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Immunogenicity and protective efficacy of influenza vaccination

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1. Introduction

Influenza is a highly contagious, airborne respiratory tract infection that affects an estimated 9% of the world's population annually (Ghendon, 1992). Generally considered to be a self-limiting disease, influenza is in fact associated with considerable morbidity and mortality worldwide. Influenza affects all age groups and infection is associated with increased healthcare resource utilisation, work absenteeism and loss of productivity even among otherwise healthy adults (Keech et al., 1998). Elderly individuals and those with underlying medical conditions, such as cardiovascular or respiratory disease, appear at greatest risk of developing life-threatening complications of influenza, such as pneumonia (Centers for Disease Control and Prevention, 2001). Indeed, adults over 65 years of age currently account for approximately 90% of all influenza-related mortality (Simonsen et al., 1998; Szucs, 1999). This is cause for concern given the growth of the elderly population throughout the world.

Influenza is known to affect some 10–20% of the general population in the United States alone each year, resulting in 114,000 hospitalisations and 20,000 deaths annually (Simonsen et al., 1997, 2000). Associated direct medical costs are US$ 1–3 billion (€ 0.97–2.92 billion), with indirect medical costs (including lost earnings due to illness and lost future earnings due to death) estimated to be in the order of US$ 10–15 billion (US Congress Office of Technology Assessment, 1981). A French study conducted in 1989 found total healthcare costs attributable to influenza to be FF1.9 billion, (equivalent to € 290 million), with a cost to society of FF14.3 billion (€ 2.18 billion) (Levy, 1996). More recent German data suggest the total annual costs of influenza to be in the order of US$ 2.9 billion (€ 2.83 billion) (Szucs et al., 2001).

Prevention is considered to be the most effective method of reducing the socio-economic burden of influenza (Szucs, 1999; CDC, 2001). Immunoprophylaxis with inactivated virus remains the most common approach. Current influenza vaccines are usually trivalent, containing two influenza A and one influenza B subtypes. The antigenic composition of the vaccine is reviewed annually and varies to match the strains most prevalent in the hemisphere. This paper will review available data concerning the link between the immunogenicity and efficacy (effectiveness) of currently available influenza vaccines and discuss whether measurement of immunological efficacy alone is adequate to predict the expected clinical effectiveness of influenza vaccination.

2. Materials and methods

In order to quantitatively assess the link between vaccine immunogenicity and efficacy, a computerised literature search was undertaken using MEDLINE (National Library of Medicine, Bethesda MD, USA) and Excerpta Medica (Elsevier Science BV, Amsterdam, Netherlands) databases. Key words used in the search were antibody, protection, influenza, immunogenicity and efficacy. Abstracts of each retrieved article were reviewed and papers were selected for inclusion according to their relevance. The reference lists

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of these selected papers were also then reviewed to identify any other relevant papers for inclusion.

3. Definitions

Vaccination usually has the direct effect of inducing protective immunity in the vaccinated subject. For most vaccine-preventable diseases, vaccination usually also has the indirect effect of producing herd immunity for the population (that is, reducing transmission in the general population). Indeed, the ability of a vaccine to protect against infection can be expressed in a number of different ways: presence of antibodies, seroconversion, increase of geometric mean titre in adults (subjects aged 18–60 years old and elderly aged >60 years old) (CPMP, 1999).

Immunogenicity refers to the ability of a vaccine to induce an immune response (antibody- and/or cell-mediated immunity) in a vaccinated individual. Immunity to influenza infection in man is a multifactorial phenomenon and the relative importance of virus virulence, innate immunity, specific serum IgG antibody, cell-mediated immunity and local antibodies remains to be determined. However, available data appear to indicate a clear correlation between resistance to infection and levels of IgG antibody to haemagglutinin (HA), an antigen expressed on the surface of influenza viruses (Potter and Oxford, 1979), as shown in Fig. 1.

Vaccine efficacy (VE) is defined as the percentage reduction in attack rates in the vaccinated compared to the unvaccinated populations: vaccine efficacy can be calculated using the classic formula of Greenwood and Yule (1915): (1—relative risk), where the relative risk is of developing disease (Chen and Orenstein, 1996). By convention, VE results are multiplied by 100 and expressed as a percent. Vaccine efficacy is a measure under ideal conditions of the level of direct protection against a disease in subjects who have been vaccinated compared with subjects who have not been vaccinated. (For example, a vaccine with 95% VE may reduce the probability of infection by 95%, given equal exposure to infection in all vaccines, or completely prevent infection in 95% of vaccines and confer no protection in the other 5%.) Vaccine efficacy refers to potential efficacy since a vaccine may lose some or all of its protective power if it is used under less than ideal conditions (inadequate refrigeration, improper administration). Randomised, controlled clinical trials under field conditions thus measure efficacy of a vaccine as it has been stored, handled, and administered (Comstock, 1994). The direct protective effect of influenza vaccination can be affected by a number of factors. These include the closeness of the antigenic match between the vaccine and the infecting virus, how the vaccine is handled and administered, and the characteristics of the target population, such as comorbid medical conditions, use of medications that might influence immune function, prior influenza vaccination and high prevaccination antibody titres (Demicheli et al., 2000). Many studies do not correct for such biases (Demicheli et al., 2000). Consequently, it is generally accepted that results of many vaccine trials may represent an underestimate of true vaccine efficacy (Beyer et al., 1989; Hirota et al., 1997; Palache, 1997).

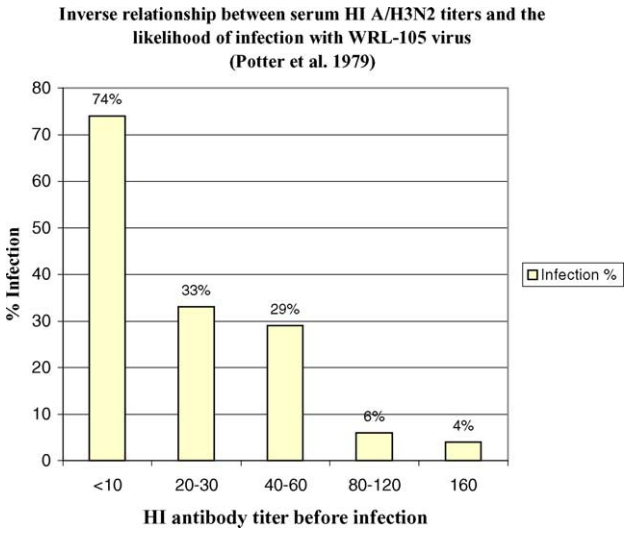

Fig. 1. Relationship between HI titres and the likelihood of infection (Potter and Oxford, 1979).

Vaccine effectiveness, by contrast, refers to the level of protection that a vaccine can be expected to achieve under ordinary field conditions of a public health programme (Fedson, 1998). The effectiveness of a vaccine is not only dependent on its efficacy, but also on the conditions under which the vaccine is used and characteristics of the target population (Comstock, 1994). Vaccine effectiveness is therefore a measure of the direct and indirect effects of immunisation and is typically assessed by means of observational, epidemiological studies. In practice, this distinction between vaccine efficacy and effectiveness is frequently ignored and the term vaccine efficacy tends to be used universally with attendant confusion (Chen and Orenstein, 1996).

Attack rate expresses the disease contagiousness. The attack rate is the number of new cases during the exposure period divided by the number of people in the population who could catch the disease. It is usually reported per 100,000 population.

4. Results

4.1. Rationale for using antibody determination as a surrogate marker of protection

The importance of quantitative and qualitative laboratory surrogate markers to predict vaccine efficacy is well recognised (Käyhty, 1998). The most usual method is to evaluate the immunogenicity of a vaccine by determination of pre- and post-vaccination antibody concentrations. Serological studies are performed for practical reasons. Antibody

assays are relatively easy to perform and yield rapid results, while assessment of cellular response is far more laborious and difficult to standardise.

It is reasonable to assume that the efficacy of a new vaccine candidate can be inferred from immunogenicity studies and antibody assays if the function of the antibody is known. Recovery from influenza virus infection involves a variety of humoral (antibody) and cell-mediated immune mechanisms (Couch and Kasel, 1983). To prevent infection, involved immune mechanisms must account for viral subtype specificity, reduced cross-reactivity of immunity for succeeding antigenic variants, duration of immunity, and immunity at the mucosal surface. Anti-HA antibodies inhibit the attachment of the influenza virus to target cell membrane receptors, thus neutralising virus infectivity. Depending on their concentration, these antibodies can provide complete protection from infection or merely limit disease severity (Brydak and Machala, 2000).

The most commonly used reference method for the assessment of anti-HA antibody levels is the haemagglutination inhibition (HI) test (CDC, 2002). This method uses the ability of influenza virus to agglutinate red blood cells, with agglutination inhibited by anti-HA antibodies specific to the viral strain. HI antibody titres are read as the reciprocal of the highest serum dilution causing complete inhibition of agglutination. They can be measured by a number of laboratory tests, and the results can be presented as the percentage conversion, i.e. the percentage of subjects with protective levels of titres in the population. HI can be defined using the vaccine strains or the wild strains isolated during the influenza season.

4.2. Relationship between antibody level threshold and protection

The efficacy of influenza vaccination has been assessed by immune response studies, challenge studies, field trials and case control studies (Ahmed and Nicholson, 1996).

Challenge studies in healthy young volunteers, using both wild type and live attenuated influenza virus, have allowed identification of antibody levels consistent with protection under experimental conditions (Delem, 1977; Goodeve et al., 1983). Results of these studies demonstrate a positive linear correlation between pre-challenge HI antibody titres and percentage protection. Similarly, HI antibody titres appear inversely correlated with the duration of viral shedding and disease severity (Potter and Oxford, 1979). Analysis of antibody levels following vaccination with inactivated virus or natural exposure to held pathogen also shows higher post-vaccination HI antibody titres to be associated with lower rates of infection on subsequent exposure to influenza virus (Hobson et al., 1972; Dowdle et al., 1973; Masurel and Laufer, 1984). In one study of servicemen during a natural influenza A epidemic, the probability of clinical infection was found to be closely correlated with pre-epidemic homologous HI antibody titre, with an attack rate of only 1.5% among men with a titre of 1/16 compared with 18% in those without detectable antibodies (Meiklejohn et al., 1952). Further serological tests in 2854 men who had not received influenza A vaccine found no cases of influenza in those with HI antibody titres of 32 or greater. Another study of 556 children during a more recent influenza outbreak reported similar findings, with protection from infection found to be closely correlated to the presence of antibodies to the outbreak strain (Davies and Grilli, 1989). Attack rates of approximately 80% were seen for each of the three influenza virus serotypes among children with no detectable antibodies compared with 18% among those with intermediate and high level HI antibody to the challenge strain (equivalent to titres of 40–80 and $\geq$160, respectively).

This inverse correlation between HI antibody titre and susceptibility to influenza infection is well documented (Potter and Oxford, 1979), and is apparent for experimental challenge with live attenuated virus and inactivated virus vaccines as well as natural infection (Clements et al., 1986; Belshe et al., 2000).

Most results indicate that following immunisation with inactivated virus vaccines, HI antibody titres in the range of 30–40 are required to confer 50% protection against infection (protective dose 50 or PD50) (Hobson et al., 1972). Higher antibody titres (120–160) are associated with a higher degree of protection (PD90) (Wesselius-De Casparis et al., 1972; Masurel and Laufer, 1984; Palache, 1997).

Protection studies have allowed influenza vaccine efficacy (effectiveness) to be established, particularly in the elderly. The efficacy of conventional influenza vaccines in healthy adults aged less than 65 years typically ranges from 80 to 90% when the vaccine closely matches the epidemic viral strain (Palache, 1997). However, these vaccines appear less effective for the prevention of clinical illness in elderly subjects (Ershler, 1988; Vetel et al., 2002). Although protection afforded in the elderly is less, vaccine can be relatively effective in preventing hospitalisation and death in the general elderly population. (Ahmed et al., 1997; Fedson et al., 1993; Foster et al., 1992; Gross et al., 1988, 1995; Mullooly et al., 1994; Nichol et al., 1994, 1998; Patriarca et al., 1985). However, effects on hospitalisations are not so great for the high risk elderly. For example, Nichol et al. (1998) found that while vaccination over six seasons was associated with an overall reduction in hospitalisations of 39% for pneumonia hospitalisations, 32% for respiratory conditions and 27% decrease for congestive heart failure, within the high risk elderly sub-group, reductions were only 29% for pneumonia and influenza and 19% for all respiratory conditions. Indeed, while influenza vaccination has been shown to reduce mortality by 74% in institutionalised elderly individuals and 47% in those living in the community, respective figures for prevention of clinical influenza are lower, between 5% (Strassburg et al., 1986) and 30–40% (Patriarca et al., 1985). One possible explanation for these findings may be the lower antibody response to currently available influenza

vaccines seen in older subjects (Phair et al., 1978; Keren et al., 1988).

4.3. Factors which may affect immune response

4.3.1. Impact of age and high-risk conditions

The humoral immune response to both natural influenza virus infection and influenza vaccine may be influenced by a number of factors, including age, the presence of comorbid medical conditions and concurrent use of medications that might influence immune function (Couch and Kasel, 1983; Demicheli et al., 2000). Many studies have shown HI antibody response to influenza vaccination to be lower in older adults, although conflicting data have been reported, with some studies finding no differences or even improved responses compared with younger control subjects (Beyer et al., 1989; Ahmed and Nicholson, 1996). Studies in patients considered to be at high risk of serious post-influenza complications, including the elderly and those with pulmonary disease, renal disease, diabetes mellitus, cancer, haemophilia or HIV infection, have also yielded conflicting findings (Brydak and Machala, 2000). While some studies have found humoral response to influenza vaccine to be reduced in these high-risk groups, others have demonstrated responses to be comparable to those seen in healthy control subjects. Furthermore, although in some cases immunological responses to influenza vaccination for the study group as a whole were considered to be poor, individual patients were found to have HI antibody titres considered protective against infection in healthy subjects (Bernstein et al., 1999).

The level of immune response indicative of protection against influenza infection in such high-risk groups remains to be firmly established. In one paediatric study, HI antibody levels greater than or equal to 32 were found to be highly protective against influenza infection in all patient groups, with the exception of those with cancer (Kempe et al., 1989). This may be due to impaired antibody production in cancer patients, as well as deficiencies in cell-mediated immunity such as in the function of cytotoxic T cells or T helper cells. The disruption of mucosal barriers by chemotherapy may also facilitate infection in these patients, despite the presence of antibody titres sufficient to confer protection from infection in healthy controls. Similarly, although the wide variation in response to influenza vaccination in elderly subjects can be partly explained by variations in prevaccination serum HI antibody levels and the health status of the groups studied (Ahmed and Nicholson, 1996), age-related changes in immune function may also be implicated. Immune function is known to decline in mammalian species from the time of sexual maturation (Makinodan and Kay, 1980), with antibody production also decreasing with age (Kiashumoto et al., 1980).

A recent review of serological data published between 1975 and 1995 compared antibody responses following immunisation with whole-virus, split and subunit influenza vaccines (Beyer et al., 1998). A meta-analysis of 22 randomised, comparative studies was undertaken, with five of these studies allowing vaccine comparisons in the elderly. Results of this meta-analysis failed to reveal any clinically relevant differences in serological response to the different vaccine types in any of the age groups studied. The level of consistency between published serological and clinical data is a strong indicator that, despite numerous intrinsic confounding factors in individual studies, antibody response is generally predictive of clinical efficacy and that influenza vaccination has a true protective effect. However, the intrinsic large interstudy variation in serological outcome cautions against deriving generalised conclusions from the findings of individual influenza vaccination studies. Various authors have pointed out that the observed “vaccine efficacy” or “vaccine effectiveness” in such studies may represent underestimates of the true efficacy or effectiveness (Palache, 1997).

4.3.2. Effect of previous exposure to influenza antigens

Because the haemagglutinin and neuraminidase molecules of influenza A virus subtypes share some antigenic determinants, yet also possess subtype- or strain-specific determinants, the secondary response during re-infection comprises two coincident responses: a secondary response to the common antigenic determinants of the initial immunising and challenge viruses, but also a primary response to the virus not previously encountered (Ahmed and Nicholson, 1996). Prior exposure to influenza antigens, whether as a result of naturally acquired infection or previous vaccination, may therefore influence antibody production in response to subsequent influenza vaccination, with high pre-vaccination HI antibody titres reported to compromise immunogenicity and clinical response (Demicheli et al., 2000). However, results of a recent large meta-analysis failed to find any consistent statistical differences in serological protection rate for repeat annual versus single influenza vaccination (Beyer et al., 1999).

5. Discussion

Currently available inactivated influenza vaccines offer substantial protection against influenza, particularly in terms of limiting disease severity and reducing the potential for serious complications (Couch, 2000; Podda, 2001). However, the efficacy of these influenza vaccines may be influenced by a range of different of factors, including age, health status and use of concurrent medications, prior vaccination and prevaccination HI antibody titres. Clinical effectiveness in adults aged less than 65 years may be as high as 70–90%, but is generally lower in older adults aged $\geq$65 years, typically ranging from 30 to 40% (Palache, 1997; Strassburg et al., 1986). One possible explanation for this finding may be the lower antibody response to currently available influenza vaccines seen in older subjects (Phair et al., 1978; Keren et al., 1988). Indeed, the need for influenza vaccines with improved

Table 1
CPMP recommendations for the immunogenicity of an influenza vaccine (CPMP, 1997)

Immunogenicity criteria	Adult subjects (18–60 years old)	Elderly subjects (>60 years old)
Percentage seroconversion at day 21 (%)	>40	>30
Increase in GMT from day 0 (vaccination) to day 21	>2.5	>2
Proportion seroprotected at day 21 (HI titre ≥1:40) (%)	>70	>60

Seroconversion: ≥four-fold increase in HI antibody titre to a titre ≥1:40.

immunogenicity compared with those currently available is well recognised (Ershler, 1988; Couch et al., 1997).

Many influenza vaccines currently in development will be replacement vaccines rather than entirely new products and, as such, they are unlikely to be evaluated in traditional efficacy trials (Fedson, 1998). The importance of quantitative and qualitative laboratory surrogate markers to predict vaccine efficacy is well documented (Käyhty, 1998). Available data clearly indicates that the clinical protection afforded by influenza vaccines is closely correlated with their immunogenicity. Consequently, for influenza vaccines, it is generally accepted that vaccine-induced haemagglutinin inhibition antibody titres measured against influenza antigens from strains causing disease in the community are a good surrogate marker of clinical efficacy. HI antibody titres ≥1:40 are generally considered to represent the protection threshold beyond which it is unlikely that serious illness will occur (Brydak and Machala, 2000). In Europe, the CPMP now relies on immunogenicity results to determine the clinical acceptability of influenza vaccines and has defined three immunogenicity endpoints to be met by all new vaccines (CPMP, 1997). These are shown in Table 1.

In contrast to the US, influenza vaccines in Europe are now tested annually for immunogenicity as part of the marketing approval procedure. According to these requirements, the mean fold increase (MFI) in HI antibody titres following influenza vaccination in individuals aged 18–60 years should exceed 2.5, with at least 70% of those vaccinated having HI antibody titres ≥1:40 (protection rate) and at least a four-fold increase in HI antibody titres seen in at least 40% (response rate). In patients aged over 60 years, influenza vaccination should be associated with an MFI in HI antibody titres greater than 2.0, with a protection rate of at least 60% and a response rate of greater than 30%.

Finally, it has been observed that immunogenicity could underestimate the level of protection. One of the reasons could be that no antibodies are found in the serum of a patient which has been infected a long time ago, since the decrease of antibody level can bring it below the detection threshold. Such a patient will, however, recognise the antigen on further contact and will rapidly develop a secondary reaction. This could explain the resistance of older subjects when H1N1 virus subtype reappeared in 1977 when only people younger than 20 years old were susceptible, although a number of resistant subjects had no detectable antibodies. H1N1 virus subtype had circulated widely between 1947 and 1957 (Dowdle, 1999).

In conclusion, there is a clear link between immunogenicity and vaccine effectiveness, but due to factors such as herd immunity and the possibility of resistance to reoccurring strains after considerable periods of time, the relationship may not be straightforward to quantify accurately.

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