Seasonal influenza vaccination and the risk of infection with pandemic influenza: a possible illustration of non-specific temporary immunity following infection

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Four Canadian studies have suggested that receipt of seasonal influenza vaccine increased the risk of laboratory-confirmed infection with 2009 pandemic influenza A(H1N1). During the influenza season of 2009 in Victoria, Australia, this virus comprised 97% of all circulating influenza viruses for which sub-typing was available. We found no evidence that seasonal influenza vaccine increased the risk of, or provided protection against, infection with the pandemic virus. Ferret experiments have suggested protection against pandemic influenza A(H1N1) 2009 from multiple prior seasonal influenza infections but not from prior seasonal vaccination. Modelling studies suggest that influenza infection leads to heterosubtypic temporary immunity which is initially almost complete. We suggest these observations together can explain the apparent discrepant findings in Canada and Victoria. In Victoria there was no recent prior circulation of seasonal influenza and thus no temporary immunity to pandemic influenza. There was no association of seasonal influenza vaccine with pandemic influenza infection. In Canada seasonal influenza preceded circulation of the pandemic virus. An unvaccinated proportion of the population developed temporary immunity to pandemic influenza from seasonal infection but a proportion of vaccinated members of the population did not get seasonal infection and hence did not develop temporary immunity to pandemic influenza. It may therefore have appeared as if seasonal vaccination increased the risk of infection with pandemic influenza A(H1N1) virus.

Introduction

Four Canadian studies have recently suggested that receipt of seasonal influenza vaccine increased the risk of infection with 2009 pandemic influenza A(H1N1) 1.4–2.5-fold [1]. The authors of these studies advanced two hypotheses to explain these unexpected observations. Firstly they suggested that the seasonal influenza vaccine effectively blocked cumulative infections with seasonal influenza viruses, thus preventing the induction

of cross-reactive immunity which may have protected from pandemic influenza A(H1N1) infection. They referred to this as the ‘cross-protection block hypothesis’ but argued that unrealistically high values for seasonal influenza vaccine effectiveness and seasonal influenza attack rates needed to be assumed for this hypothesis to produce odds ratios consistent with their observations (Appendix G in reference [1]). Secondly, based on the concept of antibody-dependent enhancement (ADE) of virus replication, they argued that vaccination against one or more influenza strains actually increased the risk of infection with a subsequent heterosubtypic strain that was antigenically remote from any of the vaccine strains [1]. According to this hypothesis, low levels of pre-existing weakly heterotypic or heterosubtypic antibodies promoted virus endocytosis and subsequent replication, increasing viral load production. In ferrets challenged with a lethal virus following immunisation with a non-adjuvanted human vaccine known not to provide protection to naïve animals, the previous vaccination with a heterosubtypic strain appeared harmful [2]. This observation supported the hypothesis of possible ADE, although we believe these studies might not be transferable to humans.

In Victoria, Australia, we found no evidence of increased risk of laboratory proven pandemic influenza A(H1N1) infection in a population that had previously received only seasonal influenza vaccine [3]. Pandemic influenza occurred during the southern hemisphere influenza season of 2009 and, in Victoria, comprised more than 97% of all circulating influenza viruses for which sub-typing was available [4]. This would have been the perfect setting to have demonstrated ADE of viral replication if it were a general phenomenon, given that pandemic influenza A(H1N1) is a quadruple reassortant virus that is antigenically distant from recently circulating strains and that there was a significant antigenic distance between the vaccine and circulating strains of influenza [5]. However we found no evidence of increased risk of seasonal influenza

amongst recipients of the seasonal influenza vaccine, with an estimated age adjusted odds ratio of 0.97 (95% confidence interval (CI): 0.6–1.56) [3]. A household study in Western Australia found a similar result with an adjusted odds ratio of 1.0 (95% CI: 0.7–1.5), although this study used influenza-like illness rather than laboratory-confirmed influenza as its outcome [6]. Laboratory-confirmed influenza was the outcome assessed in both Canada [1] and Victoria [3].

Based on a series of ferret experiments we have found that experimental infection(s) with seasonal influenza decreased the risk of infection subsequent to challenge with pandemic influenza, but that vaccination with adjuvanted seasonal influenza vaccine provided neither protection or enhancement, even with high levels of antibodies [7]. On the other hand, vaccination with adjuvanted human seasonal influenza vaccine protected the ferrets from seasonal influenza infection.

The temporary immunity hypothesis

We would like to suggest an alternative hypothesis to explain the findings from both Canada and Victoria. In our hypothesis recent infection with any strain of influenza would confer temporary immunity to infection with any other strain, independent of antigenic distance, but vaccination would not confer protection unless the vaccine and circulating strains were antigenically similar.

Although it is not an accepted immune phenomenon, the concept of temporary immunity has been explored in the modelling literature for a number of years. In 2003 Ferguson *et al.* reported that ‘short-lived strain-transcending immunity’ was necessary to reproduce what was known from ‘epidemiological dynamics and viral evolution at the sequence level’ in order to restrict viral diversity and produce influenza drift dynamics with seasonal patterns [8]. Without non-specific temporary immunity, simulations produce more divergent strains than are demonstrated by surveillance. The concept has subsequently been supported by other investigators, including Tria *et al.* [9], Omori *et al.* [10]; and our own modelling [11]. It has been further elaborated in a series of papers by Minayev and Ferguson [12,13].

The biology of temporary immunity

Type I interferons and other cytokines have been suggested as mediators of this phenomenon by inducing an antiviral state in infected, and neighbouring, epithelial cells [14]. In a guinea pig model of influenza infection, daily intranasal administration of recombinant human interferon alpha completely blocked transmission of pandemic influenza A(H1N1) both from and to treated animals [15]. Further, prophylaxis with interferon alpha reduced virus shedding of ferrets and guinea pigs infected with highly pathogenic influenza strains and morbidity following seasonal influenza challenge [16,17].

Protection from symptomatic infection may also be mediated by T-cell immunity, specific for conserved epitopes in heterosubtypic influenza strains [7,15,18], and B-cell immunity through antibodies specific for common epitopes, generally between homosubtypic strains [19,20]. Animal models of influenza have shown that prior infection(s) with seasonal influenza strains reduce transmission and virus shedding of pandemic influenza A(H1N1) virus [7,15].

Temporary immunity induced by previous experimental infection has also been demonstrated to reduce morbidity and mortality following highly pathogenic influenza challenge [18]. We suggest temporary immunity may be mediated by a combination of innate and adaptive immune responses. Protection provided by temporary immunity may vary with age but would be expected to be immediately higher than that provided by antibody-mediated cross-protection alone.

The duration of temporary immunity is a critical issue in this hypothesis but is not yet clearly defined. On theoretical grounds Ferguson *et al.* suggested that following infection, temporary immunity would initially protect any infected person against all influenza strains before waning with time (supplementary material in reference [8]). Most models simulate temporary immunity using rate equations decaying with an exponential half life. A mean duration of temporary immunity of three months is credible in modelling with seasonality, since immunity needs only to last as long as the influenza season. If it lasts too long it does not allow the next season epidemic to start; if it is too short, too many strains proliferate.

Evidence for temporary immunity in humans

In a re-analysis of data from school surveys following the 1918-19 pandemic in England and Wales, Mathews *et al.* have suggested that temporary immunity is one of the mechanisms that need to be invoked to explain the observed wave phenomenon of that pandemic [21]. The authors also calculated odds ratios for infection with a second influenza sub-type following infection with a different primary sub-type from published studies of the influenza A(H2N2) pandemic of 1957-8 and the re-emergence of influenza A(H1N1) in 1977 [21]. Slepushkin studied a group of factory workers and reported that workers with symptoms during the seasonal influenza A(H1N1) outbreak in the spring of 1957 were less likely to be symptomatic when the new influenza A(H2N2) appeared [22]. The calculated odds ratio was 0.4 (95% CI: 0.3–0.6) [21]. Sonoguchi *et al.* reported protection from influenza A(H1N1) infection in Japanese school children who had previously been infected with influenza A(H3N2) when influenza A(H1N1) re-emerged in 1997-8 [23]. When exposure was separated only by days or weeks, the calculated odds ratios for a second infection, given primary infection with a different subtype, was calculated as 0.06 (95%

CI: 0.02–0.13) for high school students and 0.2 (95% CI: 0.08–0.3) for primary school students [21].

Extending this hypothesis, and further suggesting that temporary immunity may be conferred not only by influenza infections but also by other viral infections, is a contemporary report from Sweden that rhinovirus infection may have decreased the risk of infection with pandemic influenza A(H1N1) by what was suggested to be a cytokine-mediated phenomenon [24].

Temporary immunity following seasonal influenza virus circulation in Canada and Australia

If the temporary immunity hypothesis is valid, and if the seasonal influenza vaccine provided no protection against pandemic influenza, we would have expected no protection against pandemic influenza A(H1N1) in Victoria in 2009, when there was minimal circulation of any seasonal influenza virus prior to the introduction of pandemic influenza A(H1N1) [3]. In Victoria there was no opportunity for temporary immunity to develop.

However our expectations in Canada would have been different, given that seasonal influenza circulated with peak incidence eleven weeks before the first notified cases of pandemic influenza A(H1N1). Canadians who had received seasonal influenza vaccine had approximately 50% protection against seasonal infection [1] and would have foregone the potential temporary immunity induced by seasonal infection. However temporary immunity to pandemic influenza A(H1N1) would have been induced in unvaccinated Canadians who had a seasonal influenza infection. This may have resulted in an *apparent* increased risk of pandemic influenza A(H1N1) infection in people vaccinated against seasonal influenza.

We explored the temporary immunity hypothesis, making a range of assumptions about seasonal influenza vaccine effectiveness (VE) and seasonal and pandemic influenza infection rates (the cumulative incidence of infection). Our primary assumption was that there was no protection from pandemic influenza following receipt of the seasonal influenza vaccine. We also assumed there was no risk associated with vaccination, implying that for seasonal influenza vaccine $VE=0$ against pandemic influenza A(H1N1) infection.

In a case-control study VE is estimated as $1-OR$, where OR is the odds ratio. We considered a theoretical case-control study and calculated the OR for the outcome of pandemic infection given the exposure to seasonal vaccination. We used a method similar to that outlined in Skowronski *et al.* (Appendix G in reference [1]). We let θ_s be the seasonal infection rate, θ_p the pandemic infection rate and α the proportion of temporary immunity afforded by a recent seasonal influenza infection.

The probability of a vaccinated individual being infected with pandemic influenza A(H1N1) can be expressed as

$$p_v = [\theta_s * (1-VE) * (1-\alpha) + \theta_s * VE + (1-\theta_s)] * \theta_p.$$

This formula acknowledges there are three ways a vaccinated individual could have become infected with pandemic influenza A(H1N1): first, the individual was exposed to seasonal influenza and infected (θ_s), vaccination was not effective ($1-VE$) and there was no temporary immunity ($1-\alpha$); second, the individual was exposed to seasonal influenza but the vaccine was effective (VE), so that the individual was not infected with seasonal influenza and therefore had no temporary immunity; third, the individual was not exposed to seasonal influenza and therefore not infected ($1-\theta_s$), and hence had no temporary immunity. In each case the individual had θ_p chance of infection with pandemic influenza.

Similarly the probability for an unvaccinated individual being infected with pandemic influenza A(H1N1) (p_u) is given by

$$p_u = (\theta_s * (1-\alpha) + (1-\theta_s)) * \theta_p.$$

The odds ratio is calculated as

$$p_v (1-p_u) / ((1-p_v) * p_u).$$

We assumed a seasonal influenza VE of 70%, consistent with estimates from the Cochrane review of healthy adults for matched circulating and vaccine strains [25], and seasonal and pandemic infection rates (that is,

FIGURE

Odds ratio of seasonal vaccination comparing patients with and without pandemic influenza infection and proportion of patients with temporary immunity to pandemic influenza following seasonal influenza infection

θ_s : seasonal influenza infection rate.

Seasonal influenza vaccine effectiveness was set at 70%.

seasonal cumulative incidence of serologically confirmed infection) between 20 and 40%, broadly consistent with community studies of seasonal influenza [26] and serological studies of pandemic influenza [27]. For these parameters, we found an odds ratio between approximately 1.2 and 1.5 comparing vaccinated and unvaccinated people infected with pandemic influenza, if temporary immunity from recent previous infection was assumed to be of the order of 80-90% (Figure). As previously noted, temporary immunity was modelled to be 100% initially. The odds ratio increased for higher seasonal VE, higher cumulative incidence of infection and a higher population proportion of temporary immunity. All calculations assumed that there was no protection and no risk from seasonal vaccination against pandemic infection.

Discussion

We suggest that temporary immunity following infection may explain the apparently conflicting findings that the seasonal influenza vaccine provided no protection from pandemic infection in Victoria but increased the risk of pandemic infection in Canada. Assuming that the seasonal influenza vaccine had no effect on the risk of pandemic infection, we have shown that temporary immunity from seasonal infection will result in an *apparent* increase in risk, due to a proportion of vaccinated individuals being infected with pandemic influenza having foregone the temporary protection from seasonal infection. Using a simple susceptible–infected–recovered (SIR) model we have extended our analysis to include the effect of time, and have confirmed that the temporary immunity hypothesis can account for the apparently discrepant findings [11].

This phenomenon would only be observed where pandemic virus circulation occurred within two to three months of seasonal virus circulation, allowing sufficient time for temporary immunity to develop and to wane. This was seen in parts of the northern, but not the southern, hemisphere. Because of the timing of seasonal and pandemic virus circulation, we might also have expected to see the *apparent* harmful effect of seasonal influenza vaccine in the United States and the United Kingdom. We would not have expected to see the effect in any northern hemisphere country that experienced only one wave of pandemic influenza A(H1N1) virus circulation at the time that other countries experienced a second wave, because temporary immunity from prior seasonal influenza infection would have decayed by the time the second wave commenced. Assuming that people infected in the first wave were not infected again in the second wave, neither would we expect to see the apparently harmful effect of seasonal vaccination during a second wave in a country that experienced a first wave, again because temporary immunity from prior seasonal influenza infection would have decayed. The absence of an apparently harmful (or protective) effect of seasonal influenza vaccine during the second pandemic wave in Canada supports this expectation [28].

However, a range of VE results for seasonal vaccination against pandemic influenza infection have now been reported, only some of which can be explained by the temporary immunity hypothesis (Table). The studies from Mexico [29,30] showing protection from pandemic infection following seasonal vaccination are not consistent with one of the assumptions in our model,

TABLE

Reported odds ratios and vaccine effectiveness for the association of seasonal influenza vaccine and pandemic influenza infection, by study site, 2009

Location	2009	Odds ratio (95% confidence interval)	Vaccine effectiveness (%) (95% confidence interval)
United States, military [33]	Apr-May	2.90 (1.84, 4.57)	-190 (-357, -84)
Canada [1] x 4	Apr-July	1.4 – 2.5 (1.03, 2.74)	-68 (-174, -3)
Castellon, Spain [34]	Oct –Jan 2010	1.20 (0.62-2.34) 2008-9 seasonal influenza vaccine	-20 (-134, 38)
United States [35]	May-Jun	1.10 (0.85, 1.46)	-10 (-46, 15)
United States, university [36]	Mar-May	1.10 (0.90, 1.40)	-10 (-40, 10)
United States, school [37]	Apr	1.05 (0.91, 1.20)	-5 (-20, 9)
Castellon, Spain [34]	Oct –Jan 2010	0.96 (0.50, 1.86) 2009-10 seasonal influenza vaccine	+4 (-86, 50)
Victoria [3]	Apr-Dec	0.97 (0.60, 1.56)	+3 (-56, 40)
Western Australia [6]	May-Aug	1.00 (0.70, 1.50)	0 (-50, 30)
Mexico [30]	Apr-July	0.65 (0.55, 0.77)	+35 (23, 45)
Mexico, hospital [29]	Mar-May	0.27 (0.11, 0.66)	+73 (34, 89)

that seasonal vaccine provided no protection against pandemic infection. However both these studies have been reasonably criticised on methodological grounds [31,32]. While some protection is biologically plausible, based on the demonstration of cross-reacting antibodies to pandemic influenza A(H1N1) virus, it would be expected mostly in older people. The findings from the other studies listed in the Table are consistent with the temporary immunity hypothesis.

As described above, the temporary immunity hypothesis suggests that one would only find an *apparent* increase in the risk of pandemic influenza infection associated with the receipt of seasonal influenza vaccination where the circulation of pandemic influenza virus followed that of seasonal influenza virus within a few weeks to months. Recognising this phenomenon would depend on infection rates with both viruses and seasonal influenza vaccine coverage, with the association more evident where seasonal and pandemic influenza infection rates and seasonal influenza vaccine coverage were higher. We suggest that odds ratios up to 1.5 can be explained by this hypothesis using plausible values for infection rates and seasonal influenza vaccine effectiveness. However we agree with Skowronski *et al.* that a high level of immunity, due to temporary immunity in our hypothesis or cross protection in their hypothesis, is needed to completely explain the apparent harmful association of seasonal influenza vaccination with pandemic influenza infection [1].

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