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PNEUMOCOCCAL AND INFLUENZA VACCINATION: CURRENT SITUATION AND FUTURE PROSPECTS

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Introductory article

Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study

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*Background: The effectiveness of influenza and pneumococcal vaccination in the prevention of hospital admissions and death has not been assessed prospectively. We have therefore examined the effects of influenza and pneumococcal vaccination in individuals aged 65 years or older in a 3-year prospective study, between December 1 1998 and May 31 1999. Methods: All individuals in Stockholm County aged 65 years or older (259 627) were invited to take part in a vaccination campaign against influenza and pneumococcal infection. We recorded for all vaccine recipients (100 242) name and date of birth, and whether they had been given both or one of the vaccines. All individuals (⩾65 years) admitted to hospital in Stockholm County with influenza and pneumonia related diagnoses were identified between December 1 1998 and May 31 1999. Findings: The incidence (per 100 000 inhabitants per year) of hospital treatment was lower in the vaccinated than in the unvaccinated cohort for all diagnoses: 263 versus 484 (–46% (95% CI 34–56)) for influenza; 2199 versus 3097 (–29% (24–34)) for pneumonia; 64 versus 100 (–36% (3–58)) for pneumococcal pneumonia, and 20 versus 40 (–52% (1–77)) for invasive pneumococcal disease. The total mortality was 57% (55–60) lower in vaccinated than in unvaccinated individuals (15.1 vs 34.7 deaths per 1000 inhabitants). Interpretation: These findings show that general vaccination leads to substantial health benefits and to a reduction of mortality from all causes in this age group. (**Lancet** 2001;357:1008–11)*

BACKGROUND

Influenza and *Streptococcus pneumoniae* infections have a major impact on the health of the worldwide population and both have well established vaccination programmes. Before the study by Christenson *et al*[1] (Introductory article) there was no strong evidence to support the fact that the use of vaccination programmes reduces severe disease from either of these infections. The aim of the study was to assess the health and financial impact of vaccinating the older population against influenza and pneumococcal infection.

New recommendations for pneumococcal and influenza vaccination were issued by the Swedish National Board of Health and Welfare in the mid 1990s but before this there was a relatively low vaccination rate for both vaccines in Sweden. Following the implementation of these guidelines, this study was undertaken in Stockholm County where approximately 20% of the Swedish population lives. It was planned for three years beginning in September 1998 and this report gives an interim analysis of the results of the first 6 months.

All people aged 65 years and over (259 627 in total) were invited by post to receive both the 23-valent pneumococcal polysaccharide vaccine and the trivalent influenza vaccine during an 8 week period from September to November 1998. A vaccination rate of 39% was achieved (n=100 242). The primary end points were hospital admissions and death rates due to influenza, pneumonia of all causes, pneumococcal pneumonia, and invasive pneumococcal disease in the vaccinated and non-vaccinated cohorts. A reduction in hospital treatments and a lower all cause mortality was found in the vaccinated cohort compared with the non-vaccinated cohort. These were early results from a potentially powerful study but further analysis is still required to answer the following questions:

- As there was no randomisation, there may have been a difference in the underlying health status between the vaccinated and non-vaccinated groups.

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- The non-vaccinated group may have received the pneumococcal vaccine in previous years which was still providing protection during the study period. There may also have been individuals within the non-vaccinated cohort who were vaccinated that year outside the study programme.

Despite these points, the results support evidence from previous smaller, less powerful studies and, although these are preliminary results, they provide important data to support the campaign to encourage immunisation against influenza and pneumococcal infections in the elderly and other at risk groups.

There is good evidence to support the overall efficacy of both vaccines but there are still problems that need addressing in order to maximise the impact of the immunisation programmes. In addition, there are exciting changes in the development of newer immunisation strategies that we shall also consider in this review.

Influenza

Influenza is a common, usually self-limiting, viral infection of the respiratory tract affecting all age groups. However, the impact of this disease in high risk groups is an important public health issue. The most effective way of protecting against influenza infection is by annual vaccination.[2]

Currently, in the UK, the high risk groups identified to be targeted for influenza vaccine are those with chronic lung, heart or renal disease, diabetes mellitus, immunosuppression due to disease or treatment, those over the age of 65, and those in long term residential care.[3] It is known that people within some of these groups have an increased mortality rate secondary to the infection and its complications.[4 5]

Complications associated with influenza infection include bronchitis, secondary bacterial lower respiratory infection (usually due to *S pneumoniae* or *Haemophilus influenzae*, but involving *Staphylococcus aureus* infection in up to 20%), and otitis media in children.

The influenza viruses

Influenza viruses belong to the Orthomyxoviridae family, of which there are four genera—influenza viruses A, B, C and thogotovirus. Influenza viruses are enveloped particles with two surface glycoproteins: haemagglutinin and neuraminidase. In their cores, influenza A and B have eight single stranded negative sense RNA segments that encode 10 polypeptides. Eight of these are structural viral proteins and the other two are found in infected cells.[6]

Influenza A virus causes epidemics most years, influenza B virus causes a less severe illness and spreads less extensively, and influenza C causes only acute pharyngitis.

Influenza A shows wide antigenic variation and is antigenically labile. This produces phenomena known as antigenic shift and drift. In antigenic shift the surface glycoprotein haemagglutinin changes spontaneously and therefore the virus becomes immunologically different from previously circulating influenza A viruses. As a result, pandemics occur in populations that have no chance of developing natural or acquired immunity to the new influenza A virus. Antigenic drift, which is much more common, occurs from year to year and is a more subtle change in the surface glycoproteins with less impact on immunological recognition.

As a counter to these changes, the constituents of the influenza vaccine are altered from year to year in the hope of covering the viruses which are most likely to be circulating that winter, using information from the previous year and activity in other parts of the world. This is usually sufficient to cover antigenic drifts, but will not cover unexpected antigenic shifts.

Current influenza vaccines

Influenza vaccination programmes are used throughout the world. Currently, a trivalent inactivated vaccine is used containing two influenza A and one influenza B virus. There are two types of vaccine: subunit virion vaccines which are made up solely of the surface antigens haemagglutinin and neuraminidase, and split virion vaccines in which the viral structure has been disrupted so it contains surface and internal antigens. Both types are derived from virus grown in chick embryos and are therefore contraindicated in those with egg allergies. They both have similar efficacy and adverse effects and are given by a single intramuscular injection.

In the year 2001/2 in the UK over 11 million influenza vaccine doses were used. Year on year over the past 4 years there has been a steady increase in the number of vaccinations given (data supplied by Dr Jane Lees, Department of Health). The vaccine confers 60–90% immunity in children and adults but less for the elderly whose immune systems are not as effective and therefore have a reduced response to the initial vaccination. In response to the natural influenza virus the body mounts a protective antibody response to haemagglutinin and neuraminidase. The vaccine aims to provoke an anti-haemagglutinin immune response specific to the particular strain in the vaccine that year. A measurement of the serum haemagglutinin inhibition antibody titres reflects protection in that individual.[6]

Efficacy of the vaccine

A North American study[7] in a population aged over 45 years of age showed that influenza vaccine reduced hospital admissions (by one third) and hospital deaths (by 43–65%) due to pneumonia, influenza, and associated problems. Even in an elderly population, where it is believed there is a reduced ability to produce sufficient antibody after administration of bacterial and viral vaccines,[8] influenza vaccination can halve the incidence of clinical influenza[9] and reduce the frequency of complications from the illness.

During the influenza season the number of hospital admissions among the elderly and those with chronic lung disease may double if they are not vaccinated. Vaccination has been shown to reduce hospital admissions due to pneumonia and influenza and to reduce the number of outpatient attendances in this population group.[10] During the influenza epidemic of 1989–90 vaccination reduced mortality from influenza by 41% in adults aged over 16 years.[4] More strikingly, the mortality rate in individuals who received the vaccine for the first time in 1989 was reduced by 9% compared with 75% in those who had previously been vaccinated, suggesting that a greater benefit is achieved following repeated vaccination.

Antiviral drugs

Since the 1960s antiviral drugs in the form of adamantamines have been available for the prevention of influenza.[11] Amantadine has been available from the 1960s and rimantadine more recently. Unfortunately, resistance has emerged to these drugs and amantadine has unacceptable side effects. Another negative feature is that they are only active against influenza A and not influenza B. These drugs have fallen out of favour since the development of a new group of antiviral drugs—the neuraminidase inhibitors (NAIs)—which have the advantage of being effective against

Box 1 Advantages of neuraminidase inhibitors over older drugs

- Activity against influenza A and B strains
- Improved safety profile
- Lower potential for inducing resistance

both influenza A and B (box 1). Their mechanism of action is to block the neuraminidase surface protein on both viruses.

It has been proposed that NAIs may have a useful role in treating influenza if a vaccine is not available, ineffective, or cannot be tolerated. They may also be used as an adjunct to the vaccine for those at high risk or in the event of a pandemic involving a new strain not covered by the vaccine.[12 13] There are two NAIs currently available—oseltamivir (Tamiflu) and zanamivir (Relenza).

Oseltamivir is an oral tablet that can be taken once a day. In a large US based randomised, placebo controlled trial, non-vaccinated healthy volunteers began treatment when there was a local increase in influenza virus activity. They were treated for 6 weeks with placebo, oseltamivir 75 mg once daily or oseltamivir twice daily (150 mg).[14] The risk of influenza among subjects taking oseltamivir 75 mg and 150 mg daily was 1.2% and 1.3%, respectively, compared with 4.7% in those taking placebo. The protective efficacy of oseltamivir was 74% in both treatment groups. (Protective efficacy is the ratio of the rate of infection in the treatment group to the rate of infection in the placebo group subtracted from one and converted to a percentage, thus quantifying the protective effect of the drug.) The main side effect was gastrointestinal upset but only 0.6% of subjects withdrew from the study as a result of this.

Zanamivir has been shown to reduce the duration and severity of both influenza A and B illness when started immediately at the onset of symptoms.[15] Treatment for 5 days reduced the time to recovery from 7 to 5 days. Viral counts from nasal washings were significantly reduced in those given zanamivir, thus demonstrating the drug's potent antiviral activity locally within the respiratory tract. This could also have implications for the transmission of the infection as influenza is spread via aerosol.

A study of the efficacy of a short course (5 days) of zanamivir following exposure to influenza-like illness within the community found that prophylaxis with intranasal zanamivir was ineffective.[16] However, if given via the inhaled route, there was a reduction in the rate of influenza compared with the placebo group. The figures were not statistically significant. The study suggested that 5 days may be insufficient for post-exposure prophylaxis and longer courses may therefore be necessary.

Volunteers were given zanamivir once daily for 4 weeks to test its efficacy during an outbreak of influenza with a viral strain not contained within the current vaccine.[17] Only 14% of participants had previously been vaccinated. The primary end point was prevention of laboratory confirmed clinical influenza. Zanamivir was found to be 67% effective in preventing symptomatic infection which rose to 84% in cases of laboratory confirmed influenza with fever.

Another American study found that zanamivir had a protective effect in preventing infection when given as prophylaxis within families. Index cases with influenza were treated with zanamivir for 5 days and prophylaxis was given to the rest of the family with inhaled zanamivir for 10 days.[18] The rate of infection in the non-index cases given the active drug was reduced compared with placebo. Treatment also resulted in a shorter duration of illness by a mean of 2.5 days in the index cases. In both of these studies no resistance of the virus to the drug was found.

For most healthy people the prospect of reducing the duration and severity of symptoms from influenza is welcomed. However, for those at high risk of developing serious complications from influenza, there is little evidence that the NAIs significantly reduce the incidence of complications, the need for hospital admission, or the mortality rate. Prescribing of zanamivir in the UK remains contentious as the cost of a 5 day course is currently £24.

Zanamivir is the only NAI currently licensed in the UK. The National Institute for Clinical Excellence guidelines state that it is recommended to treat at-risk adults when influenza is circulating in the community if they are able to commence treatment within 48 hours after the onset of typical influenza like symptoms, although there is sparse evidence to support this. The at-risk group includes those over 65 years of age and those with chronic respiratory disease, significant cardiovascular disease, immunosuppression, or diabetes.

Zanamivir is not recommended for treating healthy adults with influenza as currently its only proven advantage is to reduce the duration of symptoms by about 1 day, providing the drug is started within 2 days of onset of illness due to influenza. It is not effective against other respiratory viruses that can cause similar respiratory illness. This guidance does not apply to pandemics or widespread epidemics with a new strain of influenza where there is little or no community resistance.

The future of influenza vaccines

Live attenuated vaccines

Live attenuated vaccines for influenza were first developed in the 1960s.[19] Reassortment of gene segments (within the RNA core of the virus) between wild-type strains and attenuated strains is the basis for construction of live attenuated vaccines. The viruses are cold adapted and are therefore unable to replicate at human core temperature, and are attenuated in that they are unable to cause influenza illness in humans.[20]

Cold adapted live attenuated vaccines have been tested in humans and have been found to be safe with no severe adverse effects in the very young,[21] the very old,[22] or in those with chronic lung diseases.[23–25]

Efficacy

A 5 year study from 1985 to 1990 recruited 5219 healthy people who were given either a bivalent live attenuated intranasal vaccine, a trivalent inactivated intramuscular vaccine, or placebo.[26] Overall, the live attenuated virus showed an efficacy of 85–90% against influenza A/H1N1 and 56–59% efficacy against influenza A/H3N2, whereas the inactivated vaccine had an efficacy of 75% against both.

Another placebo controlled study in 1602 children in the mid 1990s demonstrated the protective effect of the live attenuated vaccine and fewer reported episodes of influenza like illness in the vaccinated groups.[27]

Fewer studies have been done in adults. The largest of these carried out over 5 months during the influenza season reported fewer days lost from work, healthcare visits, medication use, and a significant reduction in febrile illness in those given the live attenuated vaccine compared with placebo.[28 29] There was, however, no superiority shown against the inactivated vaccine. Significantly, during this trial 70% of participants self-administered the vaccine intranasally.

In Russia the live attenuated intranasal vaccine is already licensed for children and working age adults.[30] In children vaccinated with the live attenuated vaccine at a school, herd immunity was found which was not present in a school vaccinated with the inactivated vaccine alone.[31]

A small study based in St Petersburg and performed on 600 nursing home residents showed increased immune responses in subjects given a combination of the live attenuated intranasal vaccine and the inactivated intramuscular vaccine.[32] There were fewer laboratory confirmed cases of influenza in the group receiving both vaccines than in those given the live attenuated vaccine alone, but the results were not statistically significant.

An earlier study which compared the addition of intranasal to traditional intramuscular vaccine in elderly people in long term care institutions also showed that both vaccines together provided additional protection.[22] Five hundred and twenty three elderly people with a mean age of 84 years were given intramuscular inactivated vaccine and then randomised to receive the live attenuated intranasal vaccine or placebo. Those given both active vaccines had lower rates of outbreak associated respiratory illness and influenza and lower rates of laboratory confirmed influenza A virus carriage in nasal secretions.

Advantages of intranasal live attenuated vaccine

The intranasal route appears to stimulate a stronger immune response in the respiratory mucosa than the intramuscular route. Since influenza is spread via aerosol and first impacts on respiratory surfaces, this may be a significant advantage.

It has been shown in mice models using epidermal powder immunisation via a powder delivery system that administration of an intranasal live attenuated vaccine increases the IgA response at the mucosal surface.[33] It also elicits a serum antibody response that can be enhanced by co-delivery of cholera toxin, a synthetic oliogodeoxynucleotide containing immunostimulatory CpG motifs or a combination of both in the intranasal vaccine. When the mice were then given a lethal challenge with influenza virus, the naïve mice died but all the immunised mice survived; those given the vaccine together with the adjuvant faired better.

The live attenuated vaccine has been found to be safe, effective, and well tolerated. It is genetically stable and not transmissible from the vaccinee to others. It induces immune responses at the mucosal level as well as systemically. It is also cheap, painless, and therefore easy to give in mass immunisation projects to schoolchildren, for example. This has important implications for its future use as trained professionals are not required to administer it and it could potentially become available over the counter.

It is still early days and further work is needed to establish its use in the elderly, infants younger than 15 months, and the immunocompromised before it can be recommended for routine use.

Pneumococcal respiratory infections

Community acquired pneumonia is most commonly caused by *Streptococcus pneumoniae*, a Gram positive encapsulated organism. Pneumococcal infection is a major cause of morbidity and mortality despite the use of vaccines. Increasing antibiotic resistance around the world is of major concern, so there is renewed interest in vaccine development.

There are approximately 90 capsular polysaccharides, which make a wide variety of serologically distinct organisms. Immunity to pneumococcus depends on production of anticapsular antibodies. The vaccines in current usage induce serotype specific anticapsular antibodies that provide protection against the pneumococcus.[34] These vaccines are formulations of the capsular carbohydrate from 23 serotypes which cause 85–90% of pneumococcal infections in the USA[35] and 96% of those in the UK.[36]

Box 2 High risk groups

- Chronic heart disease
- Chronic lung disease
- Chronic liver disease
- Chronic renal disease
- Diabetes mellitus
- Immunodeficiency or immunosuppression due to disease or treatment including HIV
- Asplenia or severe dysfunction of the spleen

Pneumococcal vaccine

In the UK pneumococcal vaccine is recommended for all those older than 65 years and in "high risk" groups aged between 2 and 65 years.[3] High risk groups are those who are more susceptible to pneumococcal infection and/or are more likely to suffer adverse outcomes (box 2).

Usage of pneumococcal vaccine in the UK has been variable over the past few years. In 2001, 587 149 vaccines were used compared with 842 930 in 2000. A total of 3.5 million vaccines have been used over the past 6 years (data supplied by Dr Jane Lees, Department of Health).

Vaccine efficacy

The vaccine has been shown to prevent pneumonia in low risk adults but not in those categorised as being at high risk—that is, over 65 years of age or with the risk factors listed in box 2.[37] The vaccine is 93% effective in immunocompetent adults aged under 55 years with a risk factor to indicate the need for vaccination; this falls to 46% in those over 85 years of age.[38]

Ortqvist *et al*[39] undertook a randomised trial of the 23-valent vaccine in 691 adults aged 55–80 years. No protective effect was found in the vaccination group for preventing pneumococcal pneumonia, any pneumonia requiring hospital admission, or death from all causes. A non-significantly higher rate of pneumococcal bacteraemia occurred in the placebo group, which suggests that the vaccine has a protective effect against invasive disease.

A previous study which compared the rates of pneumococcal pneumonia in two groups of elderly people aged over 65 years immunised with influenza vaccine alone or with influenza and pneumococcal vaccine together showed some protective effect of the vaccine.[40] However, this was only in a subgroup at high risk of acquiring severe pneumococcal infection—that is, subjects with chronic heart or lung disease, those living in an institution, and bedridden individuals. Overall the pneumococcal vaccine conferred no protective effect in these elderly subjects.

A retrospective 2 year study of the protective effect of pneumococcal vaccine in patients aged over 65 with chronic lung disease found that vaccination reduced the number of hospital admissions for pneumonia and overall deaths.[41]

Although pneumococcal vaccination is recommended in the high risk groups shown in box 2, there is little evidence that the vaccine is effective in the very group for which it is recommended. Indeed, the recent British Thoracic Society guidelines for the management of community acquired pneumonia in adults concluded that "while pneumococcal vaccination is recommended by the Departments of Health for all those aged two years or older in whom pneumococcal infection is likely to be more common or serious, there is no evidence that it is effective in such 'at risk' groups".[3]

Revaccination

The evidence supporting revaccination is not very strong and no clear recommendations may be drawn from it.

Pneumococcal vaccination has been shown to produce an antibody response when given to middle aged and elderly people.[42] Post vaccination antibody levels decline with time. Early studies showed a decline in antibody titres of 30–80% 3–5 years after vaccination.[43 44] Studies of the older 14-valent vaccine showed a reduction in efficacy 6 years after vaccination and with increasing age.[45]

A more recent study in Alaska[46] showed that in high risk and elderly people 6–9 years after primary vaccination, residual antibody levels to nine of 12 polysaccharide antigens were only slightly higher than levels conferred from natural immunity. Antibody levels after primary vaccination and revaccination were equivalent.

Revaccination boosts declining antibody levels. A study of the antibody responses to capsular polysaccharides of *S pneumoniae* found that, after revaccination, IgG levels returned to within 40% of original post vaccination levels.[47] Revaccination may therefore be worthwhile but the recommended time between primary vaccination and revaccination is not firmly established and should probably be anywhere between 3 years for the very elderly to 6 years for the rest of the population. The current UK recommendation is that revaccination is not normally advised except for those individuals at risk of a fall in antibody levels after 5–10 years. It should not be given within 3 years of the primary vaccination because of the risk of severe reactions to high levels of circulating antibodies.[3]

Future of pneumococcal vaccine

As described above, the current conjugate pneumococcal vaccine has its disadvantages. It is poorly immunogenic in extremes of age, especially children under the age of 3 years, and it is only specific for the strains included in the vaccine. Conjugate vaccines are limited in the number of polysaccharides that can be incorporated, thus limiting the range of protection. Also, with the increasing emergence of multidrug resistant pneumococci, it has become important to focus on developing new vaccines.

Over recent years genetic immunisation has been considered an alternative form of vaccine. Genetic immunisation uses DNA vaccines targeted at specific proteins. Recently, the most studied has been a vaccine against pneumococcal surface protein A (PspA). This is a highly variable protein found on all clinically significant pneumococcal strains and is a virulence factor.[48] Antibodies to PspA facilitate the clearance of pneumococci from the blood and protect against death in mice.[49 50] DNA vaccines have important advantages over the polysaccharide vaccine in current use (box 3), which could make DNA vaccines of significantly greater benefit in the developing world where storage in hot climates and cost are important considerations. Conjugate vaccines are too expensive for the developing world where pneumococcal disease in children may have a higher mortality than in the developed world.[51]

Studies of pneumococcal surface protein A (PspA) vaccines

Animal models

A study from the USA published in 2001 demonstrated the potential of using PspA as an effective vaccine against the pneumococcus.[52] Using two groups of mice, one vaccinated with PspA and the other with placebo, increased survival was seen in the PspA group. The mice were given a challenge to 50 times the 50% lethal dose of pneumococcus. All the mice in the PspA group survived at 21 days and the entire placebo group died within 2 days. The mice were exposed to systemic and respiratory challenges and in both cases the immunised mice had better survival rates.

> **Box 3 Advantages of DNA vaccines over the polysaccharide vaccine in current use**
>
> - DNA is easier to produce and purify, resulting in a lower cost of production and therefore potential for broader use
> - DNA vaccines are more heat stable than protein vaccines and so storage is less of a problem
> - PspA vaccines provide a wider range of protection against more pneumococcal strains than current vaccines

A dose dependent response was observed with low doses of the vaccine. With lower doses the mice took a longer time to reach a plateau antibody response. Long term immunity was also observed. At 7 months all the immunised mice survived a lethal pneumococcal challenge compared with only one of nine control mice ($p<0.0001$). Protection was noted when the mice were challenged with strains of pneumococcus different from that of the PspA in the vaccine, which suggests that there is cross protection between strains. This is an important phenomenon because it means that the vaccine can be prepared from PspA from a smaller number of strains but will confer broader protection than the polysaccharide vaccines in current use.

A previous study[53] showed that intranasal immunisation of mice with PspA induced mucosal and systemic antibody responses and provided long lasting protection against carriage of *S pneumoniae*. Cross reactivity of the PspA molecules across strains of pneumococcus was also seen. The protection it conferred was effective against mucosal challenge (intranasal and intratracheal) and also against intravenous and intraperitoneal challenges.

Human models

A study by Nabors *et al*[54] demonstrated the effectiveness and safety of a PspA vaccine in humans.[54] The safety and immunogenicity of a vaccine composed of a single recombinant PspA molecule was established from a phase I clinical trial in healthy adults. The vaccine was made up of fragments of PspA taken from the alpha helical region, which has previously been shown to be the protective portion.[55 56] Six groups (which varied by >20% of their amino acids) were identified from the portion of the alpha-helical region which has been found to be particularly effective in eliciting cross protective immunity. The study investigated the extent of the cross reactivity of the serum samples from humans immunised to PspA proteins similar and dissimilar to the immunising antigen. Immunisation with one PspA protein led to increased production of antibodies that bind to heterologous PspA proteins in vitro, proving that cross reactive humoral responses to PspA can be achieved in man. The full extent of the cross reactivity among all PspA

> **Box 4 Main findings of study by Nabors et al[54]**
>
> - PspA molecules are safe and immunogenic in human adults
> - Immune responses in vaccinated individuals were cross reactive to distantly related PspA proteins
> - The cross reactive antibodies lasted more than 6 months after vaccination, demonstrating longevity of effect.

Learning points

- There is strong evidence that the influenza vaccine works
- There is strong evidence that the influenza vaccine should be given
- An intranasal live attenuated vaccine may open the way to effective patient administered "over the counter" protection
- The study quoted in the Introductory article adds support to the recommendation for the pneumonia vaccine in those at risk
- Revaccination strategies are less clear and revaccination is not currently recommended
- Knowledge of the *S pneumoniae* genome has opened the way to developing cheap, effective, broad cover vaccines for the future

antigens studied to date is unknown. High cross reactivity is required if a few PspA molecules are to be combined into one vaccine with broad protection (box 4).

Although this appears a promising new alternative to the polysaccharide vaccine, the following issues remain to be resolved:

- It needs to be proved that the level of PspA antibody raised by vaccination is adequate to protect against naturally acquired pneumococcal strains in vivo.
- Are anti-PspA responses adequately cross reactive in children who presumably would not have been previously exposed to pneumococcal infection?

Other options involving the pneumococcal genome

Wizemann *et al*[57] recently looked at the whole genome of *S pneumoniae* to identify molecules which could be used in vaccines to offer protection against pneumococcal infection. Using sequence scanning, proteins were identified from the genome sequence. In particular, surface proteins and genes with significant homology to known virulence factors in other bacteria were selected. Ninety seven unique genes or their subfragments were expressed and purified for evaluation as potential vaccine candidates. Vaccine efficacy was tested using mice and a lethal sepsis challenge. The potential vaccine was tested for its ability to induce protective antibodies against pneumococcal challenges using PspA as the control. Six novel antigens were found to protect against the highest lethal doses of the pneumococcus and showed broad strain distribution and immunogenicity during human infection.

This study shows that there may be other proteins that could be developed into new vaccines against the pneumococcus and that there is potential for a great deal more research into the subject.

Conclusions

Influenza and pneumococcal infections cause significant morbidity and mortality every year. Effective vaccination programmes for both are currently in progress in the UK, targeting the elderly and those considered as being at high risk from serious illness—particularly those with chronic illnesses. The influenza vaccine is a trivalent inactivated vaccine and the pneumonia vaccine is a 23-valent polysaccharide vaccine. Currently, both vaccines are given intramuscularly.

Both vaccines have limitations and work is ongoing to improve efficacy and target population coverage with both. The most promising new vaccines on the horizon for the prevention of influenza are intranasal live attenuated vaccines. These have the advantage of optimising local immunity at the respiratory mucosa and being cheap and easy to administer, thus encouraging widespread use.

New types of vaccine are being developed to provide prevention against pneumococcal infection, the commonest and most serious of respiratory bacterial pathogens, and to counter the problems caused by antibiotic resistant *S pneumoniae*. Genetic immunisation appears to be a promising new concept. Pneumococcal surface protein (PspA) vaccines have been shown to be safe and effective and provide a broader protective range than the current 23-valent polysaccharide vaccine. Other effective DNA vaccines may be available that are effective against pneumococcal infection, but studies into these are still at a preliminary stage.

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