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Seasonal influenza vaccines and hurdles to mutual protection

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ABSTRACT

While vaccines against seasonal influenza are available, major hurdles still exist that prevent their use having any impact on epidemic spread. Recent epidemiologic data question the appropriateness of traditional vaccination timing (prior to the winter season) in many parts of the world. Furthermore, vaccine uptake in most countries even in high-risk populations does not reach the 75% target recommended by the World Health Organization. Influenza viruses continually undergo antigenic variation, and both inactivated and live attenuated influenza vaccines confer only short-lived strain-specific immunity, so annual revaccination is required. Improving vaccine-induced immunity is therefore an important goal. A vaccine that could confer durable protection against emerging influenza strains could significantly reduce onward transmission. Therefore, further understanding of protective immunity against influenza (including broadly cross-protective immune mechanisms such as haemagglutinin stem-binding antibodies and T cells) offers the hope of vaccines that can confer the long-lived heterosubtypic immune responses required for mutual protection. **C. Chiu, CMI 2016;22:S113**

Introduction

Vaccines are one of the major successes of modern medicine. Available cheaply and widely used, they have been instrumental in the global control of a variety of infectious diseases and their resulting complications [1]. This has been achieved by inducing robust, long-lasting immunity with vaccines that recapitulate the protective immune responses seen after natural infection with the pathogens against which they protect. However, uniquely amongst the commonly used vaccines, those against influenza provide minimal long-term protection and require annual revaccination. Therefore, it has not been possible to adequately prevent the onward transmission that results in epidemics and pandemics. Major impediments still remain to the generation of optimal influenza vaccine-induced immunity; these are related to both the fundamental biological features of the virus and to its interaction with the host. However, recent advances in our understanding of the immune response to influenza infection have revived hopes for a so-called universal vaccine, with the potential to protect both vaccinated individuals and their contacts from newly emerging virus strains [2].

Epidemiology and Delivery of Influenza Vaccination

Despite the availability of vaccines, influenza is still a major cause of morbidity and mortality worldwide. Each year, 5–15% of the world's population will suffer an influenza infection, with an estimated 3 to 5 million cases of severe disease and up to 500 000 deaths (http://www.who.int/mediacentre/factsheets/2003/fs211/en/). This results in expenditure of up to $167 billion per annum in the United States alone. This enormous socioeconomic burden has made influenza control a global priority. In temperate regions, influenza is a winter illness with epidemics during the colder months hypothesized to be related to lower temperatures, lower humidity or decreased solar radiation affecting virus transmissibility [3]. In addition, host factors such as seasonal variations in immunity and behaviour, including spending more time in contained spaces, may also play a role in transmission [4]. Some of these factors may also explain the monsoon seasonality seen in subtropical areas and the more year-round incidence found at tropical latitudes [5]. Only recently has this geographically distinct epidemiology been clearly recognized and this is beginning to have an impact on the timing of delivery of influenza vaccines. In many regions, this is still determined on a pre-winter seasonal schedule even when no winter seasonality is seen. This is complicated further in countries such as India, which, although in the Northern Hemisphere, spans temperate, subtropical and tropical zones and

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still receives delivery of Northern Hemisphere influenza vaccines in September or October, when most cases of seasonal influenza have already occurred [6].

Even in areas where seasonal influenza epidemics are a predictable occurrence and concerted public health campaigns take place, vaccine uptake is generally poor [7]. In the United States, where universal vaccination is recommended, overall vaccine uptake is approximately 44% in adults and 59% in children (http://www.cdc.gov/flu/fluvaxview/1415season.htm). Elsewhere, influenza vaccination is targeted towards high-risk groups such as the elderly, those with chronic health problems or immunosuppression and pregnant women. In the UK, vaccine coverage varies according to the group in question, from approximately 44% (in pregnant women) to 73% (in older adults) (https://www.gov.uk/government/statistics/seasonal-flu-vaccine-uptake-in-gp-patients-in-england-winter-season-2014-to-2015). Only a few countries globally have therefore achieved the target set by the World Health Organization of 75% vaccine coverage in elderly adults and those with chronic health conditions (http://www.who.int/influenza/vaccines/SAGE_information/en/). The reasons for this are complex and multifactorial (with strategies to address this having been extensively reviewed [8–12]), but in the absence of widespread coverage, even the best vaccines cannot hope to reduce onward transmission, let alone influenza vaccines, which are currently suboptimal.

Influenza Transmission

Influenza replicates primarily in the respiratory epithelium and is transmitted by droplets (>10 μm) and aerosols (<5 μm) generated by breathing, coughing or sneezing [4]. However, the exact mechanisms and relative contribution of different transmission modalities amongst human populations have been difficult to clearly establish. Thus, the role of inhalation, direct contact with droplets, indirect contact via settled particles and fomites, and conjunctival introduction remain unclear [13,14]. For example, although influenza viruses have been found to survive on surfaces for up to several days, the risk of transmission by indirect contact, while probably low, has not been accurately predicted [15]. Most studies have been limited by confounders, and the extent to which transmission data from animal models can be extrapolated to humans is unknown. It is likely that a complex interplay between the environment, viral properties including receptor specificity and host factors is responsible for determining the likelihood of any transmission event. However, most environmental and virus-determined factors are difficult or impossible to alter. Furthermore, attempting to block transmission by treating infected individuals with antivirals or behavioural modification is futile both in terms of partial effectiveness of these interventions and in our ability to identify infected individuals at an early stage [16]. This is further complicated by the fact that many influenza cases are asymptomatic while continuing to shed virus. In a large community cohort study in England from 2006 to 2011, approximately 18% of unvaccinated individuals were estimated by serologic diagnosis to have been infected, but around 77% of these were asymptomatic [17]. Thus, modulating the host response (and in particular the adaptive immune response) to infection by vaccinating before virus exposure continues to be the best strategy for both prevention of infection and, potentially, transmission.

Targets of Adaptive Immunity

An ideal influenza vaccine would induce sterilizing immunity that persisted lifelong and protected against all strains of the virus. This would protect the vaccinated individual against influenza disease and interrupt onward transmission. However, current vaccines are unable to consistently achieve any of these aims. Two major factors contribute to this: the rapid and continual alteration of virus surface proteins to evade host immunity and the inability of current vaccines to induce consistently high levels of protection [18]. In principle, protective immunity can by conferred by stimulation of humoral (antibody mediated) and/or cell-mediated (T cell) immunity [19]. These adaptive immune mechanisms are characterized by their capacity to respond more rapidly and strongly to reencounter with pathogens via immune memory. However, almost all successful vaccines currently rely on antibody-mediated correlates of protection, and many questions still remain unanswered about the role that T cells can play in vaccine-induced protection.

Haemagglutinin (HA) and neuraminidase (NA), the two major surface glycoproteins, are both recognized by the host and lead to the induction of antibodies. HA functions to allow virus attachment to sialic acid on respiratory epithelial cells, followed by membrane fusion and virus entry, while NA cleaves sialic acid, thus allowing escape of mature virions from the infected cell [20]. Both are recognized by humoral immunity, but the induction of anti-HA antibodies in particular is well recognized to correlate with protection and is the core mechanism by which all current influenza vaccines function. The HA protein (which is arranged as a homotrimer) consists of a transmembrane and two extracellular domains: a highly glycosylated and globular head (HA1) and a stalk (HA2) that is essential for the fusogenic function of HA and therefore is relatively conserved across virus strains [21]. The HA head encompasses the receptor binding site and a number of antigenic areas to which antibodies can bind [22]. These antibodies may allow virus neutralization, but the sites that they recognize are usually highly variable, undergoing a process known as antigenic drift [23]. Because there are relatively few functional constraints, variations in these areas (due to the poor copy fidelity of RNA polymerase) accumulate rapidly in response to immune pressure and gradually lead to sufficient alteration of the antigenic sites to render antibody-mediated immunity ineffective and to allow seasonal epidemics to occur. Over time, these changes have resulted in divergence of influenza A into 16 subtypes divided into two phylogenetic groups [24,25]. Thus, H1- and H5-expressing strains, which show greater sequence relatedness, are classified together in group 1, whilst H3 and H7 are found in group 2. NA is arranged similarly as a homotetramer with a head, stalk and transmembrane region linked to a short cytoplasmic tail [26]. It too is subject to antigenic drift, and there are nine NA subtypes in two groups of influenza A.

Because the genome of influenza is arranged in eight segments, HA and NA are encoded on separate RNA strands and can reassort independently [27]. This, along with varied animal reservoirs and the possibility of coinfections with more than one strain of influenza, means that new viruses can arise through genetic reassortment in animals with the capacity to infect humans and an array of distinct antigenic sites that diverge from those in recently circulating seasonal strains. This phenomenon of antigenic shift means that it is possible for the majority of the population to have little preexisting immunity against reassorted strains, thus allowing the widespread infection characterizing pandemics. This most recently occurred in 2009, when a reassorted strain comprising gene segments derived from human, swine and avian influenza viruses circulated widely and rapidly [28]. While this mostly caused a relatively mild clinical syndrome, highly pathogenic strains including avian H5N1 continue to have the potential to cross over and cause severe disease with efficient human-to-human transmission [29].

In addition to antibodies, there is substantial evidence that T cells play an essential role in immunity against influenza [19]. In