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Exposure to hepatitis B virus: guidance on post-exposure prophylaxis

PHLS Hepatitis Subcommittee

Summary

This paper summarises the views of the PHLS Hepatitis Subcommittee on prophylaxis after exposure to known and potential sources of hepatitis B virus (HBV) at work and in the community, and expands on the guidance on hepatitis B immunisation and the prevention of occupational exposure to blood given elsewhere[1,2]. It defines significant exposure and gives guidance on incident recording, risk assessment, testing and storage of incident-related blood specimens and follow-up. It recommends that HBV prophylaxis should be determined by assessment of the likely infectivity of the source and of the HBV status of the person exposed.

Background and definitions

The risk of HBV transmission associated with an exposure incident depends on the type of exposure (significant or otherwise), the HBV status of the source (infective or not), and the HBV status of the person exposed. Assessment of these will determine the need for, and choice of, post-exposure prophylaxis.

Significant exposure

A significant exposure is one from which HBV transmission may result. It may be:

(i) percutaneous exposure (needlestick or other contaminated sharp object injury, a bite which causes bleeding or other visible skin puncture)
(ii) mucocutaneous exposure to blood (contamination of non-intact skin, conjunctiva or mucous membrane)
(iii) sexual exposure (unprotected sexual intercourse).

Percutaneous exposure is of higher risk than mucocutaneous exposure, and exposure to blood is more serious than exposure to other body fluids. HBV does not cross intact skin. Exposure to vomit, faeces, and sterile or uncontaminated sharp objects poses no risk. Seroconversion after a spitting or urine spraying incident has not been reported.

HBV status of the source

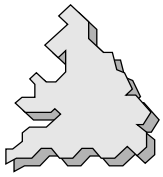
This may be:

(i) *known*: an identifiable individual for whom a positive HBsAg test result has been documented in the preceding 12 months or
(ii) *determinable*: an identifiable individual whose HBV status is unknown, but who is available for HBsAg testing or
(iii) *unknown and not determinable*: source unknown, unidentifiable, or identifiable but not available for HBsAg testing (eg, community needlestick injuries, needles from sharps disposal box, community assaults).

HBV status of the exposed person

The exposed person will be categorisable as:

(i) a known responder to hepatitis B vaccine (post-vaccination level of anti-HBs ≥10miU / ml) or



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(ii) a known non-responder to hepatitis B vaccine (anti-HBs at 2-4 months post-vaccination <10miU/ml) or
(iii) of unknown HBV status: an individual with no history of hepatitis B immunisation, or an individual who has received a complete or partial course of hepatitis B vaccine but without a documented post-vaccination anti-HBs test result, or
(iv) known to be HBsAg positive (this will be rare).

Incident reporting in the workplace

Employers have a duty to educate staff about occupational hazards and staff should be made aware of local procedures for reporting exposure incidents. Early reporting of incidents is desirable. Hepatitis B vaccine has been available for ten years, and an increasingly high proportion of those health service staff at greatest risk of occupational exposure to HBV will have received a full course of hepatitis B vaccine and will know that they have responded immunologically. These staff must also be encouraged to report exposure incidents, as a booster dose of hepatitis B vaccine may be indicated and as the incident may present a risk of transmission of blood borne viruses other than HBV.

Incident recording and risk assessment (Tables 1 and 2)

When an exposure incident is reported a history should be obtained. This should be sufficiently detailed to allow an assessment of risk to be made. It should be documented, as this will facilitate follow-up and provide a record for administrative and accident prevention purposes. Points which should be covered are shown in table 1.

The aim should be to complete risk assessment and administration of HBV prophylaxis (when indicated) within 24 hours of the initial report of the incident. It will not always be possible to achieve this but, in any event, the process should be completed within 48 hours. Occasionally, the delay between the exposure incident and the initial report may exceed seven days. There is no good evidence that administration of hepatitis B immunoglobulin (HBIG) would then be beneficial but use of hepatitis B vaccine may still be appropriate.

Serological testing and storage of serum

(i) From the source

If the source is identifiable and available for testing, a blood specimen should be obtained (regardless of any previously documented serological test results) and a serum sample stored for a minimum period of two years. This is because it may be helpful to have access to stored serum should the person exposed subsequently be found to have serological evidence of HBV infection, and because the potential for transmission of other blood borne viruses may remain even when the source is known to be HBsAg negative.

Specimens from individuals of unknown HBV status should be tested promptly for HBsAg. Most laboratories will be able, if told of the urgency of the request, to provide the result on the same day. Decisions about the need for HBV prophylaxis can then be based on the result of the HBsAg test and prophylaxis, if necessary, given within 24 hours of the incident report. Where a test result will not be available within 24 hours of the incident report, the incident should be managed initially as for exposure to a known HBsAg positive source. Where the source is an individual known to be HBsAg positive at the time of the incident, immediate HBsAg testing of the sample will not be necessary. In the unusual situation where the source is an

Table 1 Accidental exposure to HBV: points to cover in the incident record*

Person exposed:
- name, date of birth, sex
- occupation
- contact telephone number and address
- name, address and telephone number of GP
- hepatitis B vaccine history
- dates and results of tests for anti-HBs

Exposure:
- date and time of incident
- date and time of report
- place (eg, hospital/community)
- exposure (percutaneous/sexual/mucocutaneous/other)
- material involved (blood/other body fluid)
- further details (including risk of other blood borne viruses)

Source:
- identifiable/unknown
- for identifiable sources:
  - name, date of birth, sex
  - contact telephone number and address
  - hospital number or
  - name, address and telephone number of GP
  - results of tests for HBsAg and HBeAg/anti-HBe

* Copies of a sample form are available from the Hepatitis Section, CDSC

Table 2 Management of reported HBV exposure incidents

1. Record details of exposure incident (Table 1)
2. Assess significance of exposure:
   – if significant, obtain blood specimen (>5ml serum) from person exposed and arrange testing and/or storage
   – if non-significant, assess likelihood of future exposure to risk
3. Assess infectivity of source
   – if source identifiable and available for testing, obtain blood specimen for urgent HBsAg test and/or storage
   – if source refuses consent, manage as though exposure to HBsAg positive source
   – if source unidentifiable or unavailable, manage as exposure to source of unknown HBV status
4. Assess HBV susceptibility of person exposed
5. Give initial HBV prophylaxis (Tables 3 and 4) (HBIG is not indicated more than 7 days after the incident)
6. Arrange follow-up appointments for further doses of hepatitis B vaccine
7. Arrange follow-up appointment at 6 months post-exposure to obtain final blood specimen from those with significant exposure or who are given hepatitis B vaccine for continuing risk

Table 3 HBV prophylaxis for reported exposure incidents

HBV status of person exposed	Significant exposure			Non-significant exposure	
	HBsAg positive source	Unknown source	HBsAg negative source	Continued risk	No further risk
≤1 dose HB vaccine pre-exposure	Accelerated course of HB vaccine* HBIG x 1	Accelerated course of HB vaccine*	Initiate course of HB vaccine	Initiate course of HB vaccine	No HBV prophylaxis Reassure
≥2 doses HB vaccine pre-exposure (anti-HBs not known)	One dose of HB vaccine followed by second dose one month later	One dose of HB vaccine	Finish course of HB vaccine	Finish course of HB vaccine	No HBV prophylaxis Reassure
Known responder to HB vaccine (anti-HBs ≥10 miU/ml)	Booster dose of HB vaccine	Consider booster dose of HB vaccine	Consider booster dose of HB vaccine	Consider booster dose of HB vaccine	No HBV prophylaxis Reassure
Known non-responder to HB vaccine (anti-HBs <10 miU/ml 2-4 months post-vaccination)	HBIG x 1 Consider booster dose of HB vaccine	HBIG x 1 Consider booster dose of HB vaccine	No HBIG Consider booster dose of HB vaccine	No HBIG Consider booster dose of HB vaccine	No HBV prophylaxis Reassure

* An accelerated course of vaccine consists of doses spaced at 0, 1 and 2 months. A booster dose is given at 12 months to those at continuing risk of exposure to HBV.

individual who is unwilling to provide a blood specimen, the exposure incident should be managed as for exposure to a known HBsAg positive source. This is because those who refuse to provide a specimen may be more likely to be HBsAg positive than those who consent to testing.

(ii) From the person exposed

An initial post-exposure blood specimen should also be obtained from the person exposed (regardless of their HBV status) and serum stored for a minimum period of two years. It has been the practice in some laboratories to test this specimen immediately for HBsAg. The logic is, that if the exposed person is HBsAg positive, HBV prophylaxis will not be required. In fact, the chance of the person exposed being found to be HBsAg positive will usually be very small. It was recently shown that, of nearly 3000 UK health service staff tested in one centre for HBsAg after reporting a significant exposure incident, only one was HBsAg positive[3]. Testing of exposed persons for HBsAg is, therefore, not cost effective.

If the person exposed has never received hepatitis B vaccine, or has previously received only a single dose, measurement of anti-HBs levels in the initial post-exposure specimen is also unlikely to be useful. Measurement of anti-HBs levels may be worthwhile in those exposed persons who have previously received two or more doses of vaccine. It will not always be possible, however, for laboratories to provide a same day anti-HBs result, and for this reason initiation of HBV prophylaxis for a reported exposure should not be delayed for more than 24 hours from the initial incident report. The cost of providing an urgent anti-HBs testing service – which may have to operate out of hours – should be balanced against any likely savings in HBV prophylaxis. Where the person exposed can be shown to have had a level of anti-HBs ≥100miU/ml† at or around the time of the exposure, further HBV prophylaxis for the incident will not be required.

Post-exposure prophylaxis (Tables 3 and 4)

(i) After significant exposure to an HBsAg positive source

Those exposed persons with no history of having received hepatitis B vaccine, and those who have previously received only one dose of vaccine, should be offered a single dose of HBIG (Table 4) and an accelerated course of hepatitis B vaccine. The latter consists of vaccine doses at 0, 1 and 2 months; a booster dose is given at 12 months to those at continuing risk of exposure to HBV. HBIG and the initial dose of hepatitis B vaccine should be given concurrently at different sites. Hepatitis B vaccine should normally be given intramuscularly into the deltoid region in adults and the anterolateral aspect of the thigh in infants.

Exposed persons who have previously received two or more doses of hepatitis B vaccine, but who are of unknown HBV status, should be offered a dose of vaccine at the time of the incident, followed by a further dose one month later. Known responders to hepatitis B vaccine should be offered a single booster dose of vaccine. Known non-responders to hepatitis B vaccine should be offered a single dose of HBIG within 24 hours of the report of their exposure. A booster dose of hepatitis B vaccine may be offered at the same time.

(ii) After significant exposure to an unknown source

The risk of HBV transmission after an unknown source exposure in the UK is very low. It will depend on the prevalence of HBsAg and HBeAg in the population. This

† An anti-HBs level of 100miU/ml is considered to reflect an adequate response to the vaccine and to confer protective immunity. Levels of anti-HBs between 10 and 100 miU/ml may indicate a response to the vaccine but one that may not necessarily confer immunity and may require boosting.

Table 4 Dosage of hepatitis B immunoglobulin

Age in years	HBIG dose
0 – 4	200 iU
5 – 9	300 iU
10 or more	500 iU

will vary with locality and might be expected to be higher in inner city areas. Seroprevalence surveys of women attending antenatal clinics in inner London have found an HBsAg prevalence of 0.5% to 1%[4,5]; whereas 4% of homosexual male attenders at a London genitourinary medicine clinic were HBsAg positive[6].

Although the needles involved in community needlestick injuries are often believed to have been discarded by injecting drug users, this will not always be so. Furthermore, not all injecting drug users are HBsAg positive. A recent (and continuing) survey of the prevalence of anti-HBc (a marker for present and previous HBV infection) in the saliva of injecting drug users in England and Wales in 1991 found that only 427 (31%) of 1375 tested had detectable anti-HBc[7]. If it is assumed that all these infections were acquired in adolescence or adulthood, that 10% of those infected in adult life will develop persistent HBV infection and remain HBsAg positive, and that 20% of these will also be HBeAg positive, then the likely prevalence of HBeAg in such injecting drug users is about 1 in 160.

CDSC has never, to date, received a convincing report of HBV transmission having occurred after an unknown source needlestick exposure and it is suggested that HBIG has little part to play following such incidents. The risk of HBV transmission after percutaneous exposure to HBeAg positive blood has been estimated to be 30%; HBV transmission might thus be expected to occur in around 1 in 500 unknown source percutaneous exposures. Trials of the use of hepatitis B vaccine, with and without HBIG, for the prevention of transmission of HBV from HBeAg positive mothers to their babies (where, without intervention, the risk of transmission is over 80%) suggested that hepatitis B vaccine alone prevented between 70% and 85% of infections and that the addition of HBIG to the regimen conferred protection on an extra 10 - 15% of infants[8]. If it is assumed that hepatitis B vaccine given without HBIG will similarly prevent 70 - 85% of possible infections after percutaneous exposure, and that the use of HBIG in addition would prevent a further 12.5%, then HBIG could be expected to prevent HBV transmission in around 1 in 4000 (ie, 500 x 100/12.5) unknown source percutaneous exposures.

The present cost (excluding administrative costs), of an adult dose (500iU) of HBIG is £93. The estimated cost of giving HBIG in addition to hepatitis B vaccine, to prevent a single case of HBV infection as a result of an unknown source percutaneous exposure, is of the order of £400,000. Corresponding estimates of the cost of preventing a case of persistent HBV infection and death from acute hepatitis B are £4 million and £40 million, respectively. These estimates are conservative, because they leave aside considerations of the frequency with which discarded needles are contaminated with blood and the rate of decay of HBV infectivity in the environment. It is suggested, therefore, that HBIG should be used after unknown source exposures only in those known to be non-responders to hepatitis B vaccine. These individuals should be offered a single dose of HBIG within 24 hours of reporting the incident (and may be offered a booster dose of hepatitis B vaccine at the same time).

Exposed persons with no history of hepatitis B vaccination, and those who have previously received only one dose of the vaccine, should be offered an accelerated course of hepatitis B vaccine (doses spaced at 0, 1 and 2 months with a booster dose at 12 months for those at continuing risk of exposure to HBV). Those who have previously received two or more doses of hepatitis B vaccine, but are of unknown HBV status, should be offered a single dose of the vaccine. Known responders to hepatitis B vaccine will not require prophylaxis after unknown source exposure incidents, though the occasion may provide an opportunity to give a 'routine' booster dose of HB vaccine.

(iii) After exposure to an HBsAg negative source or after non-significant exposure

Although specific HBV prophylaxis will not be required for the incident itself, exposed persons who have not previously received hepatitis B vaccine and who are thought to be at continuing risk of exposure to HBV should start a course of vaccine. Those who have received part of a course should complete it as originally planned.

Follow-up of exposed persons

Serological follow-up of exposed persons is important for several reasons. Firstly, the immune response to primary courses of hepatitis B vaccine should be documented in those at occupational risk of HBV infection; those who do not develop ≥10miU/ml anti-HBs after vaccination may benefit from additional doses of hepatitis B vaccine. Secondly, post-exposure HBV prophylaxis may fail, but the resulting HBV infection may be subclinical and detectable only by serological testing. Finally, exposures which carry a risk of HBV infection may pose a risk of transmission of other blood borne viruses, for which serological follow-up may be appropriate. A follow-up blood specimen should therefore be obtained from exposed persons six months after the exposure incident, and serum stored for a minimum of eighteen months.

Follow-up specimens from all exposed persons at continuing risk of HBV exposure, except those who were known to be responders to hepatitis B vaccine at the time of the incident and those whose post-exposure prophylaxis consisted of HBIG alone, should be tested for anti-HBs. Where anti-HBs is not detectable, the specimen should be tested for anti-HBc (and HBsAg if appropriate) in parallel with serum stored from the initial post-exposure specimen. Follow-up specimens from exposed persons given HBIG but not hepatitis B vaccine post-exposure should be tested for anti-HBc and HBsAg in parallel with the initial post-exposure specimen.

Any exposed person developing an illness compatible with a diagnosis of acute hepatitis in the six months after the exposure incident should have appropriate diagnostic tests performed at that time. HBV prophylaxis should be considered for sexual and other close contacts of any exposed person found to be HBsAg positive. Persons who become anti-HBc or HBsAg positive as a result of an exposure incident should be reported to CDSC.

Supplies of HBIG

All public health laboratories hold stocks of adult doses (500iU) of HBIG. Supplies may also be obtained from the Hepatitis Section, CDSC, where 200iU dose vials are also held (telephone 081 200 6868 ext 3404 or 3405, or out of hours via the duty doctor).

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The laboratory diagnosis of mycobacterial disease

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Summary

The diagnosis of mycobacterial disease still relies heavily on conventional microscopy and culture techniques. More modern methods, such as the Bactec 460 radiometric system and the Roche biphasic system, are becoming available but are not yet widely used. Non-culture methods eg, using molecular biology techniques or gas liquid chromatography, are being developed but are currently the province of research and reference laboratories. Disease caused by species other than *Mycobacterium tuberculosis* poses problems of diagnosis and treatment. These other species can be identified by comparatively simple techniques but, as they are widely distributed in the environment, deciding between casual contamination and true infection can be difficult. Although such infections are not a major problem in numerical terms, the variable response of patients to treatment means that conventional sensitivity testing is of little assistance, and it is necessary to seek evidence of synergy in drug combinations for the effective treatment of these infections.

Introduction

Mycobacterial infection has been the subject of much recent atttention[1-4]. Articles have highlighted the need for prompt identification and treatment of cases of tuberculosis (particularly those who are smear positive), the difficulty of diagnosing disease in children, the increase in incidence of disease associated with HIV infection, and the problem of treating infections due to opportunistic mycobacteria. The recognition of these problems and that tuberculosis is far from being eradicated has rekindled interest in the disease.

Diagnostic methods

Direct microscopy of sputum using a Ziehl-Neelsen or fluorescent stain remains the simplest and quickest method of detecting the truly infectious patient ie, the one with open pulmonary tuberculosis. It is much less useful in non-pulmonary disease and childhood disease; in these cases, it is necessary to rely on culture, which traditionally uses a solid medium – either egg-based Lowenstein Jensen or agar-based Middlebrook 7H 10, both of which can require incubation for six to eight weeks before growth is evident[5].

Culture techniques

Most mycobacteria grow more quickly in liquid, and Kirchner's medium has been used for many years for this method. It is important to recognise when growth has occurred, as subculture onto solid medium is required for identification and sensitivity testing. This has been facilitated by the Bactec 460 radiometric system (Becton and Dickinson, Oxford), which uses a Middlebrook 7H 12 broth containing a C^{14} labelled substrate. When metabolised, C^{14} labelled CO_2 is produced and is measured and displayed as a growth index by the apparatus. Growth of *Mycobacterium tuberculosis* occurs in seven to ten days and a sensitivity result can be available in another five days. However, the system is expensive and the use of radioactive labels poses problems for some laboratories[6]. A new medium, Bactec 13A, has recently been introduced which is specifically designed to accept up to 5ml of blood or a bone marrow specimen. It is particularly suitable for blood cultures from AIDS patients when a disseminated infection with *M. avium* is suspected[7].

For laboratories unable to use the Bactec system, Roche have introduced the MB Check culture system. This is a biphasic system combining a primary liquid phase in the same bottle as a solid agar-based phase. The latter incorporates both chocolate agar, to detect contamination, and a phase containing NAP (p-nitro-α-acetylamino-β-hydroxy propio-phenone), which can distinguish between organisms of the tuberculosis complex and other mycobacteria. The final part of the solid phase is a Middlebrook

Table 1 The opportunistic mycobacteria that most commonly infect man

Species	Pulmonary disease	Cervical lymphadenopathy	Localised abscesses and skin infections
*M. avium**	•	•	
M. chelonei			•
M. fortuitum			•
M. intracellulare	•	•	
*M. kansasii**	•		•
M. malmoense	•	•	
M. marinum			•
M. scrofulaceum	•	•	
M. xenopi	•		

* *M. avium* may be associated with disseminated infections, and *M. kansasii* with bone/joint/tendon infections, but these are extremely rare.

7H 10 agar from which subcultures can be made for further identification and sensitivity tests[8].

Both the Bactec and Roche systems are expensive and less relevant to the needs of developing countries, where a balance has to be struck between labour and consumable costs when deciding which system to use. The safety aspects of liquid cultures also have to be taken into consideration and weighed against a reduction in the time taken to produce a result.

Other techniques

A non-cultural method of diagnosing mycobacterial infection has been sought almost since Robert Koch first isolated the tubercle bacillus in 1882. None of the generally accepted serological tests has been adopted because of a lack of sensitivity and specificity[9]. It was hoped that DNA probes would be the answer but so far these have proved no more sensitive for diagnosis with primary specimens than direct microscopy. They are of use, however, in the rapid identification of mycobacterial strains, and probes are now available for a number of different species[10]. The original probes used a radioactive marker and had a very restricted shelf-life. Currently available probes rely on a bio-luminescent marker and last much longer. They also require only a relatively simple luminometer instead of a gamma-counter. They are particularly useful for testing Bactec vials when the growth index is approximately 300, a situation which can be achieved in four or five days with tubercule bacilli or 24 hours with the *Avium-intracellulare* complex (Accuprobe Gen-Probe Inc. Ca, USA).

The most important development has been the use of the polymerase chain reaction to amplify the DNA from as little as three bacilli in a specimen to detectable amounts[11]. This is potentially the most powerful diagnostic tool available but currently remains the province of research laboratories. It requires extreme care to avoid contamination with foreign DNA and inhibitors in specimens can halt the action of the Taq enzyme, which is essential for the amplification process. It will be some years before the test is routinely available, even in reference laboratories.

Another area receiving attention is the detection in specimens of specific substances that are only present in association with mycobacteria. This requires the use of gas liquid chromatography (GLC) linked with mass spectrometry or high pressure liquid chromatography (HPLC). Both systems are expensive and access to them is limited. They rely on the detection of tuberculostearic acid (10 methyloctadecanoic acid), mycocerosic acids, 2-alkanols, phthiocerols or mycolic acids. This is still a specialist area requiring expert knowledge and the system is very much a research tool[12]. Mycobacterial antigens have been detected in CSF specimens using rabbit antisera to BCG in an ELISA system[13] – this technique, however, requires further evaluation.

These approaches are mainly directed towards the primary diagnosis of classical tuberculosis. The laboratory diagnosis of disease due to mycobacteria other than *M. tuberculosis,* or opportunistic mycobacteria, relies totally on culture of the organism and its subsequent identification by classical cultural and biochemical methods. DNA probes, and detection of specific substances by thin layer chromatography GLC or HPLC, are being used but are restricted to reference laboratories.

Opportunistic mycobacteria

The species that most commonly cause human disease are listed in table 1. Pulmonary disease in adults and localised lymphadenopathy in children are the commonest presentations. Soft tissue infections and local abscesses can be caused by *M. fortuitum, M. chelonei* and *M. kansasii*, and superficial skin infections by *M. marinum* (fish-tank granuloma). Other species such as *M. gordonae* and *M. terrae* can cause disease but cases are extremely rare[14]. The identification of these organisms, so far as is necessary for the effective treatment of the patient, is reasonably straightforward. The system developed by Marks[15] uses a small number of simple tests such as temperature range, oxygen preference, pigmentation and Tween hydrolysis.

The true incidence of infection with opportunistic mycobacteria is difficult to determine. Tuberculosis is a statutorily notifiable disease but other mycobacterial infections are not. Laboratories are encouraged to report all new cases of disease due to opportunistic mycobacteria to the PHLS Communicable Disease Surveillance Centre. However, not all laboratories do this and, furthermore, there is no strict definition of what constitutes a 'genuine' case. All opportunistic mycobacteria are environmental organisms and can easily gain access to clinical specimens. Single isolates from sputum, for example, are unlikely to be clinically significant and even multiple isolates may be the result of colonisation of damaged lung tissue and not genuine infection.

New cases of infection due to *M. kansasii* and *M. xenopi* have remained steady at approximately 30 and 20 per year, respectively, but there has been an increase in those due to

the MAIS complex *(M. avium, M. intracellulare* and *M. scrofulaceum*), rising from 33 in 1985 to 77 in 1990. This is attributable to disease in patients infected with the human immunodeficiency virus (HIV). In the UK, HIV-infected patients are more likely to develop disease due to the MAIS complex rather than due to the reactivation of dormant tubercle bacilli, as few of those currently presenting with HIV infection harbour tubercle bacilli from an earlier infection[16]. The most common strains recovered from these patients are those of *M. avium*, rather than *M. intracellulare.* The reported incidence of MAIS infection is thought to be a considerable underestimate, partly due to the confidentiality surrounding HIV infection.

The other opportunistic mycobacterium of importance is *M. malmoense.* This was first described in 1977 and was then thought to be of little consequence[17]. Seventeen cases of pulmonary disease and five cases of cervical lymphadenopathy in children are known to have occurred between 1953 and 1981. During the 1980s the incidence rose steadily to about 35 new cases of pulmonary diseases per year and up to 19 cases of cervical lymphadenopathy. The identification of *M. malmoense* relies on the presence of a specific lipid pattern detectable by thin-layer chromatography[18].

A recent problem has been the contamination of bronchial washings with *M. chelonei* following bronchoscopy[19]. This organism is a non-pigmented, rapidly growing, psychrophile (ie, it grows better at 25°C than 37°C) which can cause localised abscesses but is most frequently present as an environmental contaminant. Its presence in bronchial washings has been due to the practice of rinsing fibre optic bronchoscopes with tap water instead of sterile distilled water.

Drug sensitivity tests

Determination of the sensitivity of *M. tuberculosis* to the drugs used in treatment is well established and there is a good correlation between *in vitro* sensitivity and *in vivo* response. This is not true for opportunistic mycobacteria but, despite this, the system used for *M. tuberculosis* has been applied to them. *M. kansasii* is sensitive *in vitro* to rifampicin and ethambutol and a nine month regimen of these two drugs appears to be effective (British Thoracic Society – personal communication). However, the situation with the MAIS complex, *M. malmoense* and *M. xenopi* is more complicated. These organisms show varying degrees of resistance to the usual anti-tuberculosis drugs, but retrospective studies have indicated that a significant majority of patients do respond to standard anti-tuberculosis chemotherapy provided it is given for two years[20,21].

There is some evidence of synergy between ethambutol and rifampicin and also streptomycin. However, current work at the Mycobacterium Reference Unit is showing that, although this may apply to the MAIS complex, it does not apply to *M. malmoense.* This species has an optimum pH of about 6.0 and most sensitivity studies have been carried out at about pH 7.0. The suboptimal pH increases the apparent sensitivity of the organism and produces spurious results.

The incidence of classical tuberculosis is likely to decline in the long term in the UK but certain groups eg, the elderly and immigrants from the Indian subcontinent, will continue to be at higher risk for some years. The chemotherapy of opportunistic mycobacterial infections requires more investigation. Exposure to environmental mycobacteria is unavoidable and infections will continue to occur.

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Leprosy surveillance

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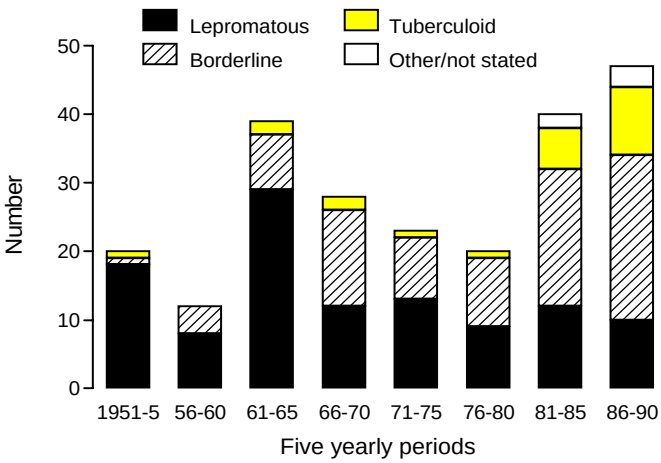
England and Wales

Leprosy became a notifiable disease in 1951 and 1507 notifications were recorded in England and Wales up to December 1990. During this time, 223 duplicates and 25 incorrect diagnoses were identified, leaving a total of 1259 registered cases at the end of 1990. Of these, 840 were males, 395 were females, and in 24 cases the sex was not recorded. The ages of these cases ranged from 3 to 86 years (mean 34 years). The commonest age group for notification was 20-29 years. The most common ethnic groups were those from the Indian subcontinent: Indians, Pakistanis and Bangladeshis comprised one third of the total cases reported. No indigenously acquired cases of leprosy have been reported in England and Wales since notification began 40 years ago.

Nine hundred and forty-five cases have left the register since notifications began, because their leprosy has been cured (482 cases); they have left the country (303) or they have died (135). Ninety-six cases have been lost to follow-up. Figure 1 shows the clinical type of leprosy for the 243 cases that remain on the register. The number of cases of borderline and tuberculoid leprosy has increased in the last decade. The clinical features recorded include anaesthesia (44%), deformity (22%), ulceration (15%), absorption or amputation (0.1%) and visual impairment or blindness (0.05%). The number of new registrations has declined steadily since reaching a peak in 1964[1], averaging 12 per year for the past five years (1986 – 11; 1987 – 11; 1988 – 13; 1989 – 18; 1990 – 9).

The ages of the nine new cases notified in 1990 ranged from 13 to 67 years, with a mean of 37 years. There were eight males and one female. Their leprosy was lepromatous in one case, borderline in four, tuberculoid in one and indeterminate in two; the type was not recorded for one patient. Five were receiving chemotherapy and four were under surveillance alone. A total of 175 patients remained on therapy, consisting of dapsone in 31%, dapsone with rifampicin in 14%, triple therapy (dapsone, rifampicin and clofazimine) in 23%, and other agents or combinations in 32% of cases.

Figure 1 Cases in England and Wales by year of notification and clinical type



The global situation

Leprosy continues to be a major public health problem in Africa, Asia, and Latin America but the global estimate has fallen from about 10 million cases a decade ago to about 5 million in 1991[2]. This improvement has been due largely to the introduction of multidrug therapy (MDT) in the early 1980s. MDT coverage continues to increase in many countries and the World Health Organisation (WHO) is committed to the global elimination of leprosy as a public health problem by the year 2000, with elimination defined as the attainment of a prevalence of less than one case per 10,000 population. The current prevalences of estimated and registered cases for the six WHO regions are given in table 1[3].

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Table 1 Estimated prevalence rates by WHO region[3]

WHO region	Population (millions)	Estimated cases		Registered cases	
		Number	Prevalence rate per 10 000	Number	Prevalence rate per 10 000
Africa	535	96 000	17.1	352 222	6.6
Americas	735	391 000	5.3	335 490	4.6
Eastern Mediterranean	400	207 000	5.2	92 606	2.3
South-East Asia	1 341	3 750 000	28.0	2 190 324	16.3
Western Pacific	1 522	238 000	1.6	110 125	0.7
Europe	852	9 000	0.1	7 021	0.1
Total	5 381	5 511 000	10.2	3 087 788	5.7

Food safety: the HACCP approach to hazard control

M C Majewski

Summary

The Hazard Analysis Critical Control Point (HACCP) approach is becoming increasingly recognised as a valuable means of identifying and controlling hazards in the food production process, and thereby ensuring that food reaching the consumer is safe. The central feature of HACCP analysis is the determination of critical control points (CCPs) – those stages in the process which must be controlled to ensure the safety of the product. Once identified, a monitoring system is set up for each CCP to ensure that correct procedures are maintained and actions taken if CCP criteria are not achieved. The chief advantage of HACCP is that it is proactive; it aims to prevent problems occurring. Although HACCP is most readily applied to manufacturing processes, attempts are being made to adapt the system to other sectors of the food industry, such as catering.

Introduction

The consumer expects to be able to purchase and eat food which is safe and has been handled hygienically during harvesting or slaughter, processing, preparation and sale. The control of food safety during all stages of the production process is a balance of self-imposed regulation by the industry and controls exerted by the food law enforcement authorities. Controls need to be preventive so that contaminated or otherwise unsafe food does not reach the consumer. Industry and governments around the world are examining systematic methods of achieving this.

One such system, Hazard Analysis Critical Control Point (HACCP) is becoming increasingly recognised by governments and the food industry as a valuable preventive and proactive system. The system was originally developed in the 1960s by the Pillsbury Company, United States Army laboratories at Natick, and the National Aeronautics and Space Administration (NASA) in a collaborative effort to develop safe foods for astronauts involved in the United States space programme. The Pillsbury Company presented the HACCP concept to the American National Conference for Food Protection in 1971 and the system has since been modified and developed by the food industry.

HACCP has received national and international recognition. The International Commission on Microbiological Specifications for Foods commended HACCP to the food industry[1]. In the United Kingdom, the report to the Government on the Microbiological Safety of Food (Chairman – Sir Mark Richmond)[2] made frequent reference to HACCP and included examples of HACCP applied to certain processes. The report recommended "that all food processes should be designed on HACCP principles" and suggested that enforcement officers should encourage industry to adopt the HACCP approach. The Codex Alimentarius Commission, established in the 1960s by the Food and Agricultural Organisation (FAO) and the World Health Organisation (WHO) to develop internationally agreed codes, has drawn up an HACCP code through an *ad hoc* group of its Food Hygiene Committee[3]. The code is an attempt to draw together the developments of HACCP over the past 20 years into an internationally agreed set of principles.

What is HACCP?

Hazard Analysis Critical Control Point (HACCP) is a systematic approach to the control of potential hazards in a food operation. A hazard is anything that could harm the consumer; it may be biological, chemical or physical. HACCP aims to identify problems before they occur, and establish mechanisms for their control at the stages in production critical to ensuring the safety of food. Control is proactive, since the identification of potential hazards and preventive measures, and the establishment of monitoring and remedial actions in advance, means that the hazard does not occur. Table 1 lists the seven principles of HACCP as set out in the Codex Alimentarius Commission code[3].

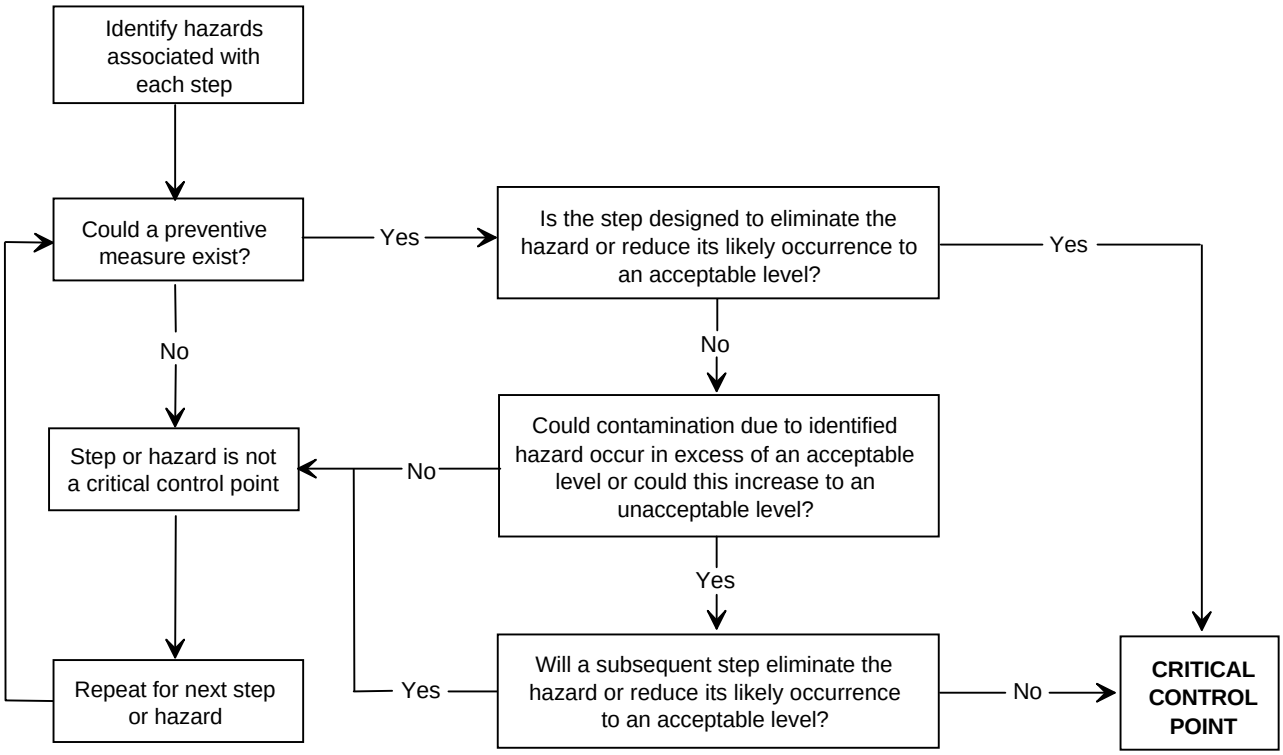
In analysing the food operation, consideration must be given to the type of raw materials and ingredients used in the process, the means available to control hazards, the likely use of the product once it is manufactured or served and the population at risk, including any epidemiological evidence relating to the safety of that product.

Table 1 Seven principles of HACCP*

1. Identify the potential hazards associated with food production at all stages up to the point of consumption. Assess the likelihood of occurrence of the hazards and identify the preventive measures necessary for their control.
2. Determine the points, procedures and operational steps (**critical control points** – CCPs) that can be controlled to eliminate the hazards or minimise their likelihood of occurrence. A 'step' means a stage in food production or manufacture eg, the receipt or production of raw materials, harvesting, transport, formulation, processing and storage.
3. Establish target levels and tolerances which must be met to ensure the CCP is under control.
4. Establish a monitoring system to ensure control of the CCP by scheduled testing or observation.
5. Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control.
6. Establish procedures for verification, including supplementary tests and procedures to confirm that HACCP is working effectively.
7. Establish documentation concerning all procedures and records appropriate to these principles and their application.

* Adapted from reference 3.

Figure 1 The HACCP decision tree*



* Adapted from reference 3.

The HACCP logic sequence

The HACCP logic sequence shows the steps required to carry out an HACCP procedure. A team is set up, consisting of technical and non-technical personnel. The product to be analysed is described and its intended use identified. An example would be a chicken product intended for consumption by the public. The flow-chart of its production is developed, and then verified by 'walking' the production area. Any alterations can be made at this stage and the flow-chart agreed. The potential hazards are then listed against each step; there may be several different hazards for any one step. Preventive measures can then be listed against each hazard. In the case of chicken, a potential hazard would be the survival of salmonellas during cooking; the preventive measure would be to ensure thorough cooking and heat penetration of the carcase.

The crux of the HACCP analysis is the determination of critical control points (CCPs). By applying the HACCP decision tree (Figure 1) the team can 'home in' on those steps which are critical to the safety of the product; set targets and tolerances for that CCP, and determine how, when and by whom the CCP is to be measured and observed. The target level is the value to be achieved at each CCP and the tolerances give the acceptable variation from that target. The target level for cooking chicken might be to heat until deep parts of the flesh reach 75°C; the tolerance could be -2°C from the target. The variables to be monitored should have a measurable value, preferably one which is quick to assess, such as temperature, time or a visual inspection-colour change. In addition, the team needs to develop instructions and procedures for dealing with deviations from the CCP tolerance values, including instructions to reprocess or dispose of the products. A system for monitoring each CCP should then be established, with appropriate record keeping and documentation. Table 2 illustrates part of a hazard analysis of the production of powdered formula milk[4] and also shows how HACCP can help identify future improvements to control hazards.

Evaluation of HACCP

The traditional approach to food safety has involved the training of food handlers, inspection of premises and end product testing by microbiological analysis of samples taken from batches or a day's production. Training and inspection remain key elements of food safety, and there are new developments to increase their effectiveness[5]. However, there are a number of disadvantages associated with end product testing:

(i) it is retrospective; the product is already made and test results may not be available for several days

(ii) it may involve product recall if a problem is highlighted; this can only be partly effective and is usually costly

(iii) it may fail to detect contaminated batches, and as it is possible to sample only a small number of units from a batch for economic reasons, unsafe units may be missed leading to the false assumption that the whole batch is safe[6]

(iv) it is expensive; expertise and facilities are needed to carry out tests

(v) it only involves a limited number of staff in hazard control.

HACCP has a number of advantages over end product testing:

(i) HACCP is proactive and preventive; prescribed remedial action can be taken quickly before problems occur
(ii) it may identify hazards that have not been experienced; it is therefore particularly useful when setting up new operations
(iii) it applies to all parts of the process rather than to samples selected for testing
(iv) it allows resources to be concentrated on critical control points rather than being spread thinly across the whole process
(v) it involves all levels of staff, not just technical personnel, and is controlled by those involved directly in production rather than microbiologists in remote laboratories.

There are, however, limitations associated with HACCP. HACCP is only likely to be successful where the principles of good hygienic practice are already in place. If the structure, equipment and cleaning standards are inappropriate, the development of an HACCP system will be difficult. An understanding of what constitutes a hazard, and of the appropriateness of preventive measures, is necessary for the system to be effective. A comprehensive HACCP system lends itself primarily to manufacturing operations but the principles of identifying hazards and introducing suitable control measures can be applied to any food operation.

Recent government initiatives

Officials in the Department of Health (DOH) and the Ministry of Agriculture, Food and Fisheries (MAFF) have taken a leading role, within the FAO/WHO Codex Alimentarius Commission, in the development of an internationally agreed definition of HACCP and its applications[3]. In addition, the government has promoted the use of HACCP through the release of a leaflet[7] which has been supplied to environmental health departments for distribution to food businesses. Technical papers, giving more detailed information about HACCP, have been provided to environmental health departments, and other articles on the subject have been published[8].

The DOH and MAFF have also been involved in the training of environmental health officers in aspects of HACCP. More than 20 workshops have been held advising officers of the basic principles of HACCP and how these can be applied in normal inspection routines. In addition, two major conferences have taken place which were targeted at the food industry, enforcement authorities and medical

Table 2 Selected critical control points in the production of powdered formula milk*

	Critical control point			
	Concentration of vitamin enriched milk	Mixing of oil and vitamin	Transportation of product	Packaging of product
Description	Two stage evaporator (stage 1: 60° - 70°C; stage 2: 50° - 60°C).	Materials mixed in a tank at 20°C.	By air through ducting into storage tanks.	In an impermeable laminate sachet.
Hazards	Drop in temperature due to halt in production. Bacteria may grow in held product.	Raw materials may be contaminated if incorrectly handled.	Contamination carried in cooling air. Cracks in ducting may allow contamination.	Laminate may be contaminated. Air supply to filler may be contaminated. Residue in filler could contaminate fresh product.
Preventive measures	Ensure correct feed to evaporator. Ensure correct temperature for both stages.	Supplier's quality assurance of raw materials.	Filter air. Inspect ducting for leaks.	Discard outer layer of laminate on spool. Filter air. Dry-clean filler to prevent residue build-up.
Target/tolerance levels	Second stage minimum temperature 48°C.	Tested product is free of pathogens.	Class 1 filters on cooling air inlets. No leaks in ducting.	First four metres of spool discarded. Class 1 filters on air supply to filler.
Action in event of deviation from target/tolerance level	Quarantine product.		Production halted if leaks discovered.	
Planned improvements	Introduction of new equipment to avoid halts in production.			Consider ultraviolet treatment to disinfect laminate.

* Adapted from reference 4.

professionals involved in food safety; further seminars are planned in England and Scotland.

Food hygiene inspections

Under Section 40 of the Food Safety Act 1990[9], various codes of practice advising on the application of legislation have been issued to enforcement authorities by the government. These include Code of Practice No. 9 on Food Hygiene Inspections which outlines the steps an environmental health officer should take when carrying out a food hygiene inspection[10]. It advises environmental health departments to prioritise visits according to relative risk and to take into account whether the food business has an effective management system in place. The Code draws the environmental health officer's attention to those parts of the operation which are critical to the safety of food. It advises that an inspection should include a preliminary assessment of the food safety hazards associated with the operation to identify areas requiring closer scrutiny. Where hazard analysis systems are already fully developed, the inspection approach should be modified; particular attention should be paid to determining whether the necessary monitoring and verification of CCPs is being carried out. Many food businesses, particularly small ones, may not have formal hazard analysis systems. In such cases the environmental health officer should have special regard to the hazards associated with the business.

There is no legal requirement to introduce HACCP, although some organisations see an effective HACCP system as part of the development of a 'due diligence' defence under Section 21 of the Food Safety Act 1990[9].

Future developments

HACCP systems are being taken up increasingly by the food industry. HACCP is mentioned in European Commission directives, in particular the proposed Food Hygiene Directive[11] and the Meat Products Directive[12]. In the United States, HACCP is already established in principle in some national legislation and has been promoted rigorously by the US government food agencies, including a recent programme aimed at the fish and shellfish industries. Conferences have been held around the world advising that HACCP should be operating in food manufacturing organisations which wish to import into the United States avoiding extensive dockside checks. There is no reason why such control of imports may not spread into other commodity sectors, and to other countries.

Although HACCP has been used primarily in food manufacturing situations, the principles of identifying hazards and suitable controls can be applied to other sectors of the food industry, eg, catering. Some large cook-chill and cook-freeze production units have been able to adopt HACCP systems, as these processes lend themselves to this type of systematic analysis. The DOH guidance on cook-chill and cook-freeze advises that HACCP should be used as a method to control hazards[13]. However, traditional catering operations have had greater difficulty in applying HACCP, partly due to the wide range of foods being processed. One of the problems that this industry faces is a general lack of technical expertise, particularly in the field of microbiology, to which caterers can turn. Many caterers may have difficulty in identifying hazards and effective controls. With this in mind, a catering industry group at Campden Food and Drink Research Association has been working with DOH and MAFF officials to develop a system suitable for catering, which identifies hazards applicable to any catering operation and provides 'generic CCPs' for the caterer. Another part of the food industry that has had difficulty in adopting the complete HACCP system has been the small retailing sector, such as small butchers and cornershops. A similar type of approach may be applied to these operations in the future.

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