulatory properties and may provide additional protection against secondary bacterial infections [13,19]. Given the limited clinical data, randomized clinical trials are the next essential step to adequately evaluate the safety and efficacy of passive immunotherapy products to prevent and treat severe seasonal and pandemic influenza.

ISCOMATRIX™ adjuvant is a potent immunostimulant that, when combined with the H5N1 vaccine, provides single-dose, prolonged protection after lethal H5N1 virus challenge in a ferret model of human influenza disease [20]. Additional benefits of this adjuvanted vaccine include cross-clade protection, reduced morbidity, decreased viral shedding, and dose sparing for pandemic application. Data obtained in the H5N1 ferret model suggest that seasonal influenza ISCOMATRIX™ adjuvanted vaccines may be able to provide broader protection than unadjuvanted vaccines in both seasonal and pandemic settings. A further major advantage may be that because implementation of a pandemic vaccination program is hampered by the delay between pandemic declaration and the production of a homologous pandemic vaccine [21], the interim use of such vaccines to induce broad protection may help to provide coverage while a homologous vaccine is developed.

Unfortunately, current efforts to increase seasonal influenza vaccine coverage above current levels have been generally inefficient and ineffective [22], hindered by the public's skepticism towards vaccines in general, and the reliance by providers and public health officials on traditional, data-driven vaccine education programs. Although progress in influenza control has been made in recent years, new approaches are required. The first priority should be the development of better influenza vaccines that address issues such as antigenic drift/shift, novel influenza viruses, immune-maturity, immunosenescence, and the need for cold-chain management. With the aging of the global population, efforts and resources should be targeted towards this rapidly growing segment of society. It is also important to draw lessons from other academic disciplines that can help to inform vaccine education, policy, and communication; 21st century transformation teams should include specialists such as behavioral psychologists, cultural anthropologists, and communication experts. Because the claims and activities of anti-vaccine activists have deleterious consequences for public health, as observed with the measles-mumps-rubella vaccine [23,24], it is imperative that we improve public education and produce a persuasive metanarrative for influenza vaccination through innovative, multidisciplinary efforts. New tools, languages, media, and metaphors that acknowledge the spectrum of ways in which different people process information are needed to increase vaccine acceptance and coverage rates. An understanding of the role of cognitive bias and individual preferred cognitive styles is essential for the development of effective patient-centric educational programs and stories/parables to influence vaccine decision making. By tailoring communications and

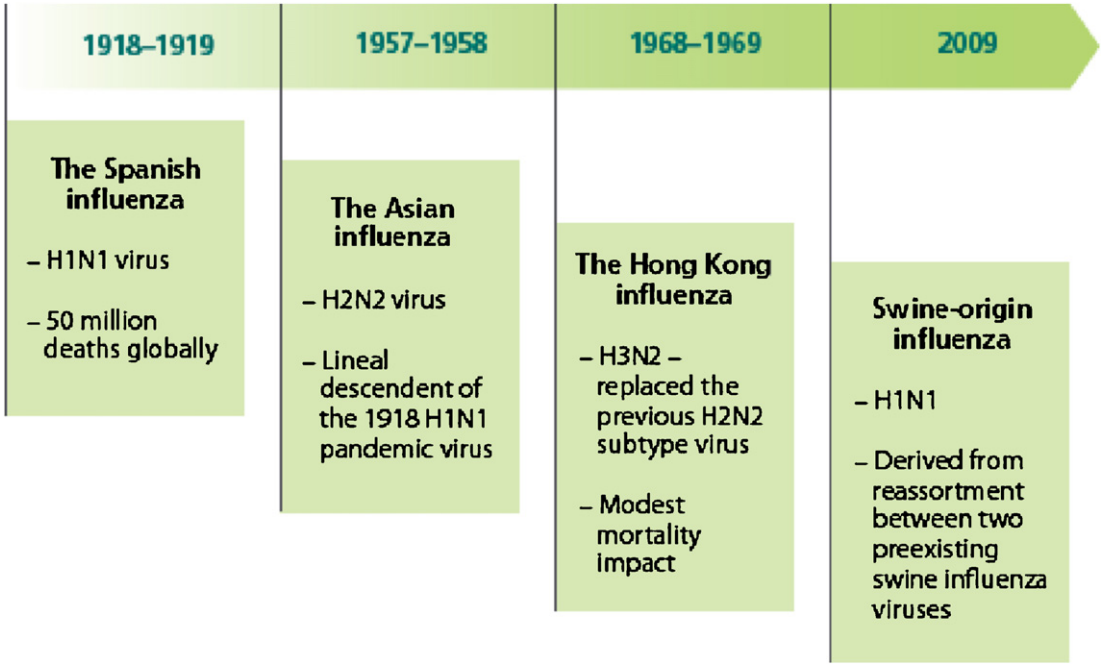

Fig. 1. Past influenza pandemics [1].

interactions to suit individual preferred cognitive decision-making styles, the likelihood of effecting desirable health decisions can be maximized. In the desired state, knowledgeable and educated healthcare providers with a compelling story and parable would lead to improved vaccine coverage and, in turn, to the control of influenza and other vaccine-preventable diseases.

2. Emergence of new variant influenza strains and lessons from the past (Douglas Fleming[2])

2.1. Overview of influenza and influenza-related mortality

A key feature of influenza A viruses is the presence of hemagglutinin and neuraminidase antigens on the outer coating of the virus. The existence of multiple hemagglutinin and neuraminidase antigens gives rise to the possibility of numerous antigen combinations, with different hosts being associated with a distinct antigen combination. Since some species, particularly aquatic birds, can be infected with a wide range of viruses, this creates opportunities for mixing the genetic components of various influenza virus strains [25]. Thus, new and unpredictable influenza viruses are constantly emerging. Although some have low transmission rates, past influenza pandemics have demonstrated that there is an ever-present risk of influenza outbreaks from emergent variant strains. The incidence and nature of influenza pandemics can be highly unpredictable, with differing age groups affected and variable seasonal patterns depending on the influenza strain [2]. This section reviews the influenza pandemics of the last 100 years, together with new variant influenza viruses that have, as yet, shown low human-to-human transmission. Lessons learned from past experiences are also highlighted.

Influenza is known to cause many respiratory illnesses and has a serious impact on hospital admissions, particularly during the winter months [26]. In general, incidence is higher in children and the elderly and, in a study in England and Wales between 1989 and 1999, was associated with an average excess mortality of 12,500 deaths per year [26]. For the period 1999–2009, the estimated annual influenza-related mortality for England and Wales was similar, at approximately 13,400 deaths per year [27]. In the US, the mean number of influenza-related deaths per year for the 1990–1991 through 1998–1999 influenza seasons was 51,203, corresponding to an average rate of 196 deaths per million person-years over the same period. All of these estimates found that >80% of fatalities were in older subjects, and estimates were higher in influenza seasons dominated by influenza A (H3) [28]. Thus, while the incidence of influenza may be declining in some areas [29], it remains a consistent healthcare problem.

2.2. Past influenza pandemics

Over the last century, 4 influenza pandemics have emerged (Fig. 1) [1]. The first of these, the so-called 'Spanish influenza' pandemic, was responsible for an estimated 50 million deaths globally [30]. The etiologic agent was identified as an avian-derived H1N1 virus, a direct antecedent of all currently circulating human influenza A viruses [1]. Unusual epidemiologic features of the Spanish influenza strain included 3 waves of pandemic within 12 months and the observation of a 'W-shaped', age-related mortality curve, with an unexpectedly high rate of mortality in healthy young adults [31].

The Asian influenza pandemic of 1957–1958 was caused by a lineal descendant of the 1918 H1N1 pandemic virus. This strain arose through acquisition of 3 avian-like gene segments, including those encoding neuraminidase and hemagglutinin [1]. The Asian pandemic strain did not display the unusual epidemiologic features that were observed with the 1918 pandemic strain.

The causative agent in the Hong Kong influenza pandemic of 1968–1969 was an H3N2 virus that replaced the previous H2N2 virus. This pandemic strain had a relatively modest mortality impact, which may have been due to accumulated antibodies to the hemagglutinin that was retained from the strain that had been previously circulating in humans [1,32].

In March 2009, a triple-reassortant H1N1 virus that originated in pigs began to infect humans in Mexico, causing serious illness [1]. Interestingly, this virus had a major clinical impact on young,

[2] *Note*: The opinions expressed in this section are solely those of the author.

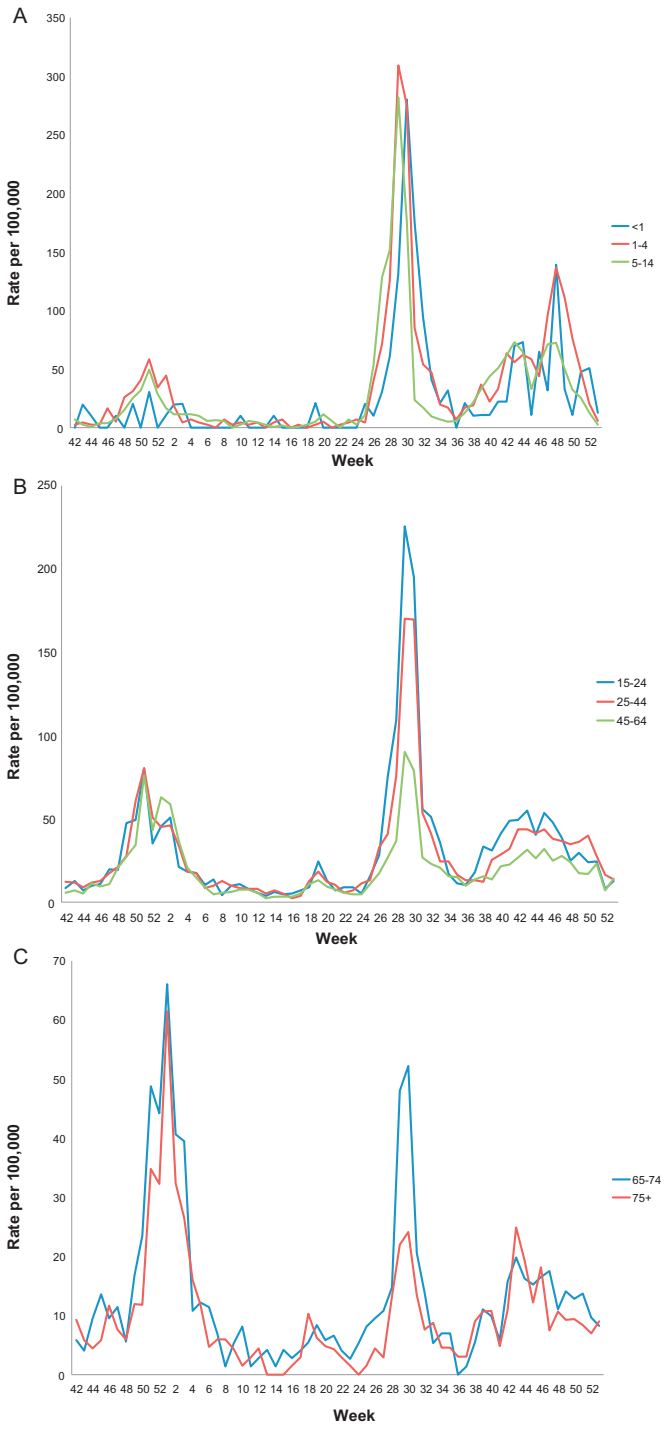

Fig. 2. Incidence of influenza-like illness per 100,000 by age group from Week 42 of 2008 through Week 52 of 2009 in England [2]. (A) Ages 1, 1–4 and 5–14 years; (B) ages 15–24, 25–44 and 45–64 years; and (C) ages 65–74 and ≥75 years. Originally published in *Hum Vaccin Immunother*. 2012 January 1;8(1):138–45 [Epub 2012 January 1]. Fig. 3 Test-negative case–control.

rather than old, people [33]. The virus was identified in April 2009 [3] and the first vaccine became available in October 2009 [34], but it was not available in large quantities until the end of that year, a delay likely to occur again in any future pandemic. In the UK, 2009 saw 2 waves of H1N1 influenza, the first peaking in July and the second in November (Fig. 2) [2]. The high incidence in July was the first time that influenza had been seen in summer over the course of 50 years of surveillance. Furthermore, incidence rates in children and young adults were much higher compared to the active influenza periods of previous years, while rates in older persons over 65 years-of-age were comparatively lower, demonstrating the unpredictable nature of influenza outbreaks [2]. Globally, a total of 18,500 deaths were virologically confirmed as caused by the 2009 pandemic influenza A H1N1 virus between April 2009 and August 2010 [35]. Furthermore, modeling data indicate that the 2009 pandemic virus caused 201,200 respiratory deaths and a further 83,000 cardiovascular deaths, with 80% of these fatalities occurring in subjects aged <65 years [36].

2.3. Lessons learned from reconstruction of the 1918 influenza virus

We know that lessons from past influenza pandemics are important to help us tackle the unpredictable pandemics that may occur in the future. An influenza A (H1N1) virus has been reconstructed from fragments of RNA recovered from the lung tissue of victims of pandemic influenza in 1918 with a view to enhance pandemic preparedness [37]. The virus has enabled researchers to trace the evolution of influenza viruses from 1918 to the present day. Although antigenic links between the 1918 and 1957, 1968, and 2009 pandemic strains were recognized, only the hemagglutinin antigenic composition of the 2009 strain is closely similar to that of the 1918 pandemic strain [38,39]. A virus that is similar to the 1918 strain, and that causes epidemics of swine flu in pigs, has been present in the pig population over the last 90 years, but for unknown reasons, it has not persisted in the human population over the same period [39]. The possibility of viruses disappearing and reappearing several decades later is one of the explanations offered to account for the emergence of an influenza pandemic. Experiments in mice have shown that there is some cross-protection between the 1918 and 2009 pandemic viruses, raising the possibility of incorporating critical hemagglutinin proteins into a new generation of influenza vaccines and indeed the notion of a universal influenza vaccine [38]. Reconstruction of the 1918 influenza virus has also led to a better understanding of the virus and host interactions that made this pandemic influenza such a severe illness and which predisposed victims to secondary bacterial infection [40].

2.4. New variant influenza strains not causing a pandemic

In recent years, the avian influenza H5N1 virus has posed a serious pandemic risk worldwide, with the World Health Organization reporting approximately 600 cases and 350 deaths over the last 10 years [5]. Despite the relatively low number of new cases, the potential for this virus to be modified leading to a new outbreak remains a serious threat [41].

Other new variant influenza strains have caused clinical illness in humans, but these have not been associated with rapid transmission. Since 2002, influenza A subtype H7 viruses have caused more than 100 cases of human infection in Europe and North America [4]. In one instance, an outbreak of H7N7 infection occurred in The Netherlands among 86 workers involved in culling of birds at commercial poultry farms, together with 3 of their family members [42]. A key feature of these subtype H7 infections was the development of conjunctivitis [4,42]. In 2010, H10N7 infection was identified in 7 poultry workers in Australia, representing the first known transmission of a low pathogenicity avian influenza virus to humans [43].

Between 1990 and 2010, swine origin influenza viruses were reported in 27 subjects, of which 21 were triple-reassortant influenza viruses (13 subtype H1N1, 1 subtype H1N2, and 7 subtype H3N2) [44]. H3N2v caused 12 human infections across 5 US states between July and December [44], and a total of 296 human

infections across 10 states between July and September 7, 2012 [45]. In these cases, pig-to-person transmission and person-to-person is suspected but not proven. A new virus variant not previously seen in humans, vH3N2, has been reported as the cause of 3 human influenza infections and contains the pandemic M gene from the H1N1 2009 pandemic virus as well as genetic material from swine-lineage triple-reassortant H3N2 viruses [46]. Close contact with pigs is the clinical common factor in these infections, which highlights the need for coordinated surveillance of human and swine influenza viruses to allow rapid detection of human infections as well as timely identification of new virus variants in swine.

2.5. Factors influencing likelihood of influenza infection and transmission

Numerous factors affect the likelihood of influenza infection and transmission. Viral properties, such as the ambient temperature that favors replication, are important [47]. Receptor-binding properties are also relevant, because influenza viruses need to bind to and enter respiratory epithelial cells in order to replicate and cause illness [48]. The mutations of the influenza virus that are constantly taking place may enhance the likelihood of transmission [49]. The resistance of the host cell, whether derived from innate immunity or from multiple exposure to previous viruses, is also clearly a factor in whether a person acquires influenza [50,51]. Large-scale vaccination programs increase population immunity and reduce the potential spread of influenza viruses, as virus replication and shedding is generally higher in children than in the elderly [52,53]. Finally, influenza virus propagation requires the availability of a susceptible host [54].

2.6. Conclusions

New influenza viruses are constantly emerging, leading to an ever-present risk of a new pandemic virus. The impact of an influenza pandemic is unpredictable, as was seen with the 2009 H1N1 virus. Thus, new vaccines are needed that exhibit a wider spectrum of influenza virus protection and a longer duration of effectiveness in order to optimize pandemic preparedness. Moreover, high-quality virologic surveillance in all parts of the world is needed in poultry and pigs as well as in humans.

3. Influenza vaccine: the safety versus efficacy paradox (John Treanor)

Inactivated influenza vaccines in a variety of unadjuvanted formulations have been used worldwide for the prevention of influenza in children, adults, and the elderly for many decades. There is substantial clinical experience with such vaccines, demonstrating that they are very well tolerated and rarely associated with severe or serious adverse events [6]. Live vaccines have not been used as extensively as inactivated vaccines, but also appear to have an acceptable safety profile [55]. However, data are increasingly suggesting that current vaccines are only moderately effective at preventing influenza illness and its complications [7]. This is especially problematic in those groups where influenza has the highest disease impact, such as infants and young children, older adults, and those with chronic medical conditions. In addition, it appears that it will be especially difficult to use standard vaccine approaches to create highly effective vaccines against some of the avian viruses identified as pandemic threats [56]. Therefore, there is considerable interest in developing influenza vaccines with improved immunogenicity and protective efficacy.

3.1. Tolerability of current influenza vaccines

Current influenza vaccines are well tolerated and have a well established safety record. Randomized, double-blind, controlled data have shown that in adults, rates of fever, myalgias, fatigue, malaise, and headaches are comparable in influenza vaccine and placebo recipients, although injection site pain is more common in vaccine recipients [57]. A large observational study of 251,600 subjects aged <18 years from 5 managed healthcare organizations did not reveal any evidence of an increase in medically attended events in the 2-week interval following influenza vaccine administration compared with control periods [58]. Vaccination with cold-adapted, live attenuated influenza vaccine (LAIV) is associated with an increased rate of rhinitis following vaccination [59], and a possible association with medically significant asthma/reactive airway disease has been reported in children aged <36 months [55]. In the US, the Vaccine Adverse Event Reporting System (VAERS) has not identified important safety issues after either LAIV or TIV in children or adults [6].

The Institute of Medicine has recently carried out a comprehensive exercise whose aim was to assess the likelihood of causality for various adverse effects in relation to a wide range of vaccines. For inactivated influenza vaccine, it was concluded that the evidence convincingly supports causality only for anaphylaxis (in subjects who are allergic to the vaccine), hypersensitivity reactions, syncope, regional pain syndrome, and deltoid bursitis [60]. There were suggestive data of an association between the vaccine and oculorespiratory syndrome, but only outside of the US. The data favored rejection of an association between the vaccine and exacerbation of asthma, and were deemed to be inadequate to accept or reject causality for other adverse events, including Guillain–Barré syndrome [60].

3.2. Efficacy of influenza vaccines

Current vaccines do not induce immunity or provide protection against influenza at optimal levels. There are very few recent randomized, controlled studies of influenza vaccine efficacy, and those that exist are mostly concentrated on the population who are least at risk (i.e., healthy, non-elderly adults). Data suggest that the efficacy of influenza vaccines appears to be less than optimal in the age groups at highest risk. For example, a randomized, controlled trial that evaluated TIV in children younger than 16 years of age observed lower rates of vaccine efficacy against influenza A H1N1 and influenza A H3N2 in those aged 1–5 years compared with the 6–10-year-old and 11–15-year-old subgroups [61]. In a placebo-controlled trial in adults aged ≥60 years, the relative risk reduction for serologically diagnosed influenza was 50% for the overall trial population, and only 23% for subjects aged >70 years [62]. Clinical trial data have been supplemented by effectiveness studies that use a test-negative case–control approach in which individuals with acute respiratory illness are tested by a real-time polymerase chain reaction (PCR) diagnostic test, and the proportion vaccinated among those with a positive PCR test is compared with the proportion vaccinated among those who test negative. In a recent study that assessed the effectiveness of US influenza vaccines during the 2010–2011 season, the overall adjusted vaccine effectiveness was 60% (95% CI: 53, 66%), while vaccine effectiveness in those aged ≥65 years was only 38% (95% CI: −16, 67%) (Fig. 3) [63]. A substantial proportion of influenza cases (30%) occurred in vaccinated individuals. Thus, even in an influenza season in which all 3 vaccine strains were antigenically similar to circulating viruses, the level of benefit was modest.

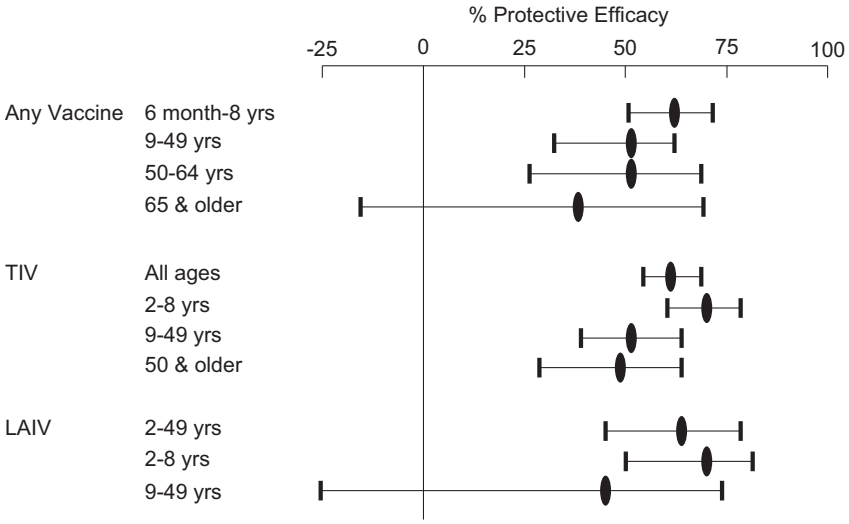

Fig. 3. Test-negative case–control vaccine effectiveness in the 2010–2011 season [63].

3.3. Strategies to enhance vaccine efficacy

Multiple strategies are being actively pursued to improve the performance of influenza vaccines (Fig. 4). In elderly subjects, high-dose influenza vaccine exhibits improved immunogenicity, as demonstrated in a recent randomized, double-blind controlled trial in adults aged ≥65 years [64]. In this study, vaccination with a high-dose TIV (containing 60 μg hemagglutinin per strain) was associated with a significantly higher rate of seroconversion and mean hemagglutination inhibition titer compared with standard-dose vaccine (15 μg hemagglutinin per strain) at 28 days post-vaccination [64]. The increased efficacy of high-dose vaccine in this study was accompanied by slightly increased rates of systemic reactions (myalgia, malaise, headache, fever) and local reactions (pain, erythema, swelling) compared with standard-dose vaccine [64]. With pandemic influenza vaccines, the addition of an adjuvant has a substantial effect on immune response and also allows dose sparing, (e.g., a study by Leroux-Roels et al. [8]), an issue of particular importance for pandemic vaccines. In children aged 6 to <72 months, the use of the adjuvant MF59, an oil-in-water emulsion, has been shown to increase the effectiveness of TIV [9]. However, in the subset of children aged 36 to <72 months in this study, the rates of systemic adverse events were slightly higher after administration of adjuvanted TIV (63%) than after administration of unadjuvanted TIV (44%) or control vaccine (50%). New discoveries related to the immune response to novel influenza viruses have also suggested the possibility of vaccines that could provide universal protection against multiple influenza subtypes, or even heterotypic protection.

However, experimental strategies for improved vaccine performance also carry risks of increased side effects or adverse events. In addition, because most of these approaches lack previous large-scale human experience, many new vaccine candidates also carry a risk of rare but potentially serious adverse events. The recent report of increased incidence of narcolepsy following the

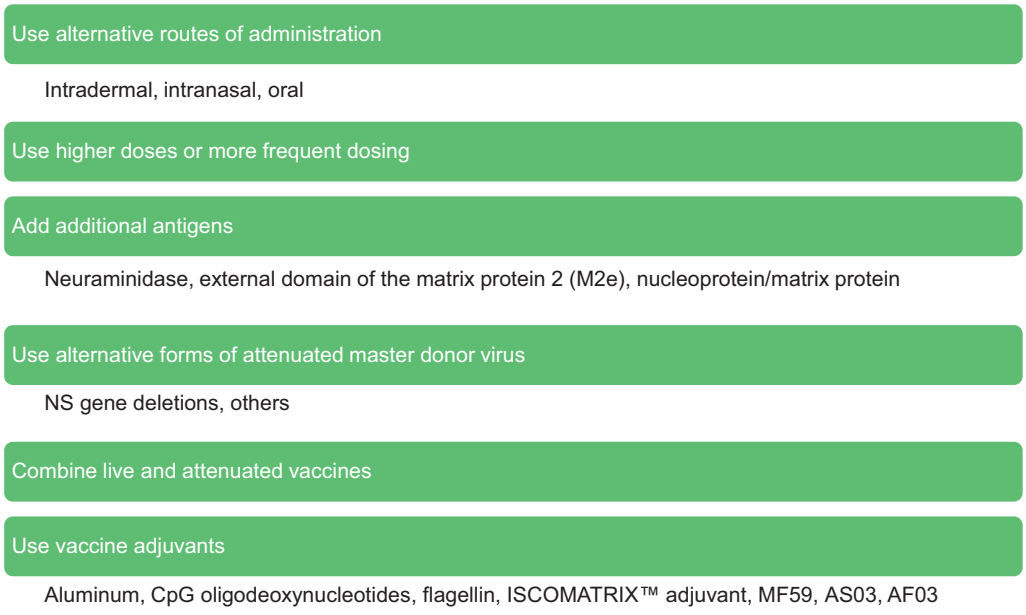

Fig. 4. Strategies to enhance vaccine efficacy.

distribution and utilization of AS03-adjuvanted pandemic H1N1 vaccine may represent such a risk [65].

3.4. Increased reactogenicity and the balance between benefit and risk

In the context of a world that already has safe and inexpensive influenza vaccines, even if they have suboptimal efficacy, how much additional vaccine reactogenicity, cost, or risk would be acceptable in the quest for greater protection? The answer to this question could depend on the populations in which the vaccine is intended for use. For example, a slightly higher rate of vaccine reactogenicity might be acceptable for a vaccine with substantially greater efficacy in a population at high risk for influenza complications, or in strategies to mitigate an influenza pandemic. To optimize these shifting balances between benefit and risk, strategies in which specific vaccine approaches are used in different populations should also be considered. Finding solutions to these difficult issues will be a critical component for the eventual development of more effective ways to control influenza and its impact on human health.

3.5. Predicting vaccine side effects

There have been 2 recent developments in the field of vaccines that may aid in the prediction of the response to a vaccine. One is the development of a systems biology approach to establish biomarkers of vaccination [11], which could also be used potentially to establish biomarkers of adverse events. Systems biology generally involves an unbiased assessment of the response of an entire system to a perturbation, the linkage of factors that behave together into modules, and correlation of the behavior of modules with vaccine outcomes, either "good" or "bad". This approach requires enormous resources in terms of data management and statistical analysis, but in theory might enable the prediction of a potential safety concern before a vaccine was licensed.

The second related development is the use of genomics to predict both vaccine responses and adverse events. For example, a recent study investigated the genetic basis for systemic adverse events following smallpox vaccination. This analysis identified 1 single-nucleotide polymorphism (SNP) in the MTHFR (methylenetetrahydrofolate reductase) gene and 2 SNPs in the IRF1 (interferon regulatory factor 1) gene that were associated consistently with adverse events in 2 clinical trials of smallpox vaccination in healthy volunteers [66]. Thus, future vaccination programs may also benefit from the implementation of genomics.

3.6. Conclusions

Current unadjuvanted influenza vaccines have a vast amount of safety experience with an acceptable tolerability profile. However, there is a clear need for an improved influenza vaccine in terms of efficacy. Novel vaccine approaches carry a potential risk of increased rates of adverse events, including reactogenicity events, and unpredictable vaccine-related serious adverse events. Thus, it has to be decided how much increased risk is acceptable for a given level of improved performance. In addition to breakthroughs in our knowledge of the immunology of influenza, other requirements include: (1) advances in the science of monitoring and detecting adverse events; (2) a better understanding of the mechanisms behind adverse events; and (3) development of methods to predict adverse events and possible individualized vaccination strategies.

4. Investigations into febrile reactions observed in the pediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine (Eugene Maraskovsky for the 2010 Southern Hemisphere Trivalent Influenza Vaccine Investigations Group)

bioCSL's 2010 Southern Hemisphere Trivalent Influenza Vaccine (CSL 2010 SH TIV), also known as Fluvax™ 2010 SH, was associated with an unexpected increase in the numbers of reports of fever and febrile convulsions (2010 SH Pediatric Adverse Events), predominantly in children younger than 5 years of age compared to previous seasons. The safety signal was first identified in April 2010 in the state of Western Australia (WA) during the third year of a government-sponsored pediatric influenza vaccination program. The febrile convulsions, which occurred at an estimated rate of 5–7 per 1000 doses [67], occurred predominantly in children younger than 5 years of age, shortly after administration of Fluvax™. bioCSL's TIVs have not been licensed for use in children younger than 5 years of age since these events. Preliminary conclusions as to the likely cause of the febrile convulsions have been drawn from a comprehensive 2-year investigation that has been monitored by the Therapeutic Goods Administration (TGA) and the Food and Drug Administration (FDA).

Methods of manufacture for all registered inactivated influenza vaccines are unique, including the inactivation and splitting agents used. bioCSL's TIV is prepared from virus grown in the allantoic cavity of embryonated eggs, purified by zonal centrifugation, inactivated by Beta-Propiolactone (BPL) and disrupted with the detergent sodium taurodeoxycholate (TDOC).

Up until April 2010, bioCSL had a long history of use of the vaccine without the identification of any significant safety concerns. Clinical studies had demonstrated that bioCSL's seasonal and monovalent 2009 Influenza A (H1N1) vaccines were immunogenic while having an acceptable safety profile in all age groups. This is consistent with bioCSL's experience with seasonal influenza vaccines prior to the 2010 SH Pediatric Adverse Events, including the first 2 years (2008 SH and 2009 SH) of the WA pediatric influenza vaccination program [68,69].

Upon the detection of the 2010 SH Pediatric Adverse Events, bioCSL commenced a thorough and systematic investigation to determine the root cause. The investigation had 3 discrete, but interlinking components:

1. A Clinical Safety Investigation to characterize the safety concern, identify risk factors and at-risk populations.
2. A Manufacturing and Quality investigation to review all process parameters and process controls which could have contributed to the safety concern.
3. A Scientific Program to identify the molecular mechanism, identify differences between manufacturers' influenza vaccines and review the feasibility for *in vitro* or *in vivo* predictive tests to assist in future vaccine production.

The Clinical Safety Investigation identified that the 2010 SH Adverse Events occurred in all pediatric age groups, but were most pronounced in recipients 6 months to younger than 5 years of age. Increased reporting was also observed in the 5 to less than 9-year age group, but the overall number of reports was substantially lower than in the younger age group. The safety signal of febrile convulsions was identified specifically in children younger than 5 years. Adverse event data in adults and children older than 9 years were analyzed, and no significant safety concerns were identified in these populations during the SH 2010 season. Continued monitoring of spontaneous post-marketing data for the bioCSL TIV and review of published safety data regarding influenza vaccine as part of routine signal detection confirms that there are no significant

safety concerns with bioCSL TIV in children 9 years and older and in adults.

Manufacturing and Quality investigations of the controlled process parameters confirmed there were no contributing factors that could be considered correlated to 2010 SH Pediatric Adverse Events. All batches were released to specification, and there was no evidence of batch-specific issues. Laboratory testing ruled out chemical and bacterial contamination. Agglomeration was also ruled out as a contributing factor due to the weight of evidence from characterization studies conducted in the Scientific Program. A detailed review of all manufacturing aspects from seed to fill and finish, including raw materials, utilities, and processes, did not identify any deviations or changes from previous seasons' formulations that would explain higher rates of febrile reactions in the SH 2010 season. There was no change in concentration of TDOC used for splitting between SH 2009 and SH 2010, and the HA profiles were comparable.

The most significant change identified during the Manufacturing Investigation was the replacement of all 3 virus strains in the 2009 SH vaccine formulation with new strains for 2010 SH. At the conclusion of the Manufacturing and Quality investigation, the potential impact of bioCSL's method of manufacture together with the strain changes could not be discounted as possible contributors to the 2010 SH Pediatric Adverse Events. This was the subject of further investigation in the Scientific Program.

Scientific Research Investigations included exploration of several *in vivo* animal models, including non-human primates, ferrets, rabbits, and newborn rats as potential models of fever and/or febrile seizure. To date, none of the TIVs tested, including the bioCSL 2010 SH TIV, induced symptoms consistent with febrile seizure in any of the *in vivo* models examined [12]. Thus, none of the animal models tested were suitable to further investigate the febrile seizure events of 2010. Consequently, *in vitro* induction of cytokine/chemokine and NF-κB (a key cellular transcription factor in cytokine production) models were explored as putative correlates of *in vivo* pyrogenicity, which may act as an indirect surrogate measure of the reactogenic potential. Although not definitive, the observation that elevations in systemic cytokine levels are observed in individuals who have undergone febrile seizures provides a logical basis for the use of these models, and mapping these cytokines/chemokines *in vitro* may act as an indirect surrogate measure of the reactogenic potential of the TIVs and monovalent pool harvests (MPHs) tested.

These studies demonstrated that the bioCSL 2010 SH TIV (and MPHs) stimulated the release of inflammatory cytokines and chemokines in adult and pediatric whole blood assays and NF-κB, in a NF-κB/SEAPorter HEK 293 cell line reporter assay [12,70] more robustly than previous season's bioCSL TIVs or TIVs produced by other manufacturers. Further investigation revealed that bioCSL TIVs and MPHs contain degraded RNA transcripts (predominantly <200 nucleotides in length) that are able to induce NF-κB when appropriately delivered into NF-κB/SEAPorter HEK 293 cells and TLR-HEK 293 transfectants [70]. This delivery appears to be facilitated by a heat-sensitive viral component such as a lipid structure, protein, or possibly a combination of these components [12,70]. The addition of a transfection lipid to heat-inactivated TIV samples restored the NF-κB activation, which highlights that delivery of the RNA is critical to inducing the NF-κB signal and that RNA content alone is not the sole factor that determines pyrogenicity of the bioCSL TIVs. NF-κB activation and cytokine/chemokine secretion can also be quenched by nucleases (Fig. 5), lipases, or increasing the TDOC concentration during manufacturing [70].

Although presence of the RNA is the trigger, its delivery is key to the induction of the cytokine/chemokine signal, and this appears to be dependent on the lipid levels present in the final TIV formulation. RNA alone from either the bioCSL TIVs or their individual inactivated/split influenza strains fail to signal in the *in vitro* assays,

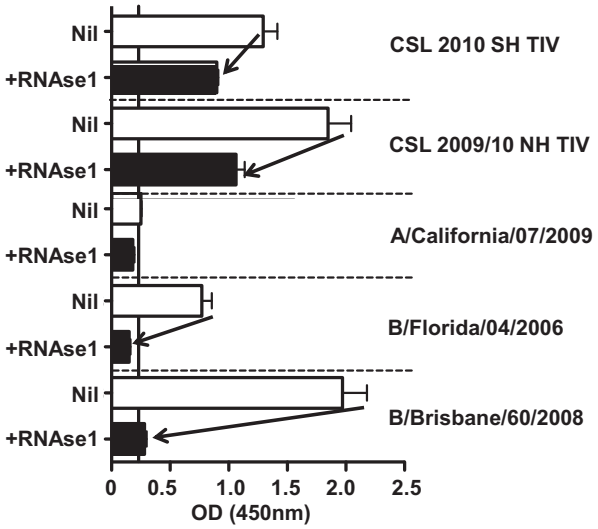

Fig. 5. RNase pre-treatment decreases NF-κB signal.

but can signal when a source of lipid is used for delivery (such as Lipofectamine 2000™) (Fig. 6). The findings also suggest that lipid content of the bioCSL-generated influenza strains inversely correlates with the concentration of TDOC [70], and most likely mediates RNA delivery *in vivo* to antigen-presenting cells (APCs) such as dendritic cells and monocytes/macrophages.

While residual whole virus may be considered a contributor to the signal, the data suggest that other viral structures/complexes including virosomes, agglomerates, and/or split virus that contain both RNA and lipid may also contribute to the overall signal observed in the *in vitro* assays. However, the relative contribution

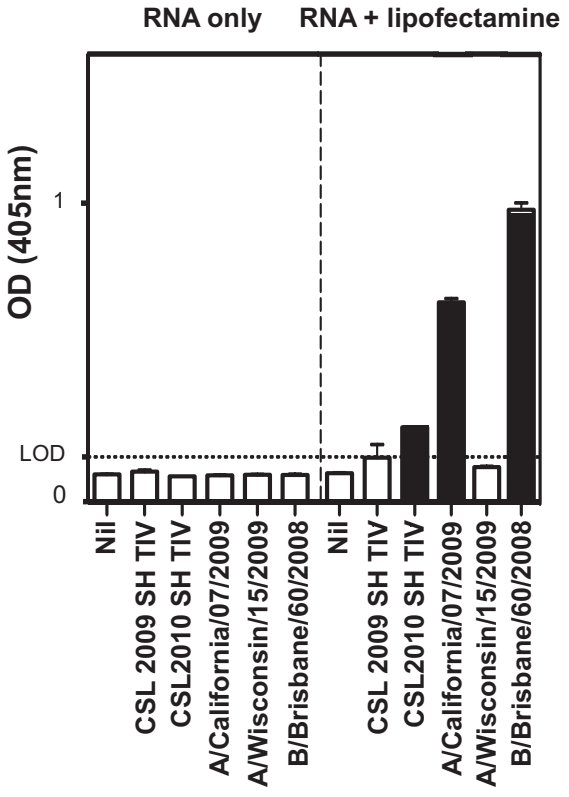

Fig. 6. RNA requires a source of lipid for delivery to signal NF-κB.

of RNA, lipid, agglomerates of split virus, and residual whole virus to the observed signals in the *in vitro* assays remains to be determined.

Acknowledging the uncertainty of available *in vitro* methodologies with respect to their relevance as a correlate of *in vivo* responses, bioCSL has concluded from its comprehensive investigations that lipids and degraded RNA fragments, which are preserved by the bioCSL method of manufacture, and the strain changes in 2010, are most likely to be the predominant factors contributing to the 2010 SH Pediatric Adverse Events. These degraded RNA fragments, using viral lipids as a carrier, appear to stimulate release of inflammatory cytokines as part of an innate immune response, which is particularly marked in some young children who can be very sensitive to these components. Review of clinical studies demonstrated bioCSL's method of manufacture is associated with a higher background rate of fever compared to another licensed TIV and it is possible the strain changes of the 2010 SH season tipped bioCSL's vaccine over a threshold, triggering febrile convulsions in some young children.

5. Passive immunotherapy for influenza prophylaxis and therapy (Thomas Luke)

The views expressed in this article by Dr. Thomas C. Luke do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the US Government. This work was prepared as part of his official duties. Title 17 U.S.C. 105 provides that "Copyright protection under this title is not available for any work of the United States Government." Title 17 U.S.C. 101 defines a U.S. Government work as a work prepared by an employee of the U.S. Government as part of that person's official duties. The work was supported by work unit number OMNIBUS III DO-0005.

Current therapies for severe seasonal and pandemic influenza include antivirals and supportive care, which have suboptimal results. The use of passive immunotherapy dates back to the 1890s, when Emil von Behring and Kitasato Shibasaburō demonstrated the efficacy of animal immune sera for the treatment of toxin and bacterial diseases [13,19]. The use of convalescent serum/plasma products prevailed in the early 20th century until the development of antibiotics and Ig products in the 1940s [13,19]. Numerous human and animal studies have reported the prophylactic and therapeutic efficacy of convalescent serum/plasma and IVIg (pooled immunoglobulins extracted from the plasma of >1000 human blood donors) [19] and hyperimmune products in cases of influenza infection, including antiviral-resistant strains, and as rescue therapy during pandemics (Fig. 7) [13]. These products contain cross-reactive or specific strain antibodies, immunomodulatory properties, and may provide additional protection against secondary bacterial infections [19]. Therefore, convalescent human plasma, IVIg, or hIVIg could be an effective therapy for seasonal and pandemic influenza.

5.1. Passive immunotherapy of influenza: evidence for potential efficacy

In the setting of human influenza, convalescent blood products were first used to treat serious influenza pneumonia during the Spanish influenza pandemic of 1918–1920 [71]. Since then, numerous additional studies have been reported. In the Soviet Union in the middle of the 20th century, a number of clinical studies were conducted that reported efficacy using a variety of Ig products for the treatment of influenza [72–76]. Studies in animals, including SCID mice, have demonstrated prophylactic and therapeutic efficacy in multiple influenza strains [77–83]. There have also been numerous case reports of the successful use of convalescent plasma or IVIg for serious human H1N1, H3N2, and H5N1 infections [15,17,18,84–87]. In addition, several reports have described the presence of cross-reactive anti-influenza antibodies in standard IVIg preparations, and the production of hIVIg specific for pandemic influenza A (H1N1) 2009 virus [88–93]. A recent open-label, prospective cohort study in Hong Kong found that convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection [16].

5.2. Meta-analysis of studies of convalescent blood products for Spanish influenza pneumonia

A meta-analysis of studies of the use of convalescent blood products for Spanish influenza pneumonia has been performed [71]. Of 27 reports that were identified, 8 studies that included a total of 1703 patients met inclusion criteria for the meta-analysis. Data regarding study characteristics, outcomes, adverse events, and quality were extracted and treatment groups were divided into early (those treated <4 days of pneumonia complications) or late (those treated ≥4 days after pneumonia complications). In these studies, convalescent whole blood, plasma, or serum was obtained from donors 1–6 weeks after recovery from influenza, and patients typically received 1 or 2 treatments. The average amount of 'plasma' in the treatment product was 100–150 mL, corresponding to approximately 2 mL/kg.

The overall crude case-fatality rate was 16% (54 of 336) among treated patients and 37% (452 of 1219) among controls. The range of absolute risk differences in death between the treatment and control groups was 8–26%, yielding a pooled risk difference of 21% [95% CI, 15%, 27%] [71]. The overall crude case-fatality rate was 19% for patients treated within 4 days of pneumonia complications and 59% (49 of 83) for patients treated at 4 days or later. The range of absolute risk difference in death was 26–50% (pooled risk difference, 41% [95% CI, 29%, 54%]). The most common laboratory finding was leukopenia, while the most common clinical findings were cyanosis and dyspnea. Although these results are promising, it should be borne in mind that none of the studies used a randomized, double-blind, placebo-controlled design [71].

5.3. Use of passive immunotherapy in pandemic influenza H1N1 2009

Recently, the efficacy of convalescent plasma treatment was demonstrated in a prospective cohort study of 93 patients with severe, pandemic H1N1 2009 infection between September 2009 and June 2010 in Hong Kong [16]. Patients received standard care ($n = 73$) or standard care plus 500 mL of convalescent plasma with a neutralizing antibody titer of ≥1:160 ($n = 20$). Standard care included oseltamivir, other neuraminidase inhibitors, and other interventions. Patients who received convalescent plasma treatment had a significantly lower mortality rate than the matched controls who did not receive convalescent plasma (20.0% versus 54.8%, respectively; $p = 0.01$). A subgroup of 44 patients in this study underwent serial measurements of respiratory tract viral load and serum cytokine response. These measurements showed that on Days 3, 5, and 7, viral loads and levels of interleukin-6, interleukin-10, and tumor necrosis factor α were significantly lower in the plasma-treated group compared with the control group ($p < 0.05$). None of the patients who received convalescent plasma developed investigational-product related adverse events during the study.

5.4. Ferret-model data

An experiment in ferrets provides evidence that passive immunotherapy may be highly efficacious in the treatment of virulent avian influenza [14]. In this study, cohorts of ferrets ($N = 4$) were infused with 10 mL of H5N1 (A/Vietnam/1203/2004)

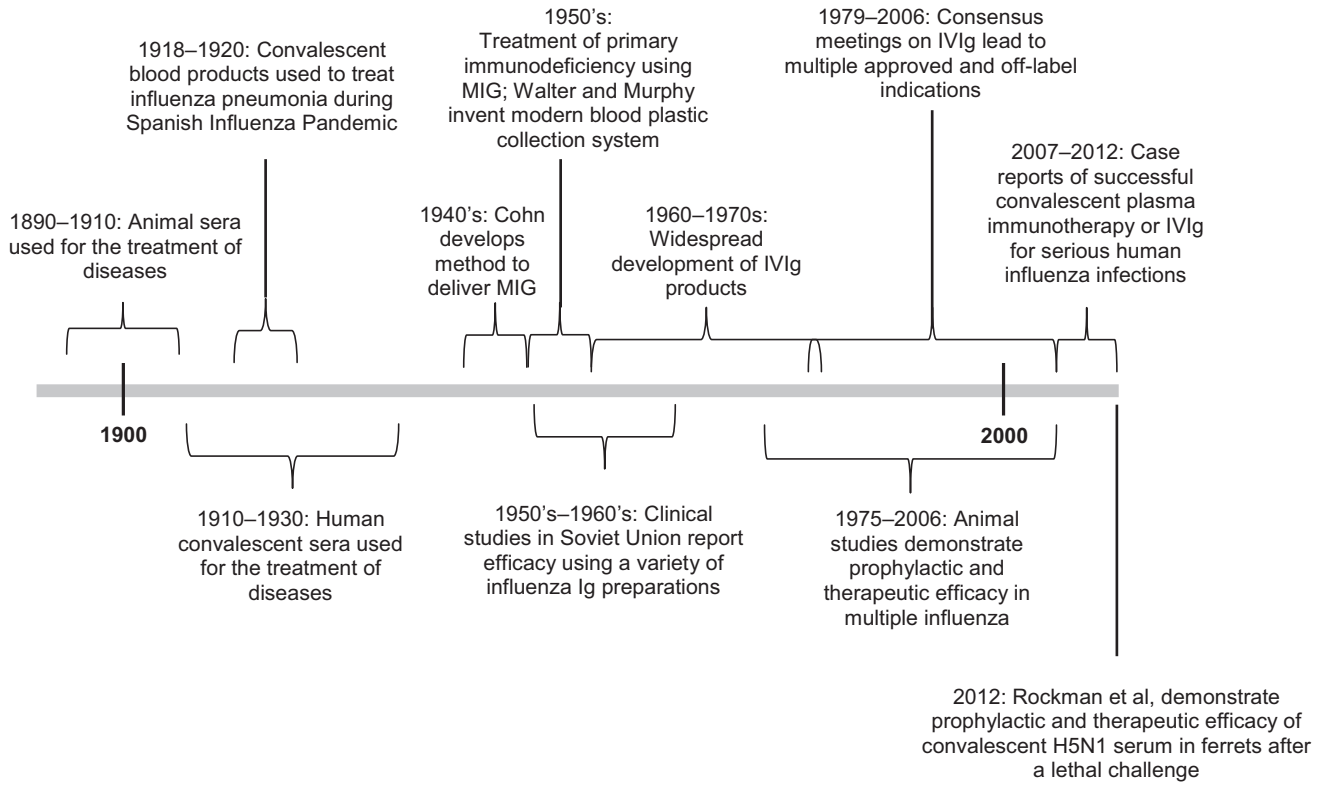

Fig. 7. Historical timeline of the development and use of passive immunity in relation to influenza [13–16,18,19,71–87,92,93,123,124]. MIG, subcutaneous/intramuscular immunoglobulin; IVIg, intravenous immunoglobulin.

convalescent serum with an hemagglutination inhibition (HAI) titer of 1:128 1 day before, 1 day after, 3 days after, or control H3N2 serum or PBS 1 day before, challenge with 10^6 EID_{50} of A/Vietnam/1203/2004 H5N1. Ferrets that received H5N1 convalescent serum achieved a relatively low HAI titer of 1:4–1:8. While no control animals survived, 100% [4/4] infused 1 day before, 75% [3/4] infused 1 day after, and 25% [1/4] infused 3 days after survived.

These results are impressive, particularly when compared to a similar study that tested the efficacy of oseltamivir in treating ferrets infected with the same H5N1 strain. In this study, cohorts of ferrets ($N = 3$) were challenged with 10^2 EID_{50} A/Vietnam/1203/2004 H5N1 (compared to 10^6 EID_{50} in the convalescent plasma study) [94]. The animals received 10 (low dose) or 25 (high dose) mg/kg of oseltamivir in divided doses for 5 days starting 1 day after viral challenge. In the low-dose oseltamivir group (resulting in a comparable AUC drug level to humans that receive 75 mg of oseltamivir twice daily), 0% [0/3] survived. In the high-dose oseltamivir group, 100% [3/3] survived. This is comparable to the 75% [3/4] survival seen in the 1 day after challenge group in the H5N1 convalescent plasma study. Additionally, in comparison to the high-dose oseltamivir group, the H5N1 convalescent plasma group had similar a similar weight loss (13%) but a lower nasal viral shedding titer of 2 $\log_{10}$ EID_{50} versus 3 $\log_{10}$ EID_{50} on Day 3 (Table 1) [14,94].

Though these were not direct comparative arms in a single study, the data suggest that administering a single dose of convalescent plasma with a moderate to low HAI titer may be as or more effective than a multiple dosing regimen of oseltamivir. A synergistic effect of co-administering antivirals and passive immunotherapy products could also result in improved outcomes but has not been studied in a ferret model at this time.

5.5. Passive immunotherapy of influenza: current state and future options

A number of future passive immunotherapy options exist. 'High' titer fresh frozen plasma has excellent potential as a strain-specific influenza treatment. This represents a 'low tech' approach with a low development and production unit cost. It also has the capability of being a local point-of-production and delivery therapeutic that is not dependent upon the delivery of antivirals from a distant supplier that may become problematic during pandemic events. However, transportation and storage require sub-zero cold-chain management, and its relatively short shelf-life of 1 year is a limitation [95]. An ongoing, multicenter phase II clinical trial is evaluating the safety and efficacy of immune plasma for the treatment of hospitalized patients with influenza A who are at risk for severe disease (ClinicalTrials.gov Identifier: NCT01052480) [96]. Patients are randomized to receive either 2 units of immune plasma plus standard care, or standard care alone. The trial is expected to recruit approximately 150 patients, of which 13 have already been recruited. The primary outcome measure is time to normalization of respiratory status at Day 28. To date, no product-related serious or unexpected adverse events have been observed.

Commercial IVIg products are currently being used for multiple indications that have been approved by the FDA [19] and standard IVIg or hyperimmune IVIg (manufactured from plasma units with a high anti-influenza HAI) have excellent potential for the treatment of severe seasonal and pandemic influenza [13]. Strain-specific and heterosubtypic anti-influenza antibodies in standard IVIg could be effective in the treatment of severe influenza. Additionally, if "universal" influenza vaccines are developed, standard IVIg products produced from donor populations that are highly vaccinated—such as in the United States, Australia, and Europe—should become

Table 1
Lethal H5N1 in ferrets: hyperimmune serum vs. oseltamivir use in 2 studies [14,94].

	Hyperimmune serum (Rockman et al. [14])	Oseltamivir (Govorkova et al. [94])	
Ferrets (N)	4	3	3
H5N1 strain/EID50	A/Vietnam/1203/2004 (10^6 EID50)	A/Vietnam/1203/2004 (10^2 EID50)	A/Vietnam/1203/2004 (10^2 EID50)
Treatment dose	10 mL serum (HAI 1:126) × 1	10 mg/kg/day for 5 days	25 mg/kg/day for 5 days
Serum concentration	HAI 1:4–1:8	Similar AUC to human dose	Higher AUC than human dose
Administration cohorts	−1 D, +1D, +3D	(+1D to 6D)	(+1D to 6D)
Euthanasia rules	10% weight loss in 7 days or organ involvement	25% weight loss and severe disease	25% weight loss and severe disease
Survival	−1 D: 4 of 4 (100%) +1 D: 3 of 4 (75%) +3 D: 1 of 4 (25%)	0 of 3 (0%)	3 of 3 (100%)

highly enriched with strain-transcendent antibodies, potentially resulting in a potentially highly effective therapy. However, one limitation to this approach is that widespread use of IVIg products for treating serious influenza could conceivably result in disruption of supply for patients with immune deficiencies and those with autoimmune disorders. Finally, although monoclonal or oligoclonal antibodies against conserved influenza epitopes have excellent potential for influenza immunotherapy, current limitations include long clinical development timeframes, costs, and the challenge of producing an adequate quantity for global demand.

5.6. Conclusions

Passive immunotherapy with convalescent serum/plasma, IVIg, and hIVIg has been extensively used for prophylaxis and treatment of infectious agents. Convalescent plasma is currently being studied in clinical trials. Standard IVIg or hIVIg could be an effective prophylaxis or treatment for seasonal and pandemic influenza, offering strain-specific antibodies against circulating influenza strains, heterosubtypic/cross-reactive antibodies, and an immunomodulatory effect and prophylaxis against bacterial infections. Randomized, controlled clinical trials using IVIg products for serious influenza are an essential next step. The concept of a universal influenza vaccine and the development of influenza monoclonal antibodies could lead to more effective immunotherapy products. When coupled with neuraminidase inhibitors, other antivirals, and supportive care, these could potentially reverse the unacceptably high rate of death that is currently associated with severe influenza.

6. Broad protection from existing vaccine technologies (Emma Ball for the Influenza Innovation Group)

Challenges raised by the emergence of an influenza pandemic include the delay between pandemic declaration and the production of a homologous pandemic vaccine. This is illustrated by recent experience in Australia during the 2009 influenza A (H1N1) pandemic, when the start of vaccination with pandemic vaccine was in October of that year, several months after the pandemic peak in Australia had passed [21]. While the use of an adjuvant may lower the dose of antigen that is required to produce immunity, this does not obviate the need for protection while a homologous vaccine is being developed. A possible strategy to address this need would be the interim use of currently available antigen formulated into a vaccine to induce broad protection.

ISCOMATRIX™ adjuvant (CSL Limited, Melbourne, Australia) is a proprietary combination of saponin, cholesterol, and phospholipid. It is a potent adjuvant that has been shown to induce strong, prolonged antibody and cytotoxic T-cell responses in both animals and humans [97]. The manufacturing process for ISCOMATRIX™ adjuvant is industrialized, the product is very stable, and it is easy to formulate, with no need for mixing at the bedside. This section describes recent data obtained with this potent immunostimulant in a ferret model of human influenza disease.

6.1. Efficacy of ISCOMATRIX™ adjuvant vaccines in the lethal H5N1 ferret model

The lethal H5N1 ferret model is considered to be a clinically relevant model of human influenza disease. Ferrets are easily infected with unadapted virus, and they exhibit the same distribution of virus receptors in the respiratory tract as humans. The outbred animals used in this model succumb rapidly to infection with H5N1 influenza virus, developing symptoms that are similar to those seen in humans, including lethargy, weight loss, diarrhea, nasal discharge, and sneezing [7]. Prior to inoculation, animals are screened to ensure that they are seronegative for relevant influenza virus strains. Challenge with a lethal dose of H5N1 influenza virus is performed intranasally under anesthesia.

This ferret model has been used to evaluate an H5N1 vaccine combined with ISCOMATRIX™ adjuvant, and the results obtained have been compared with those generated using the same antigen adjuvanted with aluminum phosphate ($AlPO_4$) [20]. After animals received a single inoculation containing 15, 7.5, or 3.8 μg of A/Vietnam/1194/2004 HA formulated with ISCOMATRIX™ adjuvant, they were protected from death after lethal H5N1 virus challenge at even the lowest dose of antigen (Fig. 8). Analysis of nasal washes revealed that the viral load in these animals was reduced by the single-dose regimen; the geometric mean titer of infectious virus in each inoculated group was significantly lower than in control animals at the corresponding time point. Moreover, none of the animals receiving a single dose of 7.5 μg or 15 μg HA plus ISCOMATRIX™ adjuvant had detectable virus in nasal washes obtained at Day 7 post-challenge. These viral-shedding data suggest a possible benefit in reducing human-to-human spread of virus in a community setting.

Other animals in this study received 2 inoculations, each containing 1.9, 3.8, 7.5, or 15 μg of HA formulated with ISCOMATRIX™ adjuvant. After a lethal H5N1 challenge, protection against death was observed in all of these animals, including those that received ISCOMATRIX™ adjuvant vaccine containing only 1.9 μg of HA per dose [20]. In addition, all of these ISCOMATRIX™ adjuvant vaccines, when administered as 2 doses, provided protection against weight loss and other signs of clinical disease. Although protection against post-challenge mortality and morbidity was also observed with animals receiving 2 inoculations of 15 μg of HA formulated with $AlPO_4$ in this study, the effectiveness of the relatively low antigen dose used in the ISCOMATRIX™ adjuvant vaccine demonstrates a dose-sparing effect that is potentially useful for pandemic application.

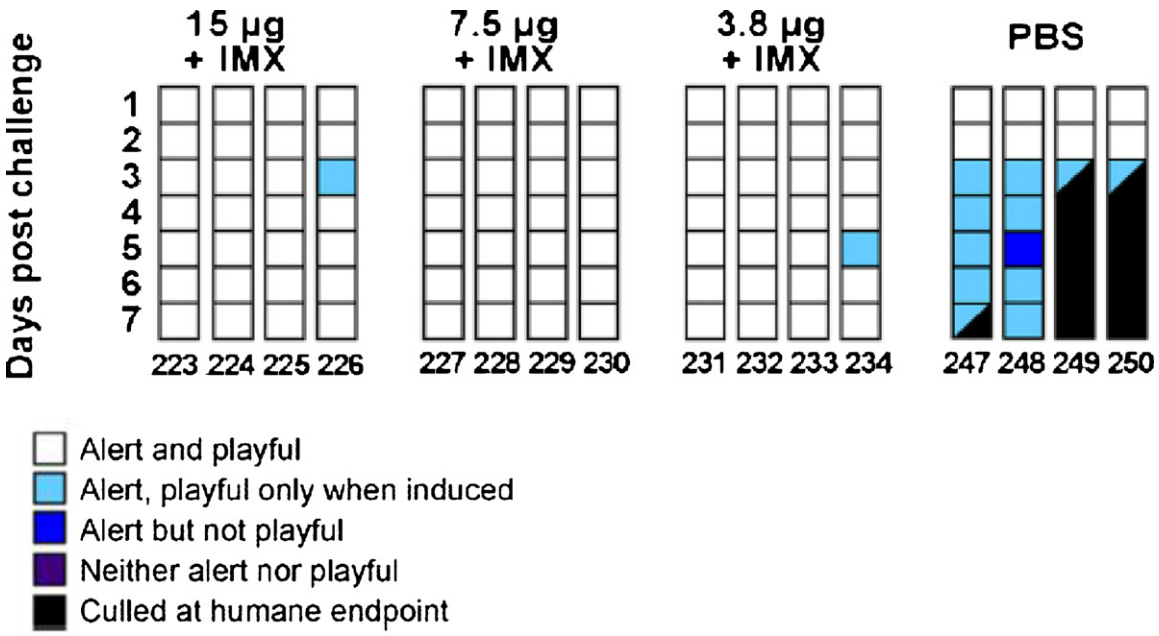

Fig. 8. Changes in activity score of ferrets immunized with a single inoculation of H5N1 vaccine formulated with ISCOMATRIX™ adjuvant [20]. Ferrets were immunized with vaccines based on the reverse engineered A/Vietnam/1194/04 (H5NA1) virus containing 3.8, 7.5 or 15 µg of hemagglutinin with ISCOMATRIX™ adjuvant and challenged 4 weeks later. IMX, ISCOMATRIX™ adjuvant; PBS, phosphate-buffered saline. Figure Copyright © American Society for Microbiology, Journal of Virology, 2009;83(15):7770–8. http://dx.doi.org/10.1128/JVI.00241-09. Reproduced with permission from American Society of Microbiology.

In ferrets who received 2 doses of ISCOMATRIX™ adjuvant vaccine containing 3.8 µg of HA per dose, protection against death and clinical disease persisted for at least 15 months after vaccination. Furthermore, in cross-clade protection experiments, double inoculation with 2 doses of 3.8 µg of HA formulated with ISCOMATRIX™ adjuvant provided protection against infection with the clade 2.1.3 virus A/Indonesia/5/05.

6.2. *Seasonal influenza ISCOMATRIX™ adjuvant vaccine*

The observation of some degree of cross-reactivity between seasonal influenza vaccines and influenza A H5N1 raises the possibility that the formulation of a readily available seasonal influenza vaccine with an adjuvant could generate a vaccine that is suitable for interim use during an influenza pandemic. This was explored further in the ferret model [98] using Fluvax™ vaccine (bioCSL, Parkville, Australia), a seasonal TIV that is produced in both the Northern and Southern Hemispheres and so is readily available essentially all year round (Fluvax™ is also marketed as Afluria™ and Enzira™).

Two doses of the trivalent Fluvax™ vaccine plus ISCOMATRIX™ adjuvant were administered 21 days apart (Days 0 and 21). This regimen was compared with 3 other vaccines: (1) Fluvax™ without adjuvant; (2) monovalent H1N1 vaccine plus ISCOMATRIX™ adjuvant; and (3) monovalent H3N2 vaccine plus ISCOMATRIX™ adjuvant. In addition, a group of control animals received injections of vaccine diluent alone. Animals were challenged with 10^6 egg infectious doses of wild type A/Vietnam/1203/2004 (H5N1) virus on Day 49 and evaluated during a 14-day post-challenge evaluation period. Outcome measures included body weight, activity score (measured on a 5-point scale), and virus isolation (rectal swab, nasal wash, oral swab, and examination of organs post mortem).

Measurements of body weight revealed that all 4 control animals suffered weight loss after the H5N1 virus challenge, reflecting clinical influenza disease, while 2 of 4 animals who received Fluvax™ alone maintained normal weight over the 14-day follow-up period. In contrast, all 4 animals who received Fluvax™ plus ISCOMATRIX™ adjuvant maintained body weight post-challenge. Weight maintenance in animals that received monovalent H1N1 vaccine plus ISCOMATRIX™ adjuvant was similar to that seen with Fluvax™ plus ISCOMATRIX™ adjuvant, while the weight loss in all 4 animals receiving monovalent H3N2 vaccine plus ISCOMATRIX™ adjuvant was similar to that seen in control animals. The latter observation suggests that the protection against H5N1 challenge that was observed with Fluvax™ plus ISCOMATRIX™ adjuvant is related to the H1N1 component of that vaccine.

Patterns of activity score during the follow-up period reflected patterns of weight loss; all animals in the control group and in the group that received monovalent H3N2 vaccine plus ISCOMATRIX™ reached a humane endpoint and were culled before the end of the observation period, while 2 of the 4 animals that received Fluvax™ alone reached this endpoint. All animals receiving Fluvax™ plus ISCOMATRIX™ adjuvant or monovalent H1N1 vaccine plus ISCOMATRIX™ adjuvant survived and had essentially no drop in activity score during the evaluation period.

In a separate experiment, evaluation of viral shedding revealed that the 4 animals who received Fluvax™ plus ISCOMATRIX™ adjuvant were free from virus in the upper respiratory tract at Day 7, comparable to animals that had been vaccinated with matched monovalent H5N1 vaccine plus ISCOMATRIX™ adjuvant. In animals receiving Fluvax™ alone, only 1 of the 2 animals that were alive on Day 7 was virus-free at this time point.

6.3. *Conclusions*

Data obtained in the lethal H5N1 ferret model suggest that seasonal influenza ISCOMATRIX™ adjuvant vaccines may provide broader protection than unadjuvanted vaccines in both seasonal and pandemic settings. In addition, such vaccines may have the potential to provide interim coverage during a pandemic, while homologous vaccine is being developed, and may have the potential to reduce morbidity, mortality, and disease transmission. These findings raise the intriguing concept that it may have been possible to alter the course of the 2009 pandemic with immediate use of

Table 2
Baseline vaccination rates versus Healthy People 2010 and 2020 goals: gaps persist [22,113].

Vaccine and group	Baseline rate, % (year)	Healthy People 2010 goal, %	Healthy People 2020 goal, %
Influenza[a]			
Noninstitutionalized, 18–64 years	27 (2008–2009)	60[b]	80
Noninstitutionalized, ≥65 years	66 (2008–2009)	90[b]	90
Healthcare workers	53 (2008–2009)	60	90
Pregnant women	11 (2008–2009)	NA	80
Pneumococccal			
Noninstitutionalized, ≥65 years	61 (2009)	90[b]	90
Noninstitutionalized, high-risk, 18–64 years	17 (2009)	60	60
Institutionalized adults	72 (2009)	90	90
Zoster			
≥60 years	10 (2009)	NA	30
Hepatitis B			
Healthcare workers	74 (2009)[c]	93	90

NA, not available.
[a] Results reported for the 2008–2009 influenza season.
[b] Also at high-risk.
[c] Received at least 3 doses of hepatitis B vaccine.

a seasonal influenza ISCOMATRIX™ adjuvant vaccine. Therefore, evaluation of seasonal influenza ISCOMATRIX™ adjuvant vaccines in humans appears to be warranted as the next step in development.

7. New approaches in policy, communication, and science (Gregory Poland)

Recent decades have seen progress towards improved influenza vaccine coverage in highly developed countries. Providers, public health officials, employers, and payers have made considerable efforts to achieve what has been accomplished. In particular, significantly improved influenza vaccine coverage has been achieved in elderly patients in the US. However, in other subgroups in the US (e.g., adults age 18–50 years with high-risk medical conditions, pregnant women, and adolescents), there has been incremental progress, but significantly suboptimal coverage levels remain. For the most part, influenza vaccines are readily available, but significant problems still exist: providers are uninformed about the need for and benefits of vaccines and the risks of influenza; public health organizations and the government are disconnected from demographics, patients, and the delivery of vaccines; payers have a short-term focus; the public tends to be suspicious and mistrustful of vaccines; and politicians are uninformed of public health needs. The purpose of this section is to briefly discuss the current state of influenza vaccine coverage, and to review the priorities for improved influenza vaccines and improved vaccination policies and communication efforts.

7.1. Influenza vaccine coverage

Influenza vaccine is predominantly used only in Western countries, with very low rates of use in Eastern and developing countries. Influenza vaccination rates fluctuate, with marked variability in use from year to year. This is driven largely by the public's perception (real or imagined) of the risk of influenza for a given season, rather than necessarily by meaningful data. Most current efforts aimed at increasing influenza immunization rates are inefficient and are not resulting in significant gains in vaccine coverage. For example, in the US in 2008, only 25% of non-institutionalized adults aged 18–64 years, 28% of pregnant women, and 45% of healthcare workers were vaccinated against seasonal influenza [22]. These percentages compare poorly with Healthy People 2010 and 2020 goals for these groups of 80%, 80%, and 90%, respectively. This seems to reflect a more general phenomenon, with similar gaps also seen with other vaccines such as pneumococcal and hepatitis B vaccines (Table 2) [22]. Clearly, new approaches to increase influenza vaccine coverage are required.

7.2. Influenza vaccination: priorities for the future

7.2.1. Improved vaccines

The first priority should be more efficacious influenza vaccines, particularly among high-risk groups (i.e., elderly, immunocompromised, others). These are needed to address issues such as antigenic drift and shift, which are difficult to respond to in a timely manner with current methods of vaccine manufacture, novel influenza viruses, immuno-immaturity, immunosenescence, and the need for cold-chain management for current vaccines. There are still some residual egg-allergy issues that need to be addressed, and there is a requirement for fairly highly trained healthcare workers to administer the vaccines. All of these issues are exacerbated by the annual requirement for influenza vaccination.

Some progress has been made, however. We have begun the process of moving from a '1 vaccine, 1 dose fits all' public health approach to a more personalized or individualized approach [10,99]. There has been an evolution from single product to multiple specific products, from egg-based vaccines to cell-based vaccines, and the shift from trivalent vaccine to quadrivalent vaccine is imminent. Multiple routes of vaccine administration are now available, as are adjuvanted influenza vaccines, at least in Europe. There is also the longer-term possibility of moving from antigen- or strain-dependent vaccines to universal influenza vaccines, which may in turn enable a move from annual vaccination to a small number of lifetime vaccine doses.

7.3. The elderly and immunosenescence

Following the post-war 'baby boom' in the middle of the last century, all Western countries are now faced with the healthcare and financial implications of the exponential growth in the number of people age 65 years and older. This is exacerbated by the decreasing birth rates that are simultaneously observed in these countries [100]. In the US, for example, it is predicted that in 2030 there will be 71.5 million people age 65 years and older, which is more than double the figure for 2000 (Fig. 9) [22]. In the US, the fastest growing segment within this age group are those age 85 years and older [101]. This has clinical and public health implications, as such elderly subjects tend to have poor immune responses to currently available influenza vaccines. Therefore, it is important that efforts and resources are directed towards an understanding of the immunosenescence process, and the development of influenza

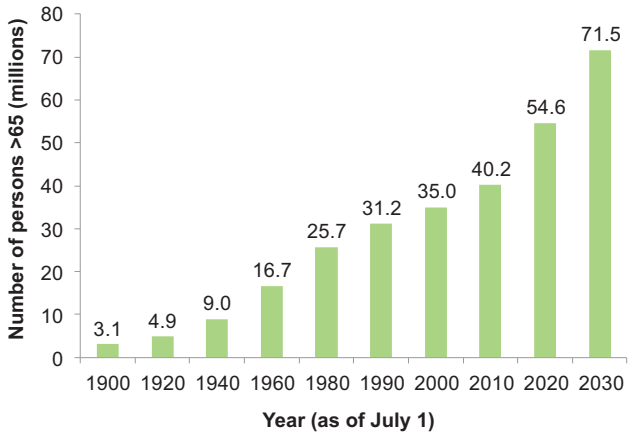

Fig. 9. Estimated number of persons aged >65 years in the US from 1900 to 2030 [125].

vaccines and vaccine technologies that can overcome immunosenescence and provide protection for the elderly. Another important focus should be the funding of vaccine delivery for all elderly members of society and the development of a worldwide recommendation for the use of influenza vaccination, similar to what is done for other vaccines (e.g., tetanus and measles vaccines).

7.4. Vaccinomics

Vaccinomics builds on our previously published "immune response network theory" to understand the critical immunogenetic drivers of the immune response to a vaccine antigen(s), and utilizes this information to conceive and design novel vaccine candidates. "Vaccinomics" refers to the coming era of predictive or individualized vaccinology. By combining current key inquiries regarding pharmacogenetics and pharmacogenomics in the fields of clinical pharmacology and vaccinology, the goal is to provide each group, subgroup, or person with a safe and effective vaccine [10,99,102–108].

Progress in our understanding of the mechanisms underlying heterogeneity in inter-individual immune responses to vaccines is rapidly advancing and will advance the field of personalized and predictive vaccinology [10,99]. This is being driven by advances in the fields of immunology, genetics, molecular biology, and bioinformatics, and our increasing understanding of the human genome. Predictive vaccinology will help guide the selection of a specific vaccination strategy by facilitating the identification of subjects who are likely to exhibit a prophylactic/therapeutic response or, conversely, experience a significant adverse event to a particular vaccine. An example of how genetic variation affects the immune response to a vaccine comes from work we have done with measles vaccine, where it has been found that subjects with a single-nucleotide polymorphism in the gene for SLAM (signaling lymphocyte activation molecule, CDw150) produce significantly lower titers of antibodies after live measles vaccination compared to subjects without the mutation [109]. The impact of this SNP on the response to measles vaccine is biologically plausible, since the SLAM receptor is involved in the binding of the measles hemagglutinin and entry of the virus into cells. By identifying and understanding the effect of genotype on immune phenotype, new vaccine candidates can be engineered to mitigate the effects of this genetic polymorphism. In addition, a vaccinomics approach will help to predict the number of vaccine doses likely to be needed to induce an immune response, and, as illustrated, inform the design and development of new vaccine candidates [10,99].

7.5. New approaches to communication

An individual's decision to accept or not accept vaccination is driven by 3 critical reasons that can simplistically be described as fear (of disease or of vaccine), bandwagoning (social pressure), and coercion. Understanding these key motivators should inform our efforts at improving vaccine coverage. Rather than adhering to conventional influenza vaccination education programs (usually designed by highly analytic healthcare providers), it is important to draw lessons from other academic disciplines that can help to drive new transformational and innovative educational programs. Thus, there is a need for 21st century teams to design educational materials that include psychologists, designers, sociologists, cultural anthropologists, behavioral psychologists, communication experts, and experts in the use of the new social media. The latter is a particularly important source of health information, particularly for younger members of society [100].

Cultural biases have a large impact on attitudes about vaccines, and the history of anti-vaccinationists [24] is as old as the history of vaccination itself. With few exceptions, it seems that the emergence of a new vaccine is met with significant resistance against it. The claims and activities of anti-vaccinationists have adverse public health consequences, as was observed after a controversial claim [23] that the measles-mumps-rubella vaccine played a causative role in the development of autism [110]. One problem is that members of the public who use the Internet to obtain information on vaccines may be overwhelmed by the immense volume of incorrect or anti-vaccine information that can be found there. There is a spectrum of vaccine decision-making factors that determine whether an individual is pro-vaccine or vaccine-hesitant or anti-vaccine. Those with an anti-vaccine stance may be people who lack a scientific grounding, have denialist or innumerate patterns of thinking, or have low-complexity cognitive styles [111]. Conventional, 'left-brain' highly data-driven approaches are unlikely to be successful in implementing change in these scenarios. To counter the anti-vaccine movement, it is imperative that we improve public education and persuasion through innovative, multidisciplinary efforts, and an understanding how our patients and the public make decisions about vaccine acceptance or rejection.

7.6. Conclusions

Most current efforts to improve influenza vaccine coverage are neither highly innovative nor efficient. As a result, significant gains in vaccine coverage remain elusive. A compelling, memorable metanarrative for influenza vaccination that leads to sustained demand for vaccines is lacking. Priorities should include improved influenza vaccines, and a focus on vaccination of the elderly, who are a burgeoning section of society across the globe. Attainment of the goal of almost universal vaccine coverage is hindered by the need to contend with anti-vaccinationists and by the human tendency to make systematic errors in judgment and choice. A tactical plan that is informed by the science of motivation and change, and which uses multidisciplinary transformation teams, is needed to improve public education and, ultimately, improve coverage rates and reduce morbidity and mortality.

8. Cognitive styles and influenza vaccination: The architecture of a new metanarrative (Caroline M. Poland)

Following a decades-long period of progress and substantial achievements in population-level vaccination against many diseases, the field of vaccinology has experienced a reversal of public attitudes and support, with concerns over the efficacy and safety of vaccines now commonplace. While this has been fostered in part

by an active and substantial anti-vaccine movement [24], a contributing factor is the advent of "media-based consumerism" [112], whereby the pervasiveness of the Internet and social networks endows equal credence on all ideas, regardless of their accuracy and validity. These factors have likely contributed to the failure of many Healthy People 2010 vaccination goals for the US population to be met (Table 2) [113]. At the clinical level, the public's suspicion of vaccines is resulting in outbreaks of vaccine-preventable diseases such as measles [110,114] and mumps [115].

Despite widespread public concerns about vaccine safety and efficacy, little attention has focused on the evaluation of current vaccine education and messaging initiatives. The process and content of educational efforts and framing are critical to increasing awareness, knowledge, and behavior, thereby encouraging vaccine acceptance and use, and increasing coverage rates. Traditionally, the language of 'reason and consciousness' [116] has been used by healthcare providers and issues of reality perception and reality construction are ignored, even though data clearly demonstrate that humans make decisions not by reason, but by emotional projection and cognitive frames that together form stories and parables that dictate their decisions [117].

In his 1985 book, *Amusing Ourselves to Death*, media theorist Neil Postman noted that "The clearest way to see through a culture is to attend to its tools for conversation . . . our languages are our media. Our media are our metaphors. Our metaphors create the content of our culture." [118]. This is relevant to the field of vaccinology generally, and vaccine education specifically, as new tools, new languages, new media, and new metaphors are needed to increase vaccine acceptance and coverage rates.

8.1. The nature of beliefs, cultural frames, and cognitive bias

Vaccines and the public health are fundamentally about moral values, as noted by our tendency to assign words such as "good" or "bad" to health decisions involving these issues. Not being vaccinated against influenza and having to be hospitalized is something that is labeled 'bad', whereas taking active steps to be protected against influenza and remain healthy is deemed to be 'good'. Thus, moral values are articulated as words, which are defined relative to at least one frame or belief. Furthermore, as Turner [117] and others would suggest, people think and make decisions in terms of systems of frames, which are assembled into concepts and beliefs that they believe to be moral and sensible. Cognitive biases are a system of concepts or frames that structure our brains and thinking, and which can mislead us regularly on an unconscious basis [119]. People make decisions about vaccines and other healthcare issues in a variety of ways, drawing on heuristics, emotion, data, and other factors to arrive at a decision. However, the important point is that regardless of how people choose to make their decisions, all are using a particular or preferred cognitive style while making those decisions, with many of their biases unnoticed to them in their decision making.

8.2. The Preferred Cognitive Style and Decision-Making Model

Using the frameworks of cognitive psychology, motivational interviewing [120], and the Health Belief Model [121], I developed a model to understand health decision-making termed the Preferred Cognitive Style and Decision-Making Model. This model integrates the fields of medicine and psychology and can be used to explain and define new methods for educating and motivating patients to make explicit and more rational medical decisions generally, and decisions about needed vaccines specifically [111]. Using motivational interviewing, the healthcare provider asks the patient guiding questions to help them determine what they value and what their fears are, in the hope that the responses received will help the healthcare provider lead the patient to make a healthy decision. Using the Health Belief Model, the healthcare provider discusses perceived risk with the patient, whether that is fear of being vaccinated or of not being vaccinated, as well as the patient's perceived susceptibility to the illness and perceived benefit of engaging in a particular health decision. With both of these techniques and other similar techniques, the underlying rationale is that the healthcare provider is not telling the patient what to do; instead, they are engaging in a meaningful conversation with that patient to guide them toward choosing a healthy behavior for themselves.

The Preferred Cognitive Style and Decision-Making Model recognizes at least six common cognitive styles: denialist, innumerate, fear-based, heuristic, bandwagoning, and analytical (Table 3) [111]. For each cognitive style, examples of the main effects of and types of verbal expression have been identified, and methods of communication and approaches suggested. For example, for patients with a fear-based cognitive style, a verbal expression of their viewpoint might be: "I heard that vaccines are harmful, so I'm not going to vaccinate my child." In such a situation, providing the patient with data (an analytical approach) is unlikely to motivate them because there is substantial fear and emotion inherent in that decision. A better approach might be to talk to them about their fear, understand what the source of that fear is and process that with them. For these patients, using a technique such as social norming approaches may reassure them that they are not alone in having fears about vaccinating their children, and this might be helpful so they are more open to engaging in a constructive conversation, and subsequent choice.

An awareness of different cognitive styles can also be used to shape public health educational campaigns. This is exemplified by a recent public health campaign for human papillomavirus (HPV) vaccine that portrayed HPV as "sexually transmitted cancer". This campaign did not rely on data per se, but instead took note of the fact that the word 'cancer' is associated with fear and emotion to invoke or project a story in the target audience's mind. Such an approach will reach a fear-based cognitive style in a much more direct way than simply handing over a fact sheet containing data. Regardless, it is apparent that the most effective campaigns are likely to be those that appeal to a variety of preferred cognitive and decision-making styles—suggesting that the standard approach of a single style be abandoned.

8.3. The role of education

Given that there is a spectrum of cognitive styles that, in turn, influence decision-making styles, it is clear that new education methods are needed to educate both the public and providers about the value of vaccines. This likely means, in the case of influenza (and perhaps other) vaccines, abandoning most current education efforts, as influenza vaccine coverage has reached a ceiling, despite repeated use of conventional educational approaches. Future efforts should involve harnessing meaningful media—for instance, the use of social media for adolescents and younger adults, and behavioral research, which should be used to inform and direct education activities. It is also important to bear in mind that the ways in which healthcare workers and patients process information tend to be markedly different (Fig. 10). Whereas healthcare workers may prefer fact-based language and scientific arguments, patients often have a preference for pictures and stories, and seek empathy from their healthcare provider [116]. These differences serve to remind us that a spectrum of educational approaches is required in order to engage different individuals and groups effectively.

A critical foundation in education is the connection between a story, or how someone organizes their learning, which is projected, story upon story, into a parable [117]. This is illustrated by

Table 3
Cognitive decision-making styles and educational strategies with message framing specific to each style (adapted from [111]).

Cognitive style	Main effect	Verbal expression	Approach
Denialist	Disbelieves accepted scientific facts, despite overwhelming evidence. Prone to believe conspiracy theories	"I don't care what the data show, I don't believe the vaccine is safe"	Provide consistent messaging repeatedly over time from trustworthy sources, provide educational materials, solicit questions, avoid "hard sell" approach, use motivational interviewing approaches
Innumerate	Cannot understand or has difficulty manipulating numbers, probabilities, or risks	"One in a million risk sounds high, for sure I'll be the 1 in a million that has a side effect, I'll avoid the vaccine"	Provide nonmathematical information, analogies, or comparators using a more holistic "right brain" or emotive approach
Fear-based	Decision making based on fears	"I heard vaccines are harmful and I'm not going to get them"	Understand source of fear, provide consistent positive approach, show risks in comparison to other daily risks, demonstrate risks of not receiving vaccines, use social norming approaches
Heuristic	Often appeals to availability heuristic (what I can recall equates with how commonly it occurs)	"I remember GBS happened in 1977 after flu vaccines, that must be common, and therefore I'm not getting a flu vaccine"	Point out inconsistencies and fallacy of heuristic thinking, provide educational materials, appeal to other heuristics
Bandwagoning	Primarily influenced by what others are doing or saying	"If others are refusing the vaccine there must be something to it, I'm going to skip getting the vaccine"	Understand primary influencers, point out logical inconsistencies, use social norming and self-efficacy approaches
Analytical	Left brain thinking, facts are paramount	"I want to see the data so I can make a decision"	Provide data requested, review analytically with patient

the public's behavior during the influenza pandemic of 2009–2010, when surprisingly few people received pandemic vaccine despite widespread media reports, education campaigns, knowledge dissemination, and access to vaccines. The principles of story (i.e., "injecting a foreign substance into you is dangerous"), projection (i.e., "I remember Guillain–Barré syndrome occurred in some people who got the 1976 H1N1 vaccine"), and parable (i.e., "so this new vaccine is a 'new' substance and must also be dangerous—I better not get it—new vaccines are dangerous and something bad could happen") have been proposed by us to assist in explaining this poor uptake rate.

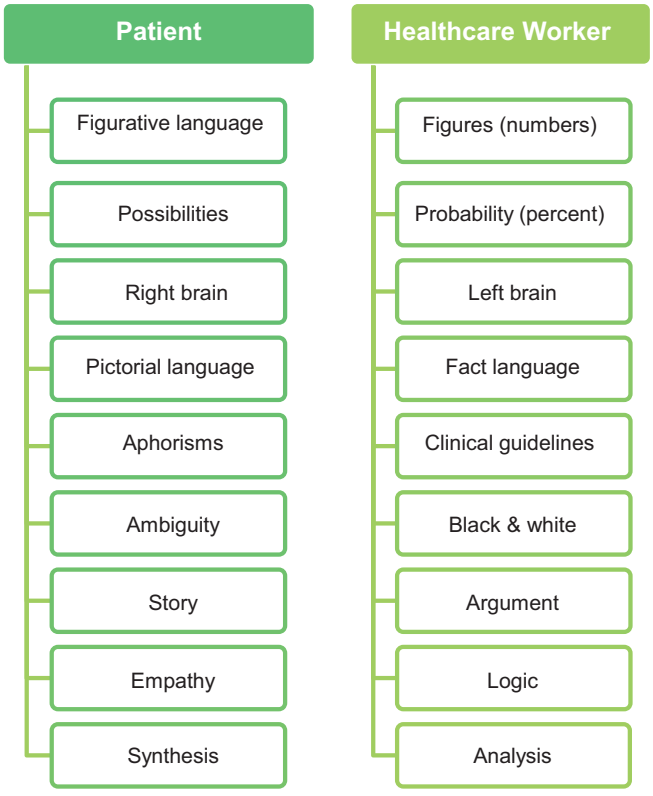

Fig. 10. Contrast between information-processing styles in healthcare workers and patients (adapted from [116]).

In the desired state, knowledgeable and educated healthcare providers and the populace with a compelling story and parable would lead to nearly universal vaccine coverage and the control of influenza and other vaccine-preventable diseases. This will likely not be achieved until a new language and communication style is used within the healthcare network—informed by findings from cognitive psychologists, sociologists, cultural anthropologists, and media-savvy educators.

8.4. Conclusions

Ample data demonstrate that people make fundamentally flawed decisions, including health decisions, due to unconscious biases. This leads to systematic errors in judgment and choice. It is therefore necessary to understand the role of cognitive bias and preferred cognitive and decision-making styles in order to develop individual and group educational programs and metaphors to influence vaccine decision making. The Preferred Cognitive Style and Decision-Making Model assists in understanding how people make decisions about health behaviors such as vaccine acceptance or rejection. The concepts outlined here can and should be used in the development of the architecture of a new metanarrative for public health campaigns to increase influenza vaccine coverage.

9. Summary

Seasonal and pandemic influenza produce substantial morbidity and mortality. Even though pandemic influenza occurs sporadically, on average once every 40 years [1], the presence of seasonal H3 and H1 endemic strains poses an ever-constant threat to billions of humans annually. Past influenza pandemics, including the 1918 H1N1 Spanish influenza, the Asian H2N2 influenza pandemic of 1957–1958, the Hong Kong H3N2 influenza pandemic starting in 1968 and, more recently, the 2009 swine-origin H1N1 influenza pandemic originating in Mexico [1], teach us that influenza pandemics will continue to arise in the future and in ways that are currently highly unpredictable.

The influenza threat also highlights the need for worldwide surveillance to identify changes in circulating seasonal strains in humans, and to identify those zoonotic strains that have pandemic potential. Surveillance must also be year round—as evidenced by the H1N1 swine influenza pandemic of 2009–2010 in the UK, which

occurred during an unexpected time of year (summer) and affected young adults and children at higher rates compared to the influenza active periods of previous years [2]. Finally, the burden of influenza highlights the desire for influenza vaccines that are highly effective, extremely safe, ubiquitously available, and inexpensive. This is particularly important now that many, including the US Centers for Disease Control and Prevention, recommend that all individuals over 6 months of age receive influenza vaccination [122].

A "perfect" influenza vaccine would have all of these attributes. However, in reality, enhancing the virtue of one of these attributes can negatively influence the others. In the context of a world that already has safe and inexpensive influenza vaccines, even if they have suboptimal efficacy [7], we must question how much additional vaccine reactogenicity, cost, or risk would be acceptable in the quest for greater protection. Although serious adverse events, such as narcolepsy [65], are rarely associated with current influenza vaccines, they may have long-term consequences and, moving forward, the public may be less inclined to accept newer vaccines with even greater reactogenicity. Recent developments in the field of vaccines, such as systems biology and genomics, may be the answer to developing influenza vaccines with greater efficacy and more predictable vaccine responses compared with currently available vaccines, thus mitigating, or at least potentially predicting severe vaccine adverse events and reactogenicity [11,66]. We should consider the influence these burgeoning areas of science have on the future of individualized vaccinology approaches to influenza vaccines.

Another emerging modality for influenza prophylaxis or treatment is the area of passive immunotherapy. Extremely interesting anecdotal and animal evidence case reports and non-randomized clinical trials using passive immunotherapy in cases of severe seasonal and pandemic influenza infection have been conducted since the beginning of the 20th century [13,19]. The next step to assess efficacy and safety is to conduct randomized clinical trials. Current [96] and future clinical trials on passive immunotherapy are essential if this modality will result in widespread use in the clinical setting.

The concept of a 'universal influenza vaccine' was rekindled with the reconstruction of the 1918 Spanish influenza virus [38]. Incorporation of critical HA proteins/epitopes into the next generation of influenza vaccines may one day lead to a universal vaccine and eliminate the need for annual vaccination while providing protection against future pandemic influenza viruses. In turn, a universal vaccine could also generate the production of influenza monoclonal antibody(ies) and lead to more effective immunotherapy products (such as current IVIg products becoming hIVIg by virtue of being collected from individuals having been vaccinated with the universal vaccine).

This article also highlights the possibility of broader protection from existing vaccine technologies. Data from Rockman et al. [98] provide compelling evidence as to the efficacy of a vaccine containing H5N1 antigen combined with ISCOMATRIX™ adjuvant to induce broad protection from lethal H5N1 influenza. This shows us that currently available antigens combined with the right adjuvant have the potential for interim use between pandemics and during the lag time between pandemic identification and development of a homologous vaccine. Thus, we must ask ourselves, given the promising ISCOMATRIX™ adjuvant research, would it have been possible to alter the course of the 2009 pandemic with immediate use of seasonal influenza ISCOMATRIX™ adjuvant vaccine?

During this symposium—aptly titled, 'New Wisdom to Defy an Old Enemy'—a key area of this new wisdom is the promising concept of 'vaccinomics,' an individualized approach to influenza vaccination [10]. The goal of this personalized, predictive approach is to not only improve the practice of vaccinology, but also to generate new vaccine candidates.

Finally, the creation of safer, more effective, influenza vaccines should be coupled with significant efforts to increase vaccination rates in the US and developed countries, followed by developing countries. Educational efforts to change public attitudes must be designed and implemented in order to improve vaccine acceptance, with an overall goal of nearly universal vaccine coverage and, ultimately, the control of influenza and other vaccine-preventable diseases.

Conflicts of interest statement

Dr. Poland received remuneration to present at the symposium sponsored by bioCSL. He is the chair of a Safety Evaluation Committee for investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co. Inc., bioCSL, Avianax, Sanofi Pasteur, Dynavax, Novartis Vaccines and Therapeutics, and PAXVAX Inc. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

Dr. D.M. Fleming received remuneration to present at the symposium sponsored by bioCSL. He has recently provided consultancy services to GSK in relation to the burden of illness attributable to influenza and RSV infection. He has also served on advisory boards to Novartis, Med Immune, and Sanofi Pasteur concerned with the burden of illness due to influenza and the effectiveness of influenza vaccines.

Dr. Treanor received remuneration to present at the symposium sponsored by bioCSL. He is on the scientific advisory board of Novartis and Immune Targeting Systems. He has received grants and/or contract funding from Sanofi, Pfizer, Protein Sciences, Ligocyte, and Glaxosmithkline. He has non-commercial grant support from the National Institute of Health and the Centers for Disease Control and Prevention.

Dr. E. Maraskovsky is an employee of CSL Limited, Parkville, Australia.

Dr. Luke received remuneration to present at the symposium sponsored by bioCSL. He has no commercial interests in influenza vaccines or therapeutics.

Dr. E. Ball is an employee of bioCSL, Melbourne, Australia.

Ms. Poland has offered consultative advice on the behavioral aspects of vaccine decision making to Merck Research Laboratories.

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