IN-DEPTH REVIEW

Specific immunization issues in the occupational health setting

David Baxter

Abstract This article looks at the components of an effective occupational health vaccination programme and also reviews the legal basis for them. It addresses the issue of vaccine licensing including pre-clinical, clinical and post-licensing studies. It explores screening for vaccine preventable diseases in the occupational health setting and then addresses particular issues around hepatitis B, chicken pox, tuberculosis, measles, rubella, diphtheria, polio, mumps and hepatitis A.

Key words Occupational health vaccine programmes; screening for vaccine preventable infections (hepatitis B, chicken pox, influenza, Neisseria meningitidis C, tetanus, diphtheria, polio, mumps and hepatitis A); vaccine licensing.

Introduction

This article is the last in a series of three looking at the use of vaccination in the occupational health (OH) setting. The first article (Article 1) looked at the innate and adaptive responses to invading pathogenic microorganisms and the mechanisms of recognition and elimination of invading pathogens as the basis for immunization. The second article (Article 2) addressed active and passive immunity and the types of vaccines used by OH practitioners. This third article will look at the requirements for an effective vaccination programme as part of a comprehensive OH service delivered to people from a range of occupational, ethnic, linguistic and other diverse backgrounds. It will address how vaccine safety is assured, vaccine licensing is obtained and how screening for vaccine-preventable infections is undertaken; it will also review vaccine-related OH issues around hepatitis B, chickenpox, influenza, Neisseria meningitidis C, tetanus, diphtheria, polio, mumps and hepatitis A.

Provision of an OH vaccination programme

Ensuring health and safety in the work environment is of paramount importance and it is underpinned by extensive legislation. The Health & Safety at Work Act 1974, Control of Substances Hazardous to Health Regulations 2002, Reporting Injuries Diseases and Dangerous Occurrences Regulations and Management of Health Safety Welfare Regulations 1999, in particular, inform the development and implementation of an effective employee OH care programme.

The adoption of safe working practices together with immunization will significantly improve the protection of the individual worker from specified vaccine-preventable disease (VPD) whose risk of infection is increased in the health care setting [1].

The health care worker’s (HCW’s) duty of care also means that they should be immunized where possible and appropriate to ensure that they cannot transmit infection to their patients [2,3].

Risk assessment (for those both currently in post- and pre-employment) will identify whether the HCW has regular clinical contact, social contact or is handling clinical specimens (including pathogenic microorganisms). Within these three broad groups, further risk stratification will be required to ensure that the worker is fit to safely undertake a particular job. Effective workplace monitoring should identify if and when staff move between these three groups/jobs and lead to a reassessment of their needs.

Vaccines that may be appropriate to the health setting include those that are offered as part of the childhood/adolescent programme, those required because of specific risks associated with a particular job and those that are needed to prevent transmission to an individual patient. The vaccines that should be considered in the above situations are not mutually exclusive.

Childhood/adolescent vaccinations include diphtheria, tetanus and acellular whooping cough–Haemophilus influenzae type b conjugate vaccine–inactivated poliomyelitis vaccine, Neisseria meningitidis type C conjugate vaccine
Vaccine safety

Ensuring that a HCW is offered a safe vaccine is based on appropriate testing both prior to and after introduction of a vaccine together with maintaining high-quality manufacturing methods. Early vaccine trials were not conducted as thoroughly as current standards would now require—from either the scientific or ethical perspective. Indeed the first written reports were not vaccine trials at all but rather descriptions of the effects of vaccines administered to a few people.

The requirement for rigorous testing of vaccines was recognized by Pasteur at the end of the 19th century who correctly anticipated two of the key requirements for a modern vaccine trial, namely the need for controls and the importance of measuring the vaccine’s effectiveness.

Modern trials generally take a minimum of 10 years and are divided into two stages, pre-clinical and clinical. The estimated costs for both on average exceed $200 million with the primary expense being the clinical studies. Since any vaccine trial involves carrying out tests on human subjects and given that such research is (at least) potentially hazardous, the aim must be to conduct them in such a manner that minimizes any risk to participants. The following structured test programme describes the process [5].

Pre-clinical

Trials start with pre-clinical studies in animals. Their purpose is to establish that the trial vaccine is likely to be protective (i.e. proof of principle) and does not have any serious side effects; it also helps in working out the likely dose. Studies are usually carried out in at least two different animal species, including pregnant females. If the animal trials are successful, then the studies move into human testing and are divided into the following four phases.

Clinical

Phase I studies use the prototype vaccine for the first time in humans. Vaccine doses, much smaller than used in animals, are given to a few volunteers (10 or 20) to test how the innate and adaptive immune systems respond to the vaccine, to determine the risk of immediate adverse reactions and to estimate the dose of vaccine needed for it to work. Study participants are very closely monitored for side effects for at least 28 days after the vaccine has been administered. Volunteers are often drawn from the pool of scientists involved in the vaccine’s development since their detailed knowledge means that they are usually in the best position to decide whether the prototype vaccine is likely to work and be safe.

Phase II studies are carried out to extend knowledge about the vaccine’s effectiveness and safety using information obtained from the previous Phase I volunteer studies. Normally, Phase II studies (which may be multiple) will involve a total of 100–200 people. It is an advantage if people given the vaccine during a Phase II study are similar to those who will be offered the vaccine after it is licensed. Participants in the trials are closely monitored for any side effects of the vaccine. A number of Phase II studies are usually carried out in order to get a more complete idea of the vaccine’s effectiveness and side effects.

A Phase III study involves giving the vaccine to larger numbers of people to characterize the prototype vaccine’s safety and effectiveness. Ideally this is a placebo controlled, randomized, double-blind study of the vaccine in a larger and more diverse population than used in the previous phases enabling the results to be applied to all people who will receive the vaccine when licensed. For vaccines aimed at protecting against common infections, the Phase III trial (often carried out as multiple trials) is designed to show whether the vaccinated groups have a significantly lower infection rate than the unvaccinated control group. For vaccines aimed at protecting against less common infections, demonstrating a reduction of disease incidence among the vaccinated group may not be logistically practical because of the large numbers of participants required. Instead, such Phase III studies are designed to establish if the vaccinated groups are more likely to be immune to infection based on immunological correlates of protection: proof that the vaccine really does reduce levels of clinical infection has then to wait until the vaccine is licensed and more widely used.

The final stage (Phase IV) is carried out after the vaccine is commercially licensed and involves following up people who have received the vaccine and monitoring them for any side effects not picked up during the earlier clinical trials. Phase IV studies, also called post-licensing surveillance, are essential for identifying rare side effects and measuring the vaccine’s overall effectiveness in disease control. In England and Wales, the Medicines and Healthcare Products Regulatory Agency (MHRA) has responsibility for these programmes.

Vaccine licensing

Vaccines may be licensed for use in England and Wales in one of three ways: first the vaccine can be licensed after submission of appropriate safety and efficacy data to the
relevant competent regulatory authority of a Member State—in England and Wales, this is the MHRA, i.e. National authorization. Second, a Community-wide licence may be issued by the European Medicines Agency, on the advice of the Committee for Medicinal Products for Human Use, i.e. Community authorization. And finally, under the mutual recognition procedure, marketing authorization can be obtained for England and Wales when the vaccine in question has received a licence in another European Union Member State [6].

Screening for VPDs in the OH setting

A HCW’s status with regard to VPDs can be determined from their vaccination records (if available), their history (if this can be accurately established) and/or serological/cell-mediated immunity screening.

There should be a programme/system in place that collects details of vaccinations received (date given, batch number, site, adverse vaccine events and a record of any vaccines refused). This should be a longitudinal record that is updated as appropriate and maintained according to current data handling and confidentiality legislation.

The core HCW-screening programmes for VPDs include hepatitis B, chickenpox, tuberculosis, measles and rubella, depending on the OH department.

Hepatitis B

All HCWs (clinical and laboratory) who may have direct contact with patients’ blood or bloodstained body fluids or with patients’ tissues should be screened and vaccinated if appropriate [7,8]. Post-vaccination serological assessment should be undertaken between 1 and 4 months after completing the primary vaccination course [4]. Current advice on the need for further immunization varies with the post-vaccination hepatitis B surface antibody (anti-HBs) level achieved.

Immunocompetent individuals whose anti-HBs level is $\geq 100$ mIU/ml should receive a further dose of hepatitis B vaccine $\sim 5$ years after the completion of the primary programme without the need for further serological testing.

Immunocompetent individuals with levels between 10 and $<100$ mIU/ml should receive one additional booster hepatitis B vaccine without the need for further serological testing. They should receive a further dose of HB vaccine $\sim 5$ years after the completion of this programme, again without the need for further serological testing.

Immunocompetent individuals whose anti-HBs is $<10$ mIU/ml should be screened for markers of infection (hepatitis B surface antigen, hepatitis e antigen, hepatitis B e antibody and hepatitis B core antibody), and if negative, they should be offered up to three more doses of hepatitis B vaccine followed by serological testing 14 months after the second course. Depending on the levels achieved, they should be managed as above. Those with persistent anti-HBs levels $<10$ mIU/ml are classified as non-responders.

**Table 1. Hepatitis B prophylaxis for exposure incidents**

<table>
<thead>
<tr>
<th>HB status of person exposed</th>
<th>Significant exposure</th>
<th></th>
<th></th>
<th>Non-significant exposure</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBsAg-positive source</td>
<td>Unknown source</td>
<td>HBsAg-negative source</td>
<td>Continued risk</td>
<td>No further risk</td>
<td></td>
</tr>
<tr>
<td>$\leq 1$ dose HB vaccine pre-exposure</td>
<td>Accelerated$^a$ course of HB vaccine plus HBIG (one dose)$^b$</td>
<td>Accelerated course of HB vaccine</td>
<td>Start HB vaccine course</td>
<td>Start HB vaccine course</td>
<td>No HB prophylaxis; reassure</td>
<td></td>
</tr>
<tr>
<td>$\geq 2$ doses HB vaccine pre-exposure (unknown anti-HBs)</td>
<td>One dose of HB vaccine with a further dose one month later</td>
<td>One dose of HB vaccine</td>
<td>Finish course of HB vaccine</td>
<td>Finish course of HB vaccine</td>
<td>No HB prophylaxis; reassure</td>
<td></td>
</tr>
<tr>
<td>Known responder to HB vaccine (anti-HBs $\geq 10$ mIU/ml)</td>
<td>Booster dose of HB vaccine</td>
<td>Booster dose of HB vaccine</td>
<td>Booster dose of HB vaccine</td>
<td>Booster dose of HB vaccine</td>
<td>No HB prophylaxis; reassure</td>
<td></td>
</tr>
<tr>
<td>Known non-responder to HB vaccine (anti-HBs $&lt;10$ mIU/ml, 2–4 months post-immunization)</td>
<td>One dose of HBIG; booster dose of HB vaccine; second dose 30 days later</td>
<td>One dose of HBIG; booster dose of HB vaccine</td>
<td>No HBIG; booster dose of HB vaccine</td>
<td>No HBIG; booster dose of HB vaccine</td>
<td>No HB prophylaxis; reassure</td>
<td></td>
</tr>
</tbody>
</table>

HBsAg, hepatitis B surface antigen.


$^a$An accelerated course is three doses at 0, 1 and 2 months with a 12-month booster.

$^b$Give HB vaccine and HBIG concurrently at different sites.
Advice on post-exposure prophylaxis also varies with the post-vaccination anti-HBs level achieved and nature of exposure (see Table 1).

HCWs known to have responded to vaccine (anti-HBs $\geq 10$ mIU/ml) should be given an additional hepatitis B vaccine (unless they have received one in the previous 12 months).

HCWs known to be non-responders (anti-HBs < 10 mIU/ml) should receive hepatitis B immunoglobulin (HBIG), together with hepatitis B vaccine, and a further dose of HBIG 30 days later if the exposure is assessed as high risk.

HCWs who are incompletely immunized should be immunized according to the schedule in Table 1.

The above guidance uses two different levels of anti-HBs antibody to determine the required response and reflects ongoing disagreement about the antibody level that correlates with protection. The level of $\geq 10$ mIU/ml is generally accepted throughout the world as protective [9,10]: the higher level of $\geq 100$ mIU/ml, preferred for example in a few countries including the UK [4], is based on the observation that breakthrough infections occurred about twice as frequently in neonates whose peak antibody level after four doses of vaccine (0, 2, 4 and 9 month schedule) was $>10$ mIU/ml compared with $\geq 100$ mIU/ml; the absolute risk for those with a level of $\geq 10$ mIU/ml was six HBV infections per 142 person-years at risk [4,10].

Chickenpox

Chickenpox susceptibility can be determined from disease history and/or serological assessment — nationally, OH departments use one of three approaches to Varicella-Zoster (VZ) virus screening among UK-born HCWs. First, since a definite history of chickenpox or herpes zoster is a good predictor for immunity with a 99% correlation between history and immunity, current Department of Health (DH; England and Wales) guidance is that only HCWs with a negative or uncertain history of chickenpox or herpes zoster should be serologically tested and offered vaccine if VZ antibody is negative [4]. Given, however, that the introduction of VZ virus can be devastating in certain health care settings (primarily maternity, special care, transplant and oncology units), a second approach has been put forward by the Association of Occupational Health Physicians in the National Health Service (NHS) [11] who recommend that NHS employers should serologically assess all HCWs working in these high-risk areas and vaccinate those found to be non-immune. The third approach, based on a zero risk strategy, is to screen all HCWs irrespective of work environment. There is no obvious mechanism for reaching a consensus among different OH departments on the optimal approach.

For HCWs born and raised overseas, a history of chickenpox is a less reliable predictor of immunity and the current recommendation is that they should all be serologically assessed at pre-employment [4].

Tuberculosis

All health care staff should be screened for susceptibility to Mycobacterium tuberculosis. Traditionally such screening uses either the presence of a BCG scar or a ‘positive’ tuberculin skin test (TST) which identifies $T_h$1 cells sensitized to M. tuberculosis proteins — i.e. delayed type hypersensitivity (DTH). The current TST is the Mantoux test with the resulting cellular inflammation maximal in 48–72 h when the test should be read: one limitation of the TST is that prior immunization with BCG vaccine also causes a DTH response thus introducing uncertainty into the test result’s interpretation.

A recently introduced alternative methodology involves detecting the cytokine interferon gamma (IFN-γ) which is released from $T_h$1 cells when they are exposed to the antigen against which they have become sensitized. Individuals exposed to M. tuberculosis generate $T_h$1 cells that recognize mycobacterial proteins as part of an adaptive immune response. The test involves incubating blood with two synthetic proteins that simulate two proteins present in M. tuberculosis — secretory antigenic target 6 and culture filtrate protein 10: these are secreted by all M. tuberculosis and pathogenic Mycobacterium bovis strains but are not present in BCG vaccine strains. Measurement of the IFN-γ levels (with both a negative and positive control) then gives a reasonably reliable assessment of the hypersensitivity state to M. tuberculosis proteins.

There is some disagreement about which HCWs should receive BCG vaccine. Current National Institute of Clinical Excellence guidance is that all susceptible (i.e. tuberculin negative as measured by a Mantoux test with $\leq 5$ mm induration) HCWs regardless of age should be offered vaccination [12]. The DH, in contrast recommends BCG only for those susceptible HCWs under 35 years of age who have regular clinical contact with an infectious patient or are working in maternity, paediatrics or departments where there are immunocompromised patients. Laboratory staff in microbiology and pathology departments, attendants in autopsy rooms and others considered to be at high risk should also be offered BCG [4]. Whichever approach is preferred the lack of data on BCG efficacy in older people necessitates that a trial be carried out to resolve this issue.

Measles

HCWs are both a potential source and recipient for the transmission of measles unless they are immune [13]. Immunity prior to 1970 was associated with wild infection and many people (>98%) born before that date are
immune. Following introduction of measles vaccine [as the monovalent (1970) and MMR (1988) preparations], circulation of wild measles reduced and individuals born after these dates are less likely to be immune unless previously immunized: current data would suggest that just >3% of HCWs are measles IgG negative on saliva and serology testing [14]. The original trials reported a vaccine protective efficacy on natural measles virus challenge after one dose of 90–95% [5]. A second MMR dose was recommended in 1994 because of this primary vaccine failure rate. Current DH guidance is that all staff should be measles immune: satisfactory evidence of protection would be documented evidence of having received two MMR doses or a positive measles antibody test; MMR vaccine, if required, should be offered to HCWs irrespective of birth date [4].

Rubella
All HCWs are serologically screened for rubella since they are a possible source and recipient of transmission unless they are immune—this is potentially a devastating infection depending on the patient group. Prior to the introduction of rubella vaccination in 1970, ~80% of the population would have been exposed to wild rubella. The original trials reported a vaccine protective efficacy on natural rubella virus challenge after one dose of between 94 and 97% depending on the virus vaccine strain [5]. Vaccination was initially targeted at pre-pubertal females and women of child-bearing age; the universal vaccination programme was introduced in 1988 and the need for a second MMR was recognized in 1994. The DH currently recommends that all staff should be rubella immune; satisfactory evidence of protection would be documented evidence of having received two MMR doses or a positive rubella antibody test [4].

Specific vaccine-related OH issues
For HCWs, these involve hepatitis B, influenza, tetanus, diphtheria, polio, mumps and hepatitis A.

Hepatitis B
The principle concern involves managing those individuals who are vaccine non-responders after six intramuscular doses: two approaches are currently available. The first is to manage them in the post-exposure situation as outlined in Table 1. The second is to utilize vaccination strategies known to enhance the immune response to vaccines in general—these include the use of additional doses, an increased vaccine dosage or a change in the route of administration. Of the three, there is good evidence that administering hepatitis B vaccine intradermally to non-responding HCWs can result in between 70 and 90% developing protective antibody titres [15,16]. Issues with intradermal immunization include the technical difficulty of the procedure, possible skin discoloration at the vaccine sites and uncertainty about the duration of the resulting adaptive response—in the latter situation, advice around HBV prone exposures should therefore be provided until these data become available.

Influenza
The key issue is to improve uptake among HCWs which is based on providing adequate information about the need for immunization and addressing common misconceptions. The rationale for the programme is primarily to protect them (if they are in an at-risk group) and to prevent their transmitting infection to susceptible at-risk patients or colleagues [17–19]. Given that there is good evidence that programmes are effective among healthy adults (and children above 6 months of age), then one would also expect such a programme to reduce absenteeism rates [20–22]. Misconceptions leading to non-uptake of vaccine appear to be the same as the general population, namely concern that it causes influenza, has serious adverse events, has limited efficacy, a belief that they cannot catch the infection and a view that the wild infection helps the immune response to mature; in addition, there is often a dislike of needles.

Neisseria meningitidis C
In addition to at-risk groups, or as part of a community outbreak, vaccination with the conjugate Men C vaccine is recommended for all individuals under 25 years and anybody going to university irrespective of age—thus, many new staff coming into health care should be protected prior to employment. HCWs as a group, however, are not regarded as at higher risk than the general population and immunization should only be offered to specific groups. Laboratory staff working with the organism should be immunized and should receive a three-yearly ACWY vaccine or other relevant vaccine depending on the risk assessment [4].

Tetanus, diphtheria and polio
A documented five-dose programme will protect against any of these infections; in the absence of an accurate vaccination history, two approaches can be considered. The first involves ascertaining the likelihood of immunization based on age, school attendance, armed forces service, Accident and Emergency Department treatment and parental views about vaccination: those with an uncertain history can be given two doses of tetanus (low dose), diphtheria and (inactivated) polio at 1- to 2-monthly intervals. The second approach uses serological screening to determine the need for further immunization. With regard to tetanus, until a decision about vaccination status is determined, HCWs should be managed as recommended in Table 2.
Table 2. Tetanus immunization following injuries

<table>
<thead>
<tr>
<th>Immunization status</th>
<th>Clean wound</th>
<th>Tetanus-prone wound</th>
<th>Human tetanus immunoglobulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fully immunized i.e. has received</strong></td>
<td>None required</td>
<td>None required</td>
<td>Only if risk especially high (e.g. contaminated with stable manure)</td>
</tr>
<tr>
<td>a total of five doses of tetanus vaccine at appropriate intervals as single antigen or in a combined vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary immunization complete, boosters incomplete but up to date</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None required (unless next dose due soon and convenient to give now)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary immunization incomplete or boosters not up to date</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A reinforcing dose of combined tetanus/diphtheria vaccine and further doses as required to complete the recommended schedule (to ensure future immunity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Not immunized or immunization status not known or uncertain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>An immediate dose of vaccine followed, if records confirm this is needed, by completion of a full three-dose course of combined tetanus/diphtheria vaccine to ensure future immunity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Mumps**

HCWs are a potential source for the transmission of mumps unless they are immune. Prior to the introduction of mumps vaccine (as MMR) in 1988, ~85% of the population would have been immune following wild infection. The original trials reported a vaccine protective efficacy on natural mumps virus challenge after one dose of ~95% [5]: more recent studies have suggested a figure between 41 and 94% depending on the number of vaccine doses received [23]. There is no DH guidance about mumps immunity but if HCWs have received two doses of MMR vaccine, then this should provide the majority with protection against mumps.

**Hepatitis A**

Hepatitis A is a largely faeco-oral borne transmitted infection with person to person spread being readily documented. Adequate standards of hygiene should control spread and as a result, the risk of hepatitis A infection among HCWs because of occupation is generally extremely low and vaccination is not routinely recommended [4].

However, health care-associated outbreaks are described and in a recent review of 26 such outbreaks (1975–2003), attack rates among nurses ranged between 15 and 27%—the corresponding figure for physicians was 3–4%: 13 of the recorded outbreaks were associated with neonatal/paediatric units [24]. A study cited by these authors reported that hospital laundry staff were at higher risk than ward staff.

Hepatitis A vaccination (together with pre-employment screening) should thus be considered where there is a likelihood of increased exposure. Seronegative laboratory workers and staff on clinical infectious diseases units are potentially at higher risk and should be offered a two-dose immunization programme with the whole virion-inactivated vaccine: hospital maintenance staff involved with sewerage systems should also be immunized; paediatric staff also appear to be at higher risk and serious consideration should be given to their being immunized if seronegative.

**Conclusions**

OH departments have a key role both in (directly) protecting their staff and (indirectly) patients from VPDs. This article has reviewed the process of vaccine licensing which is key to ensuring vaccine safety and is the basis for ensuring that staff are able to make an informed decision about the preparations they are being offered. It has also addressed the issue of screening for VPDs recognizing that departments differ in how they undertake these programmes—the need for consistency is recognized. Finally specific immunization issues were considered with recommendations made for hepatitis B, chickenpox,
measles, mumps, rubella, influenza, tetanus, diphtheria, polio and hepatitis A.

Acknowledgements

I would like to thank S. Robson, S. Gebrehewit, D. Menzies, E. Murphy and M. Falconer for their helpful comments and advice on the preparation of this article.

Conflicts of interest

None declared.

References