**Infections in children**

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**Introduction**

In developed countries, over the last four decades, the burden of infection in childhood has decreased greatly. This has, in part, resulted from improved public health and social and economic conditions, and the introduction of safe and effective vaccines. Measles, mumps, diphtheria and tetanus are diseases of such rarity that few newly appointed paediatricians will have encountered them. Perhaps the most striking example of this is the virtual disappearance in the UK of invasive infections such as meningitis and epiglottitis due to *Haemophilus influenzae* type b since the introduction of the conjugate vaccine in 1992 [1]. If the contribution of immunisation to this decrease in the burden of infection is doubted, a salutary lesson can be drawn from the effect of decreased pertussis vaccine uptake in the 1980s. In those countries where the misguided anti-vaccine campaign took hold, there was a dramatic increase in the incidence of whooping cough with its associated morbidity and mortality [2].

Despite these great improvements there is no place for complacency or a relaxation in vigilance. Infectious diseases in children still have the capacity to cause great concern. As yet, there are no widely applicable vaccines for rotavirus, which is responsible for the majority of episodes of acute dehydrating infantile diarrhoea, nor for respiratory syncytial virus which is responsible for the hospitalisation of 2.5% of infants each year. Each winter, meningococcal disease results in deaths in young children and adolescents, causing great public disquiet. The 'old' infections such as tuberculosis have not continued their expected decrease in incidence and in some parts of the UK have shown an upturn [3]. Large outbreaks of diphtheria have emerged in Eastern Europe and Russia and neonatal tetanus is still responsible for over half a million deaths each year.

In developing countries, infection is still the major cause of death in children. For example, it is estimated that over 5 million deaths each year are a result of diarrhoeal disease and twice that number are due to acute respiratory tract infection. Underlying all these infections is the ever present spectre of HIV.

In this fourth symposium on microbial disease we have drawn together a series of experts in paediatric infectious diseases to address a variety of infections in both the developed and developing world.

**HIV INFECTION IN AFRICAN CHILDREN**

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The acquired immunodeficiency syndrome (AIDS) was first recognised in East and Central Africa in 1982/1983 in Rwanda, Zaire, Uganda, Tanzania and Zambia at a similar time that it was reported in the USA (1981) [4]. This was followed by rapid spread throughout Africa with the heaviest burden in East, Central and southern Africa and to a lesser extent West Africa, especially Cote d’Ivoire. While HIV prevalence continues to increase in some countries with late arrival of the virus – namely, South Africa [5] and neighbouring states, Botswana, Lesotho, Swaziland – there are signs of a plateau or even decrease in prevalence in parts of Uganda [6]. Uganda is one of the countries where the disease was first recognised and a country that was quick to recognise the problem and introduce health education and preventive measures.

The overall HIV infection ratio of men and women in subSaharan Africa is c. 1:1.4, but in the early reproductive age group, 15–20 years, it is much higher in females and this is reflected in high HIV prevalence in women attending antenatal clinics, especially in urban areas. It is estimated that presently up to 90% of the world's children infected with HIV reside in subSaharan Africa and up to 25% of AIDS cases in subSaharan Africa are in children [5].
It is now 8–10 years since large vertical transmission studies were set up in a number of countries in Africa and Europe and much is now known about the aetiology and natural history of the disease. Research is now focused on prevention of perinatal transmission, e.g., antiretroviral therapy; prevention of infections, e.g., *Pneumocystis carinii* pneumonia (PCP); prospects for vaccines; and important problems such as transmission through breast-feeding.

### Epidemiology

The vast majority of HIV infections in children arise through mother–child transmission, although where screening of blood transfusions is inadequate perinatal transmission is still a problem (7% of HIV infections in Kigali, Rwanda [7]) and as in other parts of the world sexual abuse is an occasional route of infection. The potential for infection through use of unsterilised needles and scarification exists; the proportion of infection acquired through this route is unknown, but probably small.

In larger urban conurbations and trading centres of East, Central and southern Africa the prevalence of HIV infection in women attending antenatal clinics may be ≥20–30% [4]. In the Rakai district of Uganda, a rural area with a high HIV endemicity, 28–47% of women in trading centres and up to 10% of village women may be seropositive for HIV-1 [8]. Regional differences within countries occur; for example, in South Africa the prevalence in the Western Cape was 1.2% and in KwaZulu/Natal 14.3% [9] with more recent figures as high as 21–24% [10]. In Ghana, the prevalence in Accra is c. 2% and it is up to 10% in the Eastern region [11]. Rates of 10–15% are recorded in neighbouring Abidjan [12, 13]. Rates in Nigeria (the largest population in Africa) are c. 5–6% in some urban areas [13].

Uganda is the first country to report falling seroprevalence rates in antenatal clinics. In Kampala rates have dropped from c. 28% to 16–20% in the period 1993–1995 [14].

### Vertical transmission

Vertical transmission rates range widely and are generally higher in Africa (20–42%) than in industrialised countries (14–25%) [15]. Prospective studies are difficult to undertake, particularly with loss to follow-up and lack of laboratory facilities for early diagnosis. Table 1 outlines some of the larger well conducted studies which demonstrated a range of 25–27% for vertical transmission rates in Africa. The reasons for the higher rates in Africa compared with Europe are unclear. Women in Africa may be more likely to have higher viral load associated with symptomatic disease and nutritional deficiencies and there may be more chorioamnionitis and shedding of virus in the genital tract associated with genital ulcers. Rates in the USA are not dissimilar to Africa. In the USA, HIV in women is associated with intravenous drug use, minority groups, poverty and limited access to health care [23]. It may be that risk factors for vertical transmission are similar in some groups of women in the USA and Africa. In vertical transmission studies selection of women may affect results, particularly the proportion of symptomatic women [24]. The contribution of breast-feeding to vertical transmission is discussed below.

Timing of vertical transmission is important, particularly with regard to the opportunity for prevention, e.g., antiretroviral therapy in the perinatal period. Although there is evidence of HIV infection of the fetus in the first trimester it is probably infrequent [25, 26]. It is considered that up to two-thirds of perinatal infections occur *intra partum* or around the time of delivery, and most of the remaining one-third are within 2 months or so of delivery. Evidence for the latter is based on virological markers of infection [27], studies on twin deliveries [28] and the association with chorioamnionitis [29]. The first twin has over two-fold higher risk of infection than the second twin, probably because it lies near the cervical canal and thus may be more vulnerable to HIV-infected secretions [28]. Similarly, the presence of chorioamnionitis may assist the HIV in the genital tract to reach the fetus. Shedding of HIV-infected lymphocytes and monocyte/macrophages in genital tract secretions is particularly associated with pregnancy, cervical ectopy, cervicitis and oral contraceptives [30].

### Risk factors

Risk factors for vertical transmission are outlined in Table 2 [31–43]. High HIV-RNA viral load is associated with increased risk of infection [31], but even mothers with low viral load may infect their infants and so it does not have a strong predictive value [44]. Risk factors that

### Table 1. Prospective vertical transmission studies Europe, New York and Africa

<table>
<thead>
<tr>
<th>Place</th>
<th>Number of infants studied</th>
<th>TR (%)</th>
<th>Date of report</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECS</td>
<td>990</td>
<td>15</td>
<td>1994</td>
<td>[16]</td>
</tr>
<tr>
<td>France</td>
<td>838</td>
<td>20</td>
<td>1995</td>
<td>[17]</td>
</tr>
<tr>
<td>Switzerland</td>
<td>201</td>
<td>20</td>
<td>1992</td>
<td>[18]</td>
</tr>
<tr>
<td>Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kigali</td>
<td>218</td>
<td>25</td>
<td>1993</td>
<td>[20]</td>
</tr>
<tr>
<td>Kampala</td>
<td>387</td>
<td>26</td>
<td>1996</td>
<td>[21]</td>
</tr>
<tr>
<td>Blantyre</td>
<td>982</td>
<td>27†</td>
<td>1996</td>
<td>[22]</td>
</tr>
<tr>
<td>Abidjan</td>
<td>339</td>
<td>25†</td>
<td>1994</td>
<td>[12]</td>
</tr>
</tbody>
</table>

TR: transmission rate.

†Vaginal vertex singleton deliveries; diagnosis by PCR at 6 and 12 weeks.

HIV-1, 15%; HIV-1 + HIV-2, 19%; HIV-2, 1.2%.
Viral characteristics and protective maternal antibodies against mother's virus have been associated with reduced risk of transmission in some studies, but require further investigation. HIV-2 is associated with low mother–child transmission [46].

**Vitamin A**

Adults with HIV infection in developing and industrialised countries have low levels of blood vitamin A and low levels are associated with progression to AIDS and reduced life span [42]. In Malawi, an association between low levels of vitamin A in the mother and both vertical transmission [47] and increased infant mortality [42] has been shown. Whether this is just an association or a cause is not known. A number of intervention trials of vitamin A supplementation of HIV-infected pregnant women and infants are in progress in Africa. In South Africa, a randomised placebo controlled trial showed that vitamin A supplementation reduced overall mortality and diarrhoea-associated morbidity in HIV-infected infants, but not in controls [48].

**Breast-feeding**

Evidence for transmission of HIV through breast-feeding is based on instances where mothers have developed HIV infection postnatally either through a blood transfusion [49] or presumed sexual intercourse [33,50] and their infants have subsequently shown infection. What is not clear is the proportion of mothers infected prenatally, whose infants have not been infected during pregnancy or delivery, who may infect their infants through breast-feeding. It is assumed that the majority of such women have HIV antibodies and relatively low stable levels of virus. A meta-analysis calculated a transmission rate of 29% if the mother was infected postnatally and 14% if infected prenatally [39]. Table 3 shows the results of five studies in which infants were either breast-fed or given artificial milk. Overall there is an association with breast-feeding, but the numbers of breast-fed infants in the four studies from industrialised countries are low. The South African study has sufficient numbers in each group to show a significant difference and has an excess of 17% in the breast-fed group.

Seroreverters have been described who subsequently seroconverted, presumably through breast-feeding as late as 36 months postnatally [52]. Studies of late postnatal transmission have shown widely different results [53–56]. A study in Nairobi [54] found that 40 (44%) of 90 HIV-1 infected infants had a period of 3–9 months of seronegativity and subsequently seroconverted, presumably through breast-feeding. A large drop-out rate may have biased the results. A study in Kampala [54] found that only 3 (2%) of 142 infants born to HIV-infected mothers who were seronegative at 12–18 months (seroreverters) and continued breast-feeding, later seroconverted, presumably due to infection from breast milk. A study from Abidjan that mainly used PCR for diagnoses of HIV infection calculated a late transmission rate of 12% for HIV-1 and 6% for dually (HIV-1 and HIV-2) infected mothers [55]. No case of late transmission occurred in HIV-2-infected mothers. A similar study in Dar-es-Salaam with PCR and p24 antigen tests found that 8 (6%) of 139 uninfected children converted after 11 months of age [56].

**Table 2. Risk factors for vertical transmission**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High viral load</strong> [31]</td>
<td></td>
</tr>
<tr>
<td>Maternal symptomatic disease [29]</td>
<td></td>
</tr>
<tr>
<td>Low CD-4 counts [20, 29, 32]</td>
<td></td>
</tr>
<tr>
<td>p24 antigenaemia [20, 22, 29]</td>
<td></td>
</tr>
<tr>
<td>Serocversion during pregnancy [33]</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Sexual intercourse during pregnancy [34, 35]</td>
<td></td>
</tr>
<tr>
<td>Prematurity [36]</td>
<td></td>
</tr>
<tr>
<td>First born twin [28]</td>
<td></td>
</tr>
<tr>
<td>Chorioamnionitis [29]</td>
<td></td>
</tr>
<tr>
<td>Prolonged rupture of membranes [22, 37]</td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery [38]</td>
<td></td>
</tr>
<tr>
<td>Breast-feeding [39]</td>
<td></td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td></td>
</tr>
<tr>
<td>Viral characteristics [40, 41]</td>
<td></td>
</tr>
<tr>
<td>Protective maternal antibodies [41]</td>
<td></td>
</tr>
<tr>
<td>Vitamin A deficiency [42, 43]</td>
<td></td>
</tr>
<tr>
<td>Genetic factors (e.g., CCR5 polymorphisms)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. HIV infection rates in breast-fed and artificially fed infants**

<table>
<thead>
<tr>
<th>Country</th>
<th>BREAST-FED (%)</th>
<th>ARTIFICIALLY (%)</th>
<th>DIFFERENCE BETWEEN RATES (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland (1992)</td>
<td>2/13 (15)</td>
<td>21/128 (16)</td>
<td>-1</td>
<td>[39]</td>
</tr>
<tr>
<td>Italy (1992)</td>
<td>9/22 (41)</td>
<td>124/534 (23)</td>
<td>18</td>
<td>[51]</td>
</tr>
<tr>
<td>S. Africa (1997)</td>
<td>61/161 (38)</td>
<td>14/66 (21)</td>
<td>17</td>
<td>*</td>
</tr>
</tbody>
</table>

*G. Gray, Perinatal HIV Research Unit, University of Witwatersrand, Johannesburg. Personal Communication, 1997."
If p24 antigen is detected in breast milk it is likely to be only in the first few days [57]. Increased transmission rates have been documented in breast milk containing HIV-1-infected cells in the absence of HIV IgM at 15 days [58]. Higher HIV PCR and p24 antigenaemia levels in colostrum cell pellets than in milk suggest that colostrum may have an increased risk for infection; this of course may be balanced by high levels of HIV antibodies. A study in Kampala investigated p24 antigen and HIV-1 DNA in breast milk at c. 6 weeks after delivery by PCR [59]; p24 antigen was not detected. HIV-1 DNA was detected in similar proportions of HIV transmitters (80%) and non-transmitter mothers (72%) and the duration of breast-feeding was not significantly different in the two groups – 15.8 versus 14.4 months, respectively.

These studies suggest that there may be a higher risk of HIV infection in the first 2 weeks or so of breast-feeding. However, there may also be a risk in prolonged breast-feeding. If the risk of infection remains the same (or increases because of immunological deterioration of the mother) after the postpartum period, the risk of HIV infection through breast milk after 3–7 months may outweigh the nutritional and anti-infective benefit, once mixed feeding has been established [60, 61].

There are many questions involved in the debate regarding the safety of breast milk of HIV-infected mothers which require randomised clinical trials conducted in developing countries for clarification. Studies are under way in Kenya (randomised) and South Africa (non-randomised). It will be important to ensure that none of the artificially fed infants is breast-fed. Factors that require examination include infectivity of colostrum and early milk versus later milk, duration of breast-feeding, symptomatic, immunological and nutritional status of the mother (e.g., vitamin A levels [62]), presence of cracked nipples, oral infections and presence of teeth in the infant, and the balance of HIV load and HIV antibodies (both in breast milk and placental) and other protective factors at different stages of breast-feeding (e.g., lactoferrin and lysozyme). In the meantime, until the results of on-going studies are known, WHO/UNICEF advice, that where no safe substitutes are available, HIV-infected mothers should continue to breast-feed, is sound [63]. It should be remembered that the majority of pregnant African women presently do not have access to HIV testing and some do not want to know their HIV status because of the many implications it may have for their families.

**Clinical problems**

The clinical presentation of HIV infection in developing countries differs from that in industrialised countries, particularly with the high prevalence of infections, e.g., skin, gut, respiratory tract and malnutrition (both wasting and stunting) [64–66]. Facilities for diagnosis of opportunistic infections are limited. Many infants probably die of complications of HIV before developing criteria for AIDS. Chronic respiratory disease often associated with finger clubbing [67] and cor pulmonale [68] is common. PCP is an important cause of death in young infants [69–71]. Lymphocytic interstitial pneumonitis is seen in older children, often associated with parotid enlargement and generalised lymphadenopathy [72]. There is a strong association between HIV infection and tuberculosis [73, 74]. In Lusaka 70% of children with tuberculosis are HIV seropositive [73]. However, because of energy to tuberculin tests and lack of facilities for culture it is often difficult to confirm tuberculosis. Tuberculosis presents more commonly in children who survive the infections of early infancy [72], is associated with a higher mortality in HIV seropositive children and response to treatment is often poor [70, 73–75]. Kaposi’s sarcoma, although rare in Western countries, is relatively common in Uganda and other sub-Saharan African countries [76, 77]. *Cryptococcus neoformans* infection is uncommon in young children in both industrialised and developing countries [78]. HIV-infected children do not appear to be any more prone to malaria or its complications than non-infected children [79–81].

In areas where HIV is endemic, infected children have increased the number of admissions to already overburdened hospitals. This is reflected in prolonged admission with increased costs to both health institutions and the families [82].

**Mortality**

About 20% of infants born to HIV-infected mothers die in the first 12 months of life [20, 24, 83, 84] and c. 50% of infected infants [24]. Despite the high attrition rates a number of relatively asymptomatic HIV infected children >10 years of age attend follow-up clinics in subSaharan Africa.

**Laboratory investigations**

Many laboratories do not have routine facilities for counselling and HIV testing. PCR is only available in research centres which usually have international support. Dried blood spot specimens are useful for PCR and facilitate easy storage and transport to central laboratories [85]. HIV IgA antibody tests have a sensitivity of 80–90% by 4–6 months and high specificity after 2 months of age and may become useful low cost investigations for early diagnosis in subSaharan Africa [86–88]. False positive results may be seen in the first month of life. p24 antigen assay with ELISA is also practical for developing countries.
Sensitivity is improved by acid dissociation of p24 antigen–antibody complexes [86]. Sensitivity may be further improved by heat dissociation of p24 immune complexes [89].

Immunisation

In developing countries children born to HIV-infected mothers are immunised according to the usual expanded programme of immunisation (EPI) regimen. There have been no problems reported except for occasional problems with BCG [4]. World-wide there have been about 11 cases of disseminated infection reported in children following BCG and four in adults [90, 91]. Local reactivation with fistulisation, progressive or disseminated disease may occur months to many years after BCG, coinciding with onset of AIDS. With the large number of HIV-infected infants born throughout the world who receive neonatal BCG, no doubt there are some who develop disseminated BCG which is not recognised or not proven due to lack of facilities for culture of the mycobacteria. However, if BCG is given to infants at birth (before development of immunodeficiency) and is not given to HIV symptomatic children, the risk of dissemination appears to be low. The serological response to EPI vaccines is reduced in HIV-infected children, particularly the persistence of antibodies, compared with non-infected children [92]. Some may benefit from boosters, although serological response is impaired in children with established immunodeficiency; there is little information on efficacy. HIV-infected children would probably benefit from *H. influenzae* type b and pneumococcal conjugate vaccines if they became available in developing countries [93–95].

Social aspects

The extent of impact of paediatric HIV infection on the family and health infrastructure for children is difficult to estimate. In HIV-infected areas it is estimated that c. 6–11% of the population under 15 years of age may be orphans by the year 2000 [96]. So far, extended families appear to be able to absorb most of these children, but at a cost of even lower standards of living than expected. Chronic illness of children, frequent and prolonged admissions to hospital, drug costs in societies where cost sharing is now in operation, death of one or both parents and family separation contribute an enormous burden to already deprived families.

Prevention

The control of perinatal HIV infection in Africa has to address important implications of the place and vulnerability of women in society. These include teenage sexual abuse, economic factors that require offering sexual favours to (older) men, instability of relationships, inadequate health and sexual education, prevention and treatment of sexually transmitted diseases, and lack of an effective female condom and vaginal virucide. In urban areas of Uganda there are signs of change in sexual behaviour. Surveys comparing attitudes in 1989 and 1995 demonstrated a delay in onset of sexual intercourse, a decrease in casual sex by male youths and an increase in the use of condoms by both sexes [6].

Adequate screening of blood transfusions is essential. The preventive role of caesarian section requires further investigation [38, 45]. It is estimated that 16 caesarian sections may be necessary to prevent one infected child. A multicentre trial to examine the benefit of caesarian section has commenced in Europe. The problems and dangers of caesarian section in symptomatic HIV-infected women in hospitals in developing countries with limited facilities needs to be considered. A study of vaginal lavage with chlorhexidine during labour in Malawi failed to demonstrate reduction of HIV vertical transmission except in women with prolonged ruptured membranes [22], but it did result in a marked reduction in sepsis [97]. The results of studies on the administration of vitamin A and other micronutrients during pregnancy or at delivery, or both, in Malawi, South Africa and Tanzania are awaited. Studies on the administration of anti-HIV immunoglobulins to women during delivery have commenced in Uganda. Vaccine trials are in progress, but the heterogeneity of HIV in Africa is an obstacle [98]. Administration of antiretroviral drugs to HIV-infected women during the last trimester of pregnancy or at delivery, or both, shows the most promise. A number of collaborative studies on antiretroviral drugs are in progress in sub-Saharan Africa, investigating various combinations and administration for shorter periods, e.g., *intra partum and postpartum*. A model for developing countries using zidovudine in a short course (2–6 weeks) before delivery and orally during labour, has been estimated to reduce perinatal HIV transmission from 25% to 16.5% [99]. This would cost $20 per pregnant woman in a setting where in 1992 the median per capita expenditure on health care in subSaharan Africa was c. $14 (range $5–158).

**IMPORTED INFECTIONS IN CHILDREN: EPIDEMIOLOGICAL AND PUBLIC HEALTH PERSPECTIVES**

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Imported infections are a growing paediatric and public health problem. Various social and demographic trends are causing the number of infections imported into the UK to rise. The amount of international travel to and
from the UK has increased almost exponentially. Numbers of residents travelling abroad have more than trebled in the 25 years from 1970 to 1995 (Table 4), in addition to which the range of countries visited has become more exotic. Many more persons are visiting tropical countries where the burden of infection is higher than in the UK and where the traveller may meet infections which are novel to their immune system [100]. The risk of infection to the individual traveller from a single trip is small [101]; however, the sheer volume of travel is such that the absolute number of infections brought back to the UK is increasing (Fig. 1). Travel to the UK is also substantial and increasing. In 1994 there were over 9 million visitors to the UK, an increase of over a million compared with the total for 1992 [100]. Another factor is that the UK contains several ethnic minority groups from tropical countries. They are accustomed to travelling back to their familial countries of origin, but as first- and second-generation immigrants they often do not appreciate the risk of infection to themselves and their children. Hence they do not necessarily take the precautions appropriate for visitors to tropical countries [102]. This results in a particular over-representation of ethnic minority children among imported malaria cases [103] and the same is likely to be true of other imported exotic infections.

For all these reasons the numbers of imported infections among children are almost certainly rising. The variety of imported infections is potentially vast. This article concentrates on the epidemiological and public health aspects of the more important infections. It does not cover the issue of the diagnostic difficulties for the clinician faced with the ill individual recently returned from abroad; several publications address this issue [1, 104–106].

**Imported infection numbers**

There have been very few surveys of imported infections among children in the UK. A national postal survey of consultant paediatricians in 1976 found that between 40 and 50% of paediatricians had not seen an imported infection in the preceding year [107]. It seems unlikely that imported infections would be so rare to today’s paediatricians. However, that survey did note that children were more likely to be admitted with an imported infection than adults. Although children constitute only 4% of the travelling population, they contributed a quarter of the infections requiring admission [1]. A survey of paediatric admissions with imported infections was undertaken by Riordan and colleagues in a Birmingham hospital 20 years later. This found 65 imported infections among 58 children admitted over a 16-month period, with the commonest presentations and diagnoses being diarrhoeal disease (27 cases) and malaria (23 cases) [108].

**Table 4. Total visits abroad by UK residents**

<table>
<thead>
<tr>
<th>Year</th>
<th>Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1949</td>
<td>1.7 million</td>
</tr>
<tr>
<td>1960</td>
<td>6.0 million</td>
</tr>
<tr>
<td>1970</td>
<td>18 million</td>
</tr>
<tr>
<td>1990</td>
<td>31.2 million</td>
</tr>
<tr>
<td>1995</td>
<td>41.8 million</td>
</tr>
</tbody>
</table>


**Fig. 1.** Estimated incidence of health problems per 100,000 visits to the tropics [101].
by ethnic group and nationality indicates that African and South Asian children are disproportionately at risk and that numbers of cases have risen, particularly among African children (Tables 5 and 6). Frequently these children are returning to circumstances where risk of exposure to mosquito bites is high, much higher than experienced by the visiting expatriate tourist. This is partially because often the recalled experience of malaria of the parents of these children is of a less severe illness because of partial immunity built up from repeated childhood exposures. Consequently they do not always appreciate the risk to their children and themselves and so do not apply the appropriate precautions of using bed nets, insect repellents and anti-malarial chemoprophylaxis [103].

Meningococcal disease

Acquisition of meningococcal disease is theoretically a risk for those travelling to the so-called ‘meningitis belt’ of the tropics (Fig. 2), the extent of which varies from year to year. Outbreaks and epidemics of infection with Neisseria meningitidis group A are common and have most recently occurred in West African countries [109]. Imported cases are rare in the UK, probably because visiting tourists and other expatriates will not experience the close intimate contact needed to acquire disease, and ethnic minority children who become infected are likely to experience their disease before returning to the UK. As an effective vaccine is available against group A and C meningococci, routine vaccination is recommended for adults and children spending some time in the meningitis belt countries, especially individuals likely to come into close contact with residents living in the country, e.g., African families returning for extended visits and Muslim families going on pilgrimage to Mecca.

Gastro-intestinal infections

The risk of acquiring a gastro-intestinal infection abroad is especially high (Fig. 1). Indeed for some package tours to tropical countries it seems the norm to experience a minor gastro-intestinal upset en route. Children may be less at risk as they tend to be more conservative in their dietary habits than their parents. Surveillance of gastro-intestinal infections acquired abroad is scant. Many such infections do not enter the statistics as imported infections, because they involve the same range of pathogens as occurs in the UK and the notification system does not readily reveal the suspected country of acquisition. Laboratory reporting of specific infections to the Communicable Disease Surveillance Centre (CDSC) does reveal some specific importations. Reported bacterial infections acquired abroad include Salmonella typhi and shigellosis (both Shigella dysenteriae and Sh. boydii) with the Indian subcontinent accounting for the majority of cases. A related phenomenon is gastro-intestinal infections resulting from importation of contaminated food products. Two recent examples of this have involved Salmonella spp. being accidentally introduced into industrially produced foods. One occurred as a result of contamination of an imported infant snack with S. agona [110], the other through contamination of a baby milk produced abroad with S. anatum [111].

Table 5. Imported infections in children in the UK: Malaria, 1992

<table>
<thead>
<tr>
<th>Ethnic group/nationality</th>
<th>Age group</th>
<th>White</th>
<th>UK South Asian</th>
<th>S. Asian national</th>
<th>UK black African</th>
<th>African national</th>
<th>Other/ not stated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>2-4 years</td>
<td>2</td>
<td>19</td>
<td>8</td>
<td>11</td>
<td>17</td>
<td>1</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>5-10 years</td>
<td>6</td>
<td>23</td>
<td>9</td>
<td>8</td>
<td>20</td>
<td>3</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>11-14 years</td>
<td>11</td>
<td>13</td>
<td>6</td>
<td>8</td>
<td>33</td>
<td>2</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Child total</td>
<td>19</td>
<td>58</td>
<td>24</td>
<td>33</td>
<td>72</td>
<td>7</td>
<td>213</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>371</td>
<td>189</td>
<td>247</td>
<td>173</td>
<td>485</td>
<td>161</td>
<td>1626</td>
<td></td>
</tr>
</tbody>
</table>

Source: PHLS Malaria Reference Laboratory, 1997 (London School of Hygiene and Tropical Medicine).

Table 6. Imported infections in children in the UK: Malaria, 1995

<table>
<thead>
<tr>
<th>Ethnic group/nationality</th>
<th>Age group</th>
<th>White</th>
<th>UK South Asian</th>
<th>S. Asian national</th>
<th>UK black African</th>
<th>African national</th>
<th>Other/ not stated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2-4 years</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td>19</td>
<td>6</td>
<td>8</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>5-10 years</td>
<td>5</td>
<td>25</td>
<td>14</td>
<td>30</td>
<td>32</td>
<td>4</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>11-14 years</td>
<td>8</td>
<td>34</td>
<td>10</td>
<td>22</td>
<td>20</td>
<td>6</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Child total</td>
<td>15</td>
<td>68</td>
<td>31</td>
<td>77</td>
<td>58</td>
<td>19</td>
<td>268</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>286</td>
<td>293</td>
<td>355</td>
<td>299</td>
<td>605</td>
<td>217</td>
<td>2055</td>
<td></td>
</tr>
</tbody>
</table>

Source: PHLS Malaria Reference Laboratory, 1997 (London School of Hygiene and Tropical Medicine).
Both outbreaks were detected only because they involved particularly unusual Salmonella species. Outbreaks with commoner Salmonella spp. would probably not have been detected. With increasing international trade in raw and processed foods, such imported infections will become more common in the future.

Vaccine preventable diseases: measles

As immunisation has improved the control of the vaccine preventable diseases in the UK the relative importance of imported cases has increased. Imported infections are now the only source of cases of ‘wild’ polio (as distinct from vaccine-acquired polio) and importations are now a major source of transmission of measles. Since the measles-rubella (MR) campaign of late 1994 when 90% of school-age children were immunised, and the introduction of a routine second MMR vaccination at school entry, the number of cases of confirmed measles occurring in England and Wales has declined dramatically (Fig. 3) and indigenous transmission of measles from cases within the UK has almost entirely ceased [112]. Levels of immunity in the UK are now such that indigenous transmission has been interrupted. However, susceptible individuals still exist, especially among older adolescents and young adults too old to have been caught by the 1994 campaign and born in the years when measles coverage was poor. Imported infections are a cause of the few transmissions taking place, especially when they meet resident individuals who have remained unimmunised.

One source of such transmissions has been foreign students arriving with incubating measles which they then pass on to susceptible local counterparts [112].

Emerging and re-emerging infections

The importance of emerging and re-emerging infections has been recognised only recently (Fig. 4) [113]. In the quarter century since 1973, at least 26 new aetiological microbial agents of significance to children and adolescents have been recognised (Table 7). Some of these – e.g., hepatitis C and human herpes viruses 6 and 7 – represent newly discovered causes of well-established clinical infections. Others, such as Escherichia coli O157, HIV and Vibrio cholerae type O139 are considered to be novel to the human species. In addition, other infections such as diphtheria, syphilis and tuberculosis have made spectacular ‘come-backs’. Only a few of the new or re-emerging infections are readily encountered in the UK (E. coli O157 is one exception) and if they are appearing in this country many of these infections are encountered through travel and importations. Indeed it is considered that increased travel and commerce are potent primary causes of the emergence and re-emergence of infection [114].

Human immunodeficiency virus

The archetypal emerging infection is HIV. Never seen or detected before the 1970s, HIV infection has now
spread to every country in the world with an estimated 22–23 million persons living with HIV at the end of 1996 [115]. In the 1990s most paediatric HIV infections in children in the UK resulted from mother to child transmission. The predominant risk factor for mothers is coming from or having lived in countries where HIV is prevalent, and sexual intercourse between men and women is the predominant mode of acquisition. So far, the most important group of countries have been those in subSaharan Africa and women from those countries predominate in the statistics [116]. Information on HIV and AIDS in children in the UK is gathered by a collaboration between the Institute of Child Health of London, the PHLS and the Scottish Centre for Infection and Environmental Health (SCIEH). Data gathered include information on where
children were born. These indicate that while quite a few children were born and therefore almost certainly infected abroad they contribute only a minority of the infections occurring each year and that the proportion is not increasing (Fig. 5).

Dengue and other haemorrhagic fevers

If HIV is the classical emerging infection then dengue infection is the classical re-emerging infection. Spread by a cycle involving man and the urban-dwelling mosquito, *Aedes aegyptii*, the infection was largely controlled in many parts of the world in the 1960s by urban mosquito control programmes. Increasing urbanisation and the end of some control programmes, especially in the Americas, has led to a substantial resurgence of dengue in many parts of the world (Fig. 6–8) [117]. Dengue is now a significant problem in many parts of the world, including much of Central and South America, the Caribbean, sub-Saharan Africa, the Indian subcontinent and South-east Asia (Fig. 8). As these regions include many areas to which persons from the UK frequently travel it is not surprising that the numbers of reports of dengue imported into the UK are increasing (Table 8).

### Table 7. Diseases relevant to child and adolescent health: aetiological agents identified since 1973

<table>
<thead>
<tr>
<th>Year of Report</th>
<th>Agent</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>Rotavirus</td>
<td>Major cause of infantile diarrhoea world-wide</td>
</tr>
<tr>
<td>1975</td>
<td>Parvovirus B19</td>
<td>Fifth disease; aplastic crisis in haemolytic anaemia</td>
</tr>
<tr>
<td>1976</td>
<td>Cryptosporidium parvum</td>
<td>Acute enterocolitis</td>
</tr>
<tr>
<td>1977</td>
<td>Ebola virus</td>
<td>Ebola haemorrhagic fever</td>
</tr>
<tr>
<td>1977</td>
<td>Legionella pneumophila</td>
<td>Legionnaires' disease</td>
</tr>
<tr>
<td>1977</td>
<td>Hantaan virus</td>
<td>Haemorrhagic fever with renal syndrome (HFRS)</td>
</tr>
<tr>
<td>1977</td>
<td>Campylobacter sp.</td>
<td>Enteric pathogens distributed globally</td>
</tr>
<tr>
<td>1980</td>
<td>Human T-cell lymphotropic virus-1 (HTLV1)</td>
<td>T-cell lymphoma-leukaemia</td>
</tr>
<tr>
<td>1981</td>
<td>Staphylococcus aureus</td>
<td>Toxic shock syndrome associated with tampon use</td>
</tr>
<tr>
<td>1982</td>
<td>Escherichia coli O157:H7</td>
<td>Haemorrhagic colitis; haemolytic uraemic syndrome</td>
</tr>
<tr>
<td>1982</td>
<td>HTLV II</td>
<td>Hairy cell leukaemia</td>
</tr>
<tr>
<td>1982</td>
<td>Borrelia burgdorferi</td>
<td>Lyme disease</td>
</tr>
<tr>
<td>1983</td>
<td>Human immunodeficiency virus (HIV)</td>
<td>HIV disease including AIDS</td>
</tr>
<tr>
<td>1983</td>
<td>Helicobacter pylori</td>
<td>Peptic ulcers</td>
</tr>
<tr>
<td>1988</td>
<td>Human herpes virus-6 (HHV-6)</td>
<td>Exanthem subitum and encephalitis</td>
</tr>
<tr>
<td>1989</td>
<td>Ehrlichia chaffeensis</td>
<td>Human monocytic ehrlichiosis</td>
</tr>
<tr>
<td>1989</td>
<td>Hepatitis C</td>
<td>Parenterally transmitted non-A, non-B hepatitis</td>
</tr>
<tr>
<td>1990</td>
<td>Cyclospora cayetanensis</td>
<td>Diarrhoeal disease</td>
</tr>
<tr>
<td>1990</td>
<td>Human herpes virus-7 (HHV-7)</td>
<td>Exanthem subitum and encephalitis</td>
</tr>
<tr>
<td>1991</td>
<td>Guanarito virus</td>
<td>Venezuelan haemorrhagic fever</td>
</tr>
<tr>
<td>1992</td>
<td>Vibrio cholerae O139</td>
<td>New strain associated with epidemic cholera</td>
</tr>
<tr>
<td>1992</td>
<td>Bartonella henselae</td>
<td>Cut-scratch disease; bacillary angiomatosis</td>
</tr>
<tr>
<td>1992</td>
<td>Tropheryma whippelli</td>
<td>Tropical sprue, Whipple's disease</td>
</tr>
<tr>
<td>1993</td>
<td>Hantavirus isolates (e.g., Sin Nombre)</td>
<td>Hantavirus pulmonary syndrome</td>
</tr>
<tr>
<td>1994</td>
<td>Sábio virus</td>
<td>Brazilian haemorrhagic fever</td>
</tr>
<tr>
<td>1995</td>
<td>Human herpes virus-8 (HHV-8)</td>
<td>Kaposi's sarcoma</td>
</tr>
</tbody>
</table>

**Fig. 5.** New HIV-1 infections reported in England, Wales and N. Ireland in children born to HIV-1-infected mothers by year and place of birth (data to end 1995); UK; abroad.
**Diphtheria**

One of the most spectacular re-emergences of an infection has been diphtheria in Russia and other parts of the former Soviet Union and Eastern Block. Rates rose many-fold in the late 1980s and early 1990s for various reasons, including breakdown in vaccine production, distribution and delivery, and a loss of confidence in the safety and effectiveness of the vaccine [118]. Imported cases were seen in persons returning to or travelling from the epidemic areas. Although no imported cases were reported in the UK the threat has resulted in a change in British childhood immunisation policy in that now the school-leaving immunisation is with diphtheria and tetanus (dT) rather than tetanus alone.
Fig. 8. Countries with recent dengue and dengue haemorrhagic fever activity in 1995 [117].

Table 8. Imported infections: Dengue virus – all ages

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975-1981</td>
<td>0</td>
</tr>
<tr>
<td>1982</td>
<td>6</td>
</tr>
<tr>
<td>1983</td>
<td>11</td>
</tr>
<tr>
<td>1984</td>
<td>11</td>
</tr>
<tr>
<td>1985</td>
<td>1</td>
</tr>
<tr>
<td>1986</td>
<td>6</td>
</tr>
<tr>
<td>1987</td>
<td>1</td>
</tr>
<tr>
<td>1988</td>
<td>6</td>
</tr>
<tr>
<td>1989</td>
<td>2</td>
</tr>
<tr>
<td>1990</td>
<td>34</td>
</tr>
<tr>
<td>1991</td>
<td>12</td>
</tr>
<tr>
<td>1992</td>
<td>30</td>
</tr>
<tr>
<td>1993</td>
<td>17</td>
</tr>
<tr>
<td>1994</td>
<td>22</td>
</tr>
<tr>
<td>1995</td>
<td>42</td>
</tr>
</tbody>
</table>

Source: PHLS CDSC.

**Tuberculosis**

Tuberculosis has always been associated with migrants and imported infections [119]. Tuberculosis in children is no exception to this rule. Detailed surveys of tuberculosis are carried out in England and Wales every 5 years. Surveys in 1978/1979, 1983 and 1988 indicated that when taking into account ethnic minority, children represent <5% of the cases of tuberculosis. Rates of infection among children born in India, Pakistan and Bangladesh were an order of magnitude higher than in the indigenous population (Table 9) [120]. More recent data suggest that children from Africa are also at higher risk (J. Watson, unpublished data). While some of these infections were acquired in the UK from infectious adults, some will also have been imported. A major failing of the port health service and communicable disease control in the UK is the inability to screen and follow-up effectively migrants and travellers from countries where tuberculosis is common. Given current trends in the global epidemic of tuberculosis, the problem of imported tuberculosis can only be expected to increase [121]. Fortunately, the public health implications of tuberculosis in children are considerably less than when the disease occurs in adults, and paediatric tuberculosis in the pre-adolescent child is rarely infectious to other children [1].

**Expecting the unexpected**

Imported infections can test even the most astute and experienced clinician. The last case of imported rabies in a child in the UK was several years ago. However, the threat of rabies remains for those travelling abroad. The commonest circumstance presented to the PHLS and Consultants for Communicable Disease Control (CCDCs) for advice involves children bitten by dogs in Asia, Africa or the Middle East. Seemingly the risk is higher in children who may be unaware that they should not play with dogs abroad or who cannot readily defend themselves from rabid animals. Cases of possible exposure coming to the UK often present in this way, but they may also present without such a
convenient history. In 1996 a 19-year-old African man attended a London casualty department in an aggressive and confused state. No history was available and because of malaria parasites seen in his blood film a diagnosis of cerebral malaria was made and he was transferred to an isolation hospital accustomed to dealing with tropical infections. At the second hospital his condition rapidly deteriorated and following two cardiorespiratory arrests he died the same day. An astute clinician made the presumptive diagnosis of rabies based on the patient having frequent spasms and spitting saliva at staff. Confirmation (or otherwise) of a rabies diagnosis takes time as it requires testing necropsy specimens at a specialist centre. In this case it was considered essential not to wait but to provide post-exposure prophylaxis (vaccine and immunoglobulin) to all the close contacts of the patient on the basis of the clinician's presumptive diagnosis, which was later confirmed [122]. An impressive demonstration of clinical diagnosis by an experienced doctor, but a sad case of an imported infection that could potentially have been prevented by early application of vaccine and immunoglobulin.

Prevention and control of imported infections

The main emphasis of strategies attempting to reduce imported infections in children is usually based on protecting the individual child travelling abroad – by immunisation, chemoprophylaxis or physical protection against exposure. A number of guides to such individual-based strategies now exist, of which the most comprehensive for the UK is Health Information for Overseas Travel used in combination with Immunisation Against Infectious Disease; both are available from HMSO [102, 123]. In addition, specific paediatrics advice is contained in the Royal College of Paediatrics and Child Health Manual [1] and in a recent review by Barnett and Chen [123]. Many imported infections are acquired while the child is abroad on holiday, often on package tours that extend to ever more exotic locations. Screening of returning travellers and immigrants has frequently been suggested, but is impractical given the sheer volume of travel (Table 4). A new strategy has been to establish legislation that places more responsibility on the tour operators for the risk at which tourists are placed [124]. The fact that this is European legislation and that surveillance for some infections is extending across Europe [125] is an important feature. This reduces the likelihood of the repetition of previous instances whereby when a particular hotel or resort was associated with imported infections in persons returning to one European country, and consequently was effectively ‘black-listed’ by the country, the major outcome was that the tourists were replaced with visitors from another European country.

Conclusions

Imported infections in children are increasing and are likely to continue so to do. Some groups are particularly at risk, notably ethnic minority groups living in industrialised countries and unprepared 'package tourists' travelling to exotic locations. Emerging and re-emerging infections will change and enhance the menu of infectious disease seen among children returning to and entering the UK. This means that general practitioners, paediatricians and public health doctors will all have to be aware of the need to protect children who travel and to consider an increasing range of possible diagnoses among ill children who have recently returned to or arrived in the UK.


<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>176</td>
<td>217</td>
<td>129</td>
</tr>
<tr>
<td>Indian</td>
<td>74</td>
<td>79</td>
<td>64</td>
</tr>
<tr>
<td>Pakistani/Bangladeshi</td>
<td>61</td>
<td>104</td>
<td>70</td>
</tr>
<tr>
<td>West Indian</td>
<td>18</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Other</td>
<td>24</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>353</td>
<td>452</td>
<td>294</td>
</tr>
<tr>
<td>Born abroad</td>
<td>145 (41%)</td>
<td>118 (26%)</td>
<td>297 (10%)</td>
</tr>
</tbody>
</table>

Source: MRC Epidemiology Group [120].

*Six-month survey period.

1 All South Asian ethnic group.

**EPIDEMIOLOGY AND SURVEILLANCE OF COMMUNITY-ACQUIRED PAEDIATRIC INFECTIONS**

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Community-acquired paediatric infections cover a range of severity from mild upper respiratory tract disease to overwhelming meningococcal sepsis. While the prevalence of many of the childhood infectious diseases that were of major importance in the recent past such as diphtheria, poliomyelitis and scarlet fever have decreased as a result of successful immunisation...
programmes, rising standards of living and improvements in public health, community-acquired infections continue to be responsible for considerable morbidity, and some mortality, in the UK [126].

National epidemiological data on paediatric infections in England and Wales are available from four principal sources: reporting of notifiable diseases to the Office of Population Censuses and Surveys (OPCS), laboratory reporting to the PHLS Communicable Disease Surveillance Centre (CDSC), the Royal College of Practitioners sentinel practice reporting scheme and the reporting of selected infections to the British Paediatric Surveillance Unit. These data provide valuable information including overall disease prevalence, yearly trends in disease incidence, and seasonal and geographical patterns. This information is invaluable in planning national priorities for infectious disease control, in assessing the impact of disease interventions (e.g., Hib and MMR immunisation) and in monitoring the emergence of ‘new’ infections such as Cryptosporidium parvum and E. coli O157.

In addition to such national data, there is a role for more detailed, locally collected and analysed disease surveillance information. These data can provide valuable information to general practitioners and hospital clinicians on local patterns of infection, enable early indication of the local appearance of particular pathogens, e.g., methicillin-resistant Staphylococcus aureus (MRSA) and penicillin-resistant pneumococci, and can enhance the collaboration between hospitals and the community in infection control.

In 1991 the Department of Microbiology and Infection Control at the Royal Liverpool Children’s Hospital set up a series of studies for monitoring community-acquired infections at the local level. The objectives of those studies have been: (i) to determine the overall pattern of community-acquired infections in children admitted to the hospital; (ii) to determine the role of the laboratory in investigating community-acquired infections; (iii) to determine the yearly and seasonal patterns of infections caused by selected pathogens; and (iv) to set up a computerised surveillance system to provide a disease database for the hospital, and improved reporting to and liaison with colleagues at the district and national level.

Overall patterns of community-acquired infections

Data were collected for the period 1 Jan. 1991–31 Dec. 1992 on all children admitted with a clinical diagnosis of infection to one of the three isolation wards in the hospital. A total of 1599 cases was included; Fig. 9 shows the proportion of cases in each of the diagnostic categories included. Gastro-enteritis and bronchiolitis were together responsible for >50% of the admissions. During this study, it became apparent that only a limited number of the clinically diagnosed cases were confirmed in the laboratory and an audit of the laboratory investigation of the cases was performed.

Audit of laboratory investigation of community-acquired infections

A laboratory audit was performed for the 810 cases admitted in 1991. Overall, a causative agent was isolated from only 31% of cases. Further investigation showed that in 33%, no appropriate specimens were taken. Table 10 shows, for each of the diagnostic categories, the proportion of cases in which appropriate
Table 10. Laboratory investigation of community infections

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>n</th>
<th>Number of appropriate specimens taken (%)</th>
<th>Number of causative agents isolated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis</td>
<td>242</td>
<td>160 (66)</td>
<td>114 (47)</td>
</tr>
<tr>
<td>Other respiratory infections</td>
<td>107</td>
<td>62 (58)</td>
<td>26 (24)</td>
</tr>
<tr>
<td>Gastro-enteritis</td>
<td>189</td>
<td>126 (66)</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Fever/rash</td>
<td>114</td>
<td>78 (68)</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>66</td>
<td>56 (85)</td>
<td>20 (30)</td>
</tr>
<tr>
<td>Other</td>
<td>92</td>
<td>68 (74)</td>
<td>25 (27)</td>
</tr>
<tr>
<td>Total</td>
<td>810</td>
<td>550 (66)</td>
<td>253 (31)</td>
</tr>
</tbody>
</table>

specimens were taken and the proportion in which a causative agent was isolated. Several reasons must be considered for the cases in which appropriate specimens were taken, but no pathogens were isolated. Some cases, particularly among the ‘gastro-enteritis’ groups, may not have been caused by infection. Among the non-specific group of fever/rash, many of those are likely to have been caused by entero- or other viruses that were not included in routine diagnostic tests. Because of the difficulty of interpreting epidemiological data based on non-specific clinical syndromes, the surveillance programme from 1993 included only laboratory-confirmed infections.

**Yearly and seasonal patterns of selected infections**

**Bronchiolitis**

Seasonal epidemics of bronchiolitis continue to cause both significant morbidity in the paediatric population, and a ‘bed crisis’ each winter within the hospital. Fig. 10 shows the pattern of respiratory syncytial virus (RSV)-positive bronchiolitis for the period 1993–1996.

The remarkable similarity of the curves in each winter demonstrates how such surveillance data may assist local planning of demands on hospital resources and could help to prevent the annual crisis over beds and available nursing staff.

**Bacterial meningitis**

Data collected on cases of meningitis caused by *N. meningitidis* and *H. influenzae* and cases of meningococcal septicaemia for the years 1991–1996 are shown in Fig. 11. This shows the steep decline in cases of meningitis caused by *H. influenzae* following the introduction of Hib immunisation. Diagnosis of cases of meningococcal disease continues to present difficulties, as in each year, between 10 and 20% of cases that are unequivocal clinically, are not confirmed bacteriologically. Thus, in the yearly figures, variations in the notified cases may in part be due to different criteria for the inclusion of clinical cases. The PHLS has addressed these difficulties by revising definitions of confirmed, probable and possible cases of meningococcal disease [127] and by encouraging the use of PCR and serological diagnostic tests [128].

![Fig. 10. Seasonal pattern of RSV-positive cases of bronchiolitis.](image-url)
Enteric pathogens

There are both seasonal and yearly variations in different enteric pathogens. Fig. 12 shows the frequency of laboratory-confirmed cases of enteric pathogens in 1995 and their seasonal distribution. Rotavirus was the major pathogen in both years and is concentrated in the early months of each year.

Annual variations in bacterial enteric pathogens are shown in Fig. 13. While infections caused by Salmonella and Campylobacter spp. fluctuate from year to year, the pattern for infections with Shigella spp. shows a remarkable variation from the peak of 123 cases in 1993 to no cases in 1996. These figures reflect the total notifications for shigella infections in the region, with several significant outbreaks in 1992–1993.

MRSA

Although generally regarded as a ‘hospital pathogen’, MRSA now has a reservoir within the community. Before 1995, we had only a few cases each year, but Fig. 14 shows the dramatic increase in 1995 and 1996. Apart from four possible cases of hospital-acquired infection, all these cases were admitted directly from the community.

The computerised surveillance and reporting system

The objectives of the computerised surveillance system were to provide an in-house database for the hospital, and improved reporting of notifiable and other community-acquired infections to public health colleagues.
Fig. 13. Annual numbers of cases of Shigella ( ), Salmonella ( ) and Campylobacter ( ) infection.

Fig. 14. Number of MRSA cases, 1991–1996.

locally and nationally. Fig. 15 shows the components of the surveillance system. EPI-INFO 5 [129] was used to enter, store and analyse data. We have consistently found EPI-INFO adaptable to our particular needs for data entry, and sufficiently powerful to analyse and group data according to onset dates, post codes, organism types, etc.

The in-house database both allows regular analysis of data, providing quarterly and annual reports to clinicians, and enables a rapid response to requests for the most recent cases of meningitis, MRSA, E. coli O157, etc.

Public health liaison is achieved via the EPINET electronic link. By designing the EPI-INFO questionnaire to a compatible format for reporting to CDSC, weekly disease reports do not require hand entry of report forms (an impossible task at the height of the bronchiolitis season), but can be automatically transmitted from the EPI-INFO data by selecting the appropriate week and required organisms. The questionnaire was also designed so that all cases from a particular health district could be transmitted weekly to the appropriate CCDC, and data on all cases to the regional epidemiologist. For non-notifiable diseases, this was the only standardised system by which CCDCs
and the regional epidemiologist would be provided with regular, local data.

**Discussion**

Community-acquired infections continue to be responsible for considerable morbidity and some mortality among children in the UK. While the majority of less serious infections are managed in the community, children with more severe infections and those whose home circumstances make management in the community difficult, will be admitted to hospital. Collection, analysis and dissemination of data on these infections are valuable within the hospital and improve collaboration with public health and other colleagues in the community.

The development of such local surveillance and reporting systems in England and Wales has progressed in a somewhat ad hoc fashion. National reporting schemes, based on laboratory reports to the CDSC, provide a database which is valuable, but is not analysed for local use. Also, reporting is voluntary; not all laboratories report regularly, and among those that do, reporting is not always comprehensive. The reporting of notifiable diseases to the CCDC at each District Health Authority provides the data for the annual District Health Reports in many districts. CCDCs use these data to provide valuable quarterly reports of the occurrence and distribution of notifiable diseases in the district. However, as demonstrated in our data, notifiable diseases account for only 4–8% of the community-acquired infections responsible for hospital admissions of children. In particular, diseases such as bronchiolitis and rotavirus diarrhoea would be excluded from notifiable disease data. There is also evidence that notifiable diseases are considerably under-reported [129].

The PHLS, particularly the CDSC in England and Wales, has encouraged the development of surveillance systems, and a modification of the ‘EPI-INFO-EPINET’ strategy, based on a system termed COSURV, is now being implemented in a number of areas [130]. With the increasing national problems of community-acquired infections (E. coli O157, MRSA, S. typhimurium and S. enteritidis, N. meningitidis clusters, etc), a systematic, integrated, local, regional and national surveillance system is essential, and the need has tentatively been recognised by the NHS Executive. However, the abolition of regional health authorities, the reduced role of district health authorities and the concerns of hospital trusts with their individual budgets within a market economy do not create an environment in which the collection, analysis and dissemination of data are seen financially as high priority. Public health in England and Wales, which is based on the collection, analysis and dissemination of epidemiological data, has continually suffered from being neglected until a crisis occurs, recent examples being the Stafford Legionella outbreak leading to the Acheson Report [131], and the rise of MRSA and hospital infections leading to the Cooke Report [132]. If local surveillance systems are to be established and contribute to the health of the community, it is essential that adequate funding is made available.

The surveillance of childhood infections has an international as well as a national dimension. With the rapid advances in electronic information exchange and the increasing potential for the spread by travellers of infectious diseases (ranging from MRSA to Ebola virus) the goal of global systems linking
local, regional and national data across countries should be achievable. Such systems are being developed in Europe through the Eurosurveillance network [133], and globally by the Division of Emerging and other Communicable Disease Surveillance of the World Health Organization.

While this century has witnessed the most dramatic decline in childhood deaths caused by infectious diseases in history, new pathogens, resistance to antimicrobial agents and the continuing prevalence of infections for which no vaccines are available, make it essential that effective disease surveillance systems, linking hospitals, the community, and ultimately a global network, are maintained and developed.

**HOW TO IMPROVE OUTCOMES IN MENINGOCOCCAL DISEASE**

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**Introduction**

Meningococcal disease (MCD) engages resources in numerous areas of medicine. The incidence of MCD continues to rise. In 1996, 1112 cases of meningococcal septicemia were reported, compared with 699 cases in 1995 and 432 in 1994. Figures for meningococcal meningitis were 1160, 1101 and 948 respectively, confirming that the continuing rise is absolute and not just an artefact of classification variance [134]. Mortality runs at c. 10% overall, so that around 230 of the 2272 patients with meningococcal disease in 1996 will have died; most of these are children. Approximately 50% of cases are <2 years old and mortality is highest in this group.

If the philosophy of evidence-based medicine is applied, what evidence exists about whether interventions in MCD improve outcomes? Discussion in this article focuses on several different areas: early identification by the public; prompt diagnosis by doctors and first-line treatment in primary care; first-line treatment in hospital; and intensive care. Finally, what research initiatives will improve our knowledge?

**Early identification by public**

Education of the public is primarily the responsibility of the Health Service, which has prepared leaflets for general distribution. These leaflets do not emphasise the rash, a specific feature which is first recognised by most parents [135]. However, those attempts at dissemination of information have largely been overtaken by the efforts of charitable fund-raising bodies, such as the National Meningitis Trust, the Meningitis Research Foundation and the Karim Centre who have now distributed a variety of educational flyers. The charitable bodies use expert medical advisers and are generally keen to collaborate with the Health Service; for example, information issued by the South Cheshire Health Authority was developed in collaboration with Meningitis Merseyside and used elsewhere in the region. Concerted efforts by all interested parties might be more effective, but are unlikely to occur.

There is evidence that the media may be used both to inform [136] and misinform [137] the public about MCD. Few doctors possess media skills and this aspect of a doctor's role should be undertaken with caution. In tandem with information about the features of MCD, the media could also be used to educate the public about chemoprophylaxis in meningococcal disease. Failure of chemoprophylaxis is multi-factorial [138], but correct application and management of prophylaxis could reduce the total caseload in MCD by up to 4.5%. New evidence and new interpretations of the existing evidence continue to accrue. New guidelines on the management of clusters have recently been issued by the PHLS [139].

**Early diagnosis and first-line treatment in primary care**

In this context, doctors, especially general practitioners (GPs) and junior doctors, may need to be 'wise beyond their experience' [140], as many will only ever meet one case in a working lifetime. It is well-recognised that the early features of MCD are non-specific. Many more children present with a constellation of features that could be MCD than will prove to have the disease in the end. A diligent search for the characteristic petechial or purpuric rash in a feverish, ill child is standard advice, but is often a counsel of perfection given the conditions in which many GPs work. Junior doctors in accident and emergency or paediatric departments usually work under better conditions, but are less experienced than GPs and should be taught specifically about MCD.

GPs suspecting meningococcal septicemia or meningitis should give penicillin – advice reiterated by the Chief Medical Officer in 1997 [141]. Pooling of the best evidence available [142–144] suggests that this improves the chance of survival in meningococcal septicemia (odds ratio 2.61), although confidence intervals are wide (1.04–7.18) [145]. Other evidence supports this conclusion [146, 147]. In 1992, Liverpool GPs gave penicillin to 82% of all children referred with a diagnosis of presumed meningococcal septicaemia [148]; however, only 17% of all children with meningococcal disease received antibiotics before arrival in hospital.
Early treatment in hospital

It is vital that experienced staff are involved as soon as possible in early treatment of MCD in hospital [149]. The early management of evolving shock requires the presence of an experienced doctor. Junior medical staff and nurses must be able to recognise the underlying condition and request the assistance of these more experienced doctors. Generous use of colloid and early application of inotropes (dobutamine, dopamine and adrenaline) are essential. The capillary refill time is a crude clinical measure of success in treating shock. The core–peripheral temperature difference is the best method of assessing success of resuscitation until central venous monitoring can be obtained. Pulse rate is less helpful, and blood pressure even less informative.

At the same time as volume expansion is proceeding, the child’s condition should be evaluated. Around one-quarter of all children with MCD require admission to the paediatric intensive care unit. The Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) has become widely accepted as a tool for identifying the population at high risk [150]. It is most useful in the context of a district general hospital, where it can be used for identifying the patients who need transfer to a tertiary unit for intensive care. It is a score derived from clinical data and therefore obviates the need for time-consuming (and in MCD, unnecessarily time-wasting) laboratory tests. It has been compared with other scores and found to be the most effective score available in predicting outcome [151]. It is less useful in the intensive care population in tertiary units, although it has been used as an entry criterion in the most recent double-blind placebo-controlled trial of anti-endotoxin therapy [152] (vide infra). It is a dynamic score and should be repeated 1 h after it is first obtained as well as after any subsequent deterioration in condition. Children who achieve a score of ≥8 should be admitted or transferred to a paediatric intensive care unit (PICU).

Intensive care

Children admitted to the PICU are usually severely ill. Monitoring of vital signs, together with indwelling arterial pressure, central venous pressure and oxygen saturation monitoring are the usual minimum for the ill child with MCD. Children with a GMSPS > 7 should be ventilated electively. Further additions to inotropic support are often needed in children admitted to the PICU. Electrolyte and fluid imbalance, fits, renal impairment and multi-organ failure require special attention [153].

Research initiatives

On Merseyside there has been a strong commitment from paediatricians and the meningococcal research team to study numerous aspects of MCD. In particular there have been two double-blind placebo-controlled trials (DBPCT) of anti-endotoxin therapy in MCD. In the first, combination therapy of Pentaglobulin (a polyclonal immunoglobulin preparation) and polymyxin (an anti-endotoxin antibiotic) in patients with a GMSPS of > 7 was shown to confer no benefit after an open study had shown an apparent reduction in mortality to 30% from 71% in previous years [151]. This result emphasises the need for DBPCTs to test the value of new treatments in MCD. The subsequent international, multicentre study of human monoclonal antibody, HA-1A (Centoxin) in high-risk patients showed a 32% reduction in mortality in the treatment group to 24 (18.5%) of 130 from 37 (27%) of 137 in the placebo group [154]. This reduction failed to achieve statistical significance (p = 0.11).

Several candidate treatments merit study in phase 3 clinical trials. These range from corticosteroids in meningococcal septicemia (previously used, but unsupported by any evidence), through prostacyclin (widely adopted but never studied in a DBPCT in MCD) to novel therapies such as activated protein C and nitric oxide (NO) synthetase inhibitors. However, a multicentre, international DBPCT of recombinant bactericidal permeability increasing protein (rBPI21) is currently commencing at centres in the UK and the USA. rBPI is a protein which binds to bacteria and endotoxin, disrupting both and so taking out the initiating steps of the inflammatory cascade. Open study results suggest a substantial reduction in mortality from 19% (10 of 52) to 4% (1 of 23) in children with GMSPS > 7 (Xoma corporation, personal communication), but numbers are small and it would be optimistic to expect these results to be repeated in a DBPCT. The trial will run for c. 2 years to recruit the patient numbers predicted to be necessary by the power study.

Future topics for research

Although much research in MCD is directed at elucidation of changes in the inflammatory cascade together with the inter-individual variation that may explain differences in susceptibility and host response to meningococcal infection [155], there are several basic questions about meningococcal disease that remain unanswered. Many are issues which are commonly raised during medico-legal discussions, and serve to point out our ignorance about fundamental issues in MCD, which sometimes results in major costs to the NHS and its staff. Questions such as: how quickly does penicillin need to be given to reduce mortality in MCD? Are there patients whom penicillin does not help? How can these patients be identified? How can they be treated? Is there a critical time window for treatment of shock? What is an acceptable timescale? At what point should children be transferred to PICU facilities? What standard of care is acceptable? When does deviation from this standard fall
below the accepted standard of care? If procedures are
difficult to perform is this allowable? Answers to these
apparently simple questions are difficult to ascertain.

Summary

If outcomes in meningococcal disease are to be
improved, the focus must be on efficacy of interven-
tion. Currently there is evidence that a number of
activities are effective: education of the public to
enable them to recognise meningococcal disease –
media and support groups should be recruited and
enabled to play their part; education of doctors so that
the features of the disease are recognised and GPs give
carpenilllin before transfer to hospital; fast-track treat-
ment in hospital, with an emphasis on adequate
treatment of shock; the identification of the sickest
patients with the GMSPS; and paediatric intensive care
with elective ventilation. Research studies of new anti-
inflammatory treatments are required before their
incorporation into the recommended therapeutic arma-
mentarium.

VIRUSES AND GASTRO-ENTERITIS

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Diarrhoeal disease is one of the major causes of
mortality world-wide. In the 1990 world mortality
league table, of the 50.5 million deaths occurring in
1990 c. 3 million were due to diarrhoeal disease [156].
This placed diarrhoeal disease in fourth position,
exceeded only by lower respiratory tract infection,
cardiovascular disease and ischaemic heart disease. The
majority of deaths, estimated at 2.4 million, are in
children under 5 years and occur predominantly in
developing countries [157]. It is estimated that each
child suffers an average 2.6 episodes of diarrhoea/year
which can be as high as 6–10 episodes/year in some
African countries [158]. In Blantyre, Malawi, diarr-
hoical disease accounted for 7300 annual attendances
to the under 5s' dehydration clinic, 1219 paediatric
admissions (12% of paediatric admissions) and 183
deaths, which represented 19% of all paediatric deaths
in hospital [159]. Viruses account for 30–60% of cases
of diarrhoeal disease in children in out-patient and in-
patient surveys [160, 161].

Rotavirus

Rotavirus is a medium-sized (70 nm) unenveloped
virus with a characteristic double-shelled capsid which
gives it the wheel shape seen on electron microscopy
(Fig. 16). It has a genome comprising 11 linear double-
stranded RNA segments. Each segment encodes one or
two structural or non-structural proteins [162, 163].
Virus proteins (VP) 1, 2 and 3 are translated from the
three largest genomic segments and, together with the
genome, form the virion core. They are involved in
genome replication. The major inner capsid protein is
VP6 which is encoded on genome segment 6. VP6 is
highly antigenic and epitopes on it determine virus
group (A–G) and subgroup (I, II, I + II, or neither).
However, antibodies against VP6 are non-neutralising.
The outer capsid is composed of VP4 and VP7 (from
genome segments 4 and 9, respectively). VP4 forms
knobs on the virus surface; it is a haemagglutinin and
has receptor binding activity. For full infectivity, VP4
must be cleaved by host cell proteases to produce VP5
and VP8. Antibodies to VP4 are neutralising and thus
provide protection against infection. Epitopes on VP4
define some 20 P(protease)-types, of which, nine (3, 4,
6, 8–11, 13, 14) are known to infect man. The P-types
have been delineated by genomic sequencing and sets
of PCR primers are available. VP7 is a glycoprotein
that covers VP4 except where the knobs protrude
through it; VP7 is also involved in receptor binding.
Epitopes on VP7 define 14 G(glycoprotein)-types.
These have been delineated both serologically and by
genomic sequencing. Antibodies to the G-types are
neutralising, but are not cross-protective. Although,
thus far, infection of man by nine of the 14 G-types has
been documented, types 1–4 are encountered most
frequently [164].

The remaining proteins are non-structural (NSP) and
are involved in viral replication. NSP1 is highly
variable, but also contains two conserved zinc finger
regions. Interestingly, the apparently non-pathogenic
Indian neonatal strain 116E has only one zinc finger
[165]. NSP2, together with VP1, VP2 and VP6, forms
a replicase complex [166]. NSP3 is probably involved
in RNA transport. NSP4 is a transmembrane glycoprotein which becomes inserted into the endoplasmic reticulum [167]; also, it has recently been shown to be the first viral toxin to be described [168]. The toxic moiety is a sequence of amino acids (114–135) within NSP4 and replacement of tyrosine at position 131 abolishes toxicity [168]. However, some pathogenic rotavirus strains with histidine replacing tyrosine 131 have been described [169]. Insertion of NSP4 into cell membranes activates a phospholipase C-type pathway leading to a rise in intracellular calcium concentrations; this results in acute watery diarrhoea [167]. Thus far the effect has been demonstrated in infant mice (but not older mice) and its role in human disease is still to be elucidated. Nevertheless, it is potentially a very important discovery which might lead to a new generation of vaccines. Finally, NSP5 is an RNA-binding protein.

Rotavirus infection is as common in developed as in developing countries, but the major burden of mortality, estimated at 800 000 deaths each year, is in the developing world [170]. Nevertheless, each year in the USA it is estimated that 54 000–55 000 children are hospitalised with rotavirus, but <40 die [171]. In England and Wales it has been estimated that rotavirus accounts for 17 810 paediatric admissions [172]. In temperate countries, although rotavirus infections occur throughout the year, there are distinct seasonal peaks. In the USA and Europe this occurs from December to March. Interestingly, similar peaks from December to March have also been described in the Philippines and Bangladesh when it is clearly not wintery [173–174]. In Africa and in the Mediterranean countries, the rotavirus seasonal distribution was as for Europe and in South Africa peaks were in March–May. Throughout the rest of subSaharan Africa rotavirus is present at all times of the year, but with peaks during the dry months [175]. During each peak season several rotaviruses of different P- and G-type co-circulate. In Africa, 80% of rotavirus infections requiring hospitalisation occur in children under 1 year and 12% in those under 3 months [175], which contrasts with industrialised countries where the peak occurs in the second year of life [172].

Infection is spread faecal-orally, although it is not possible to exclude the possibility of air-borne spread. The infective dose is low (c. 10² virus particles), and the incubation period is 2–3 days [160, 167]. Infection presents with nausea, anorexia, vomiting and even upper respiratory signs, although replication of rotavirus in the respiratory tract has not been demonstrated. These signs are followed rapidly by profuse acute watery diarrhoea which lasts an average of 6 days [176]. Infection begins in the duodenum and passes down in waves to the terminal ileum, where it ceases, as rotavirus does not infect the colonic enterocytes. The diarrhoea results from the effects of NSP4 (it is presumed), decreased activity of micro-villar enzymes such as lactase [177] and eventually flattening of the villi.

The mainstay of therapy is assessment of dehydration and oral or intravenous rehydration. However, adjunctive therapies such as administration of the probiotic Lactobacillus casei strain GG [178, 179] or oral immunoglobulin [180] have been shown to decrease the frequency and duration of diarrhoea and vomiting.

Prevention of rotavirus diarrhoea would of course yield much greater benefit, especially in developing countries [181]. However, even in the USA it is estimated that a vaccine that is only 50% effective would prevent 1 million cases, 58 000 hospital admissions and 82 deaths each year [182]. Although the relative importance of the different arms of the immune system is still not entirely clear, it is clear that natural infection provides some protection against subsequent challenge. Children who have suffered one, two or three previous episodes of infection have adjusted relative risks of experiencing symptomatic rotavirus infection of 0.23, 0.17 and 0.08, respectively, and of asymptomatic infection of 0.62, 0.42, and 0.34, respectively [183].

The approach used successfully for vaccination has been to produce rhesus rotavirus re-assortents containing 10 of the 11 rhesus rotavirus genes and replacing that encoding VP7 with the four genes encoding G1–G4 genotypes. Use of this live quadrikariant vaccine at a titre of 4 × 10⁵ plaque forming units has had protective efficacies against rotavirus infection of 48–66% and against severe disease of 70–80% in both developed and developing countries [184–187]. It is of course possible for infection with other rotavirus G-types to occur and whether its introduction (it has already been approved for use in the USA) will cause a change in the G-type prevalence or drive emergence of ‘new’ rotavirus strains is unclear.

**Astrovirus**

Astroviruses are members of the newly constituted family, Astroviridae. They have a single stranded positive sense genome and are unenveloped. They are 28–30 nm in diameter with a characteristic six-pointed star appearance on their surface (Fig. 17). The genome is c. 6.8 kb with three open reading frames (Orfs). Orf 1a encodes a viral protease, Orf 1b an RNA-dependent RNA polymerase and Orf 2 structural proteins which are cleaved by the viral protease post-translationally. There are seven astrovirus serotypes which are confirmed as genotypes [188]. Serotype 1 is found most frequently, followed by serotypes 2–4 and, least frequently, serotypes 5–7 [189, 190]. Patients may be infected by two or more serotypes throughout their lifetime. Not surprisingly, outbreaks of astrovirus diarrhoea caused by the less common serotypes can
Caliciviruses and small round structural viruses (SRSV)

The classical human caliciviruses are small (30–40 nm) unenveloped RNA viruses with cup-shaped depressions in their surface also described as having a 'Star of David' shape (Fig. 19). The genome is single-stranded positive sense RNA c. 8 kb long with three open encoding frames. Orf 1 encodes non-structural proteins with helicase, protease and RNA polymerase activity, Orf 2 encodes the viral capsid protein and Orf 3 a small protein of unknown function [195]. They produce diarrheal disease by blunting of villi and depression of brush border enzymes.

The SRSVs such as Norwalk agent, Southampton, Hawaii, Lonsdale, Sapporo, Snow Mountain and Mexico are classified within the family Caliciviridae. They are smaller (27–35 nm) than the classical caliciviruses and do not have their characteristic shape. The illness they produce is sometimes termed winter vomiting disease, but they also produce nausea, abdominal cramps, headache and diarrhoea [196]. They can produce outbreaks of disease in hospitals and food-poisoning [197, 198]. Infection is followed by antibody production, but this does not necessarily give protection; the converse might be true [199]. There are a large number of caliciviruses that infect animals and it is possible that some may be zoonotic [200].

Other viruses

A number of other viruses including coronaviruses, toroviruses [190], bredavirus, pestiviruses and picobirnaviruses have been implicated as infrequent cases of diarrhoea. The picobirnaviruses have a bisegmented RNA genome [201] which can be detected on polyacrylamide gel electrophoresis of faecal extracts. They are a minor cause of diarrheal disease [161, 202].
INFECTION IN THE IMMUNOCOMPROMISED CHILD
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Introduction

Protection against infection is dependent on a complex multi-faceted defence system which has to function against a wide range of infective agents. This immune system has evolved in parallel with infectious agents, so that as micro-organisms evolve new characteristics to exploit potential infectious niches, the immune system evolves new methods of combating the infections they cause. Thus, the immune system is characterised by a series of overlapping mechanisms, some of which have become rather redundant.

During the middle decades of the 20th century, mass vaccination and the development of antimicrobial agents appeared to tilt the balance in man's favour and there was great optimism that infectious diseases had been 'conquered'. However, in recent years the emergence of virulent organisms such as HIV, MRSA, penicillin-resistant pneumococci and multi-drug resistant *Mycobacterium tuberculosis* (MDRTB) illustrates how the struggle between man and microbe still continues. Given that a diversity of microbial action has engendered an equally diverse immune system, it is perhaps not surprising that immune responses that safely eliminate one pathogen may harm an individual when used against another pathogen. In childhood meningococcal disease, an immune response leading to high circulating levels of tumour necrosis factor (TNF) is associated with a high risk of death from the septicaemic form of the illness. It may be that individuals with a tendency to produce high levels of TNF may eliminate intracellular parasites such as mycobacteria more effectively, thus decreasing the risk of clinical infections such as tuberculosis, but at the same time increase risk of death from meningococcal septicaemia. Low TNF producers may be less at risk in meningococcal septicaemia, but more at risk of progressive tuberculosis. To keep pace with the evolution of micro-organisms, the immune system had to develop some unique features with respect to its own development and control. This is best exemplified by the recently discovered complex cascade of tyrosine kinases and their complementary but antagonistic tyrosine phosphatases which are both responsible for the intracellular signalling necessary for maturation and control of lymphocyte interaction. It should not be surprising that such complex mechanisms are vulnerable both to inherited genetic defects causing primary immune deficiencies or to damage from environmental or therapeutic agents causing secondary immune deficiency. The nature and extent of the resulting immune dysfunction determines susceptibility to particular pathogens. Thus, understanding infection in immunocompromised individuals is best approached by considering the function of the components of the normal immune system and the organisms they have evolved to combat, then studying the defects that occur (both congenital and acquired) noting the pattern of susceptibility to infection that would be expected from these defects and comparing them with the infections that are seen.

The normal immune response

Many, and perhaps most, infectious agents, are eliminated by non-specific or innate effector mechanisms, and invertebrates are highly successful at resisting infection by these mechanisms alone. Secretions such as lysozyme or gastric acid destroy organisms adhering to delicate membranes, whilst the skin acts as a highly effective barrier to prevent entry of bacteria and viruses. Serum proteins such as complement and C-reactive protein bind to, and aid the destruction of, micro-organisms that reach the circulation. Interferons enable cells to resist attack by viruses and phagocytic cells such as neutrophils and cells of the monocyte-macrophage lineage engulf micro-organisms into a phagosome which then fuses with a lysosome containing bactericidal factors such as free oxygen radicals. These mechanisms are all innate and non-specific; they provide a rapid first-line defence against infection, but on occasions these systems can be overwhelmed and more particularly there is no element of memory, so that on subsequent exposure to an organism the response is no greater than on first exposure. In contrast, the adaptive immune system, which uses lymphocytes as its main effector cells, is characterised by both specificity and memory – enabling individuals to mount an increasingly powerful and finely tuned response to micro-organisms. To set up a specific immune response, an antigen presenting cell (APC) such as a macrophage must first ingest and destroy a micro-organism and then process its surface proteins before combining them with the tissue type (MHC class II) molecule expressed on its surface, before setting out on a quest to find a lymphocyte which bears the complementary surface receptor. This is no small undertaking, as each virgin lymphocyte has a different antigen receptor such that there is a lymphocyte with a surface receptor complementary to every antigen that could be constructed. To achieve this the lymphoid system has generated immense diversity such that there are c. $10^{12}$ different lymphocyte receptors, each carried on a different lymphocyte. To help in this game of immunological 'hide and seek', the immune system is organised so that there is a series of lymphoid channels and lymph nodes and well-defined trafficking patterns for both APCs and lymphocytes, thus giving the maximal opportunity for an APC to meet the appropriate lymphocyte. Once they have met, the lymphocyte is stimulated to produce tens of thousands of daughter
cells, each bearing the identical antigen receptors. In the case of B lymphocytes these produce antibody, while T lymphocytes either kill infected cells directly (CD8+ or cytotoxic lymphocytes) or else orchestrate the immune response (CD4+ or helper T lymphocytes). CD4+ lymphocytes secrete cytokines such as interferon gamma (IFN-γ), and interleukins 2, 4 and 5 (IL-2, IL-4 and IL-5). Recent evidence suggests that there are subpopulations of CD4+ lymphocytes, and that the safe and effective elimination of certain micro-organisms depends on a response from the most appropriate subpopulation. Th1 CD4+ lymphocytes secrete IFN-γ and IL-2, enabling macrophages to kill intracellular organisms such as mycobacteria and leishmanias. However, if a response is made by Th2 CD4+ lymphocytes secreting IL-4 and IL-5, these organisms are not killed, but antibody – in particular IgE – production is stimulated, a response more suited to expelling intestinal parasites.

Immunocompromised children – causes and infections

Many conditions are associated with ineffective innate or specific immunity. Premature infants have thin skin which is frequently breached by indwelling venous catheters; their neutrophils are less active and phagocyte less efficiently; their B lymphocytes make poor quality antibody and T-lymphocyte function is decreased. There is a whole range of congenital immunodeficiencies, each with a specific defect in immune recognition or response that gives a window of opportunity to specific organisms. Infection with HIV destroys CD4+ lymphocytes and their inexorable decline in number is marked by an increasing array of opportunistic infections; a small decline in immunity is associated with infection with M. tuberculosis whilst only more marked immunodeficiency allows the development of P. carinii pneumonia or disseminated cytomegalovirus infection – illustrating the importance of different degrees of CD4+ lymphocyte activity in fighting different infections.

Cytotoxic drugs are used with increasing intensity to treat malignancy and to ablate bone marrow before bone marrow transplantation (BMT). Neutropenia is their most notable effect, but T- and B-lymphocyte function is also diminished and the integrity of the skin and mucous membranes disrupted, allowing infection with bacteria, fungi and viruses. Solid organ transplantation is accompanied by the on-going risk of graft rejection, necessitating the long-term use of agents that suppress T-lymphocyte function. This favours infection with members of the herpes virus family, agents which are never fully eliminated but are normally suppressed by ongoing T-lymphocyte-mediated immunity. Time and space do not permit a full exposition of all the causes of the immunocompromised state and their consequences, but some of the more interesting and important ones will be highlighted.

Non-specific immune defects

Congenital defects of the complement system are incredibly rare. In some populations, particularly from the Mediterranean area, defects of terminal components of complement are associated with recurrent meningococcal infection, illustrating the importance of these factors in defence against complex polysaccharide-coated bacteria. Infection due to absent or ineffective neutrophil function is much more common. When neutrophils are completely absent from birth there is a great risk of death from overwhelming bacterial sepsis in the first few months of life.

Cyclical neutropenia is characterised by a waxing and waning of neutrophil numbers usually, but not always, over a 21-day cycle, each nadir usually being preceded by ‘moodiness’ and mouth ulcers, and bacterial infection can be a serious risk if neutrophil counts drop below 0.5 × 109/L. In many individuals the symptoms are irritating but not dangerous, but when there is a concomitant infection with an agent such as varicella zoster virus (VZV) infection can be much more serious, as the associated skin lesions cause a breach in non-specific barrier immune defence and the VZV may well depress lymphocyte function. In this case severe infection with group A β-haemolytic streptococci or even organisms such as Clostridium perfringens may occur. Cytotoxic chemotherapy used for treating children with cancer, or as preparation for bone marrow transplantation, also renders children neutropenic and susceptible to bacterial infection. However, chemotherapy has far more wide-ranging effects than neutropenia alone and some of the infections seen in this situation are caused by defects in other aspects of immunity. Less commonly there is a predisposition to infection because of defective neutrophil adherence and migration or ineffectual ingestion and intracellular killing of bacteria. In leucocyte adhesion deficiency there is a congenital absence of adhesion molecules on the neutrophil surface, which does not prevent neutrophils marginating on the capillary endothelial surface, but prevents transendothelial migration into infected tissues. Thus, when neutrophils are attracted towards the infected area they ‘pile up’ in the adjacent capillaries causing thrombosis and necrosis, but are unable to pass into the infective tissue. Thus one sees a rapidly expanding infective lesion with infarction, but no pus. In chronic granulomatous disease neutrophils can reach areas of infection and also ingest bacteria, but a defect in the enzyme chain that creates oxygen free radicals prevents bacterial killing within the phagolysosomes. This results in infection with intracellular organisms, particularly those that have enzymes capable of destroying the small amounts of free oxygen radicals.
created by the bacteria themselves. These patients suffer particularly from staphylococcal abscesses, including abscesses in unusual sites such as the liver. They are also prone to life-threatening aspergillus infections, and so early diagnosis and aggressive treatment are most important. Prophylactic treatment with co-trimoxazole and an antifungal agent such as itraconazole is most beneficial, and there are some data suggesting that IFN-γ may help to eradicate or even prevent infection. Defects of antigen processing are exceedingly rare, but occasionally children are unable to express MHC class II molecules due to an inability to make the regulatory proteins necessary for MHC II gene transcription. This condition, described as bare lymphocyte syndrome by some, is universally fatal due to infection with a wide range of organisms, including viruses, fungi, P. carinii and many types of bacteria. The severity and range of infection seen in this condition illustrate the central role of antigen presentation in mounting an effective immune response against all pathogens.

Specific immune defects

Severe combined immune deficiency (SCID), although uncommon, acts as a paradigm for the infective problems seen in combined T- and B-cell dysfunction due to many different causes. Absent T-cell function predisposes to viral, fungal and intracellular bacterial infection. Respiratory viruses such as respiratory syncytial virus, the parainfluenza viruses and measles virus can cause devastating and rapidly fatal pneumonitis. Adenovirus easily becomes disseminated, causing gastrointestinal and hepatic disease, as well as fulminating pneumonia. Treating viruses is difficult. Acyclovir is highly effective against herpes simplex and varicella zoster viruses and may have a role in lessening the risk of cytomegalovirus (CMV) infection following bone marrow transplantation (BMT). Ganciclovir and foscarnet have an effect against CMV, but the former is myelotoxic, and foscarnet can cause severe derangement of renal function. Nevertheless, in combination with CMV-specific immunoglobulin these agents can be life saving. Ribavirin has been used in measles and adenovirus infections, but there are no controlled data proving efficacy. Bacteria are also an important cause of infection, particularly when central venous catheters (CVCs) have been placed, in children given cytotoxic conditioning therapy before BMT. In these circumstances even a small rise in temperature may indicate bacterial infection either with a gram-positive bacterium such a coagulase-negative staphylococcus or an enterococcus, or with infection due to gram-negative rods. Empirical treatment with broad-spectrum antibiotic cover should be started at the first sign of infection before waiting for the results of blood cultures. CVC infections can now be treated successfully without removing the CVC and locking a glycopeptide antibiotic such as vancomycin or teico-planin into the infected lumen seems to increase chances of clearing CVC infection completely. Fungal infection is also a serious risk, and if bacterial cultures are negative and the temperature has not settled after 48–72 h, amphotericin needs to be added, even if fungal cultures are negative, as isolating fungi from anything other than biopsy specimens is extremely difficult. Candida and Aspergillus spp. are the most common pathogens, and whereas candida infection usually causes septicaemia, pneumonitis or occasionally ophthalmomitis, aspergillus infection can involve several sites including the liver, the lungs, paranasal air spaces and the central nervous system. In many ways, children with SCID act as a model for the infective problems seen following intensive chemotherapy or around bone marrow transplantation. In these situations, not only is there neutropenia, but there is often severely depressed T- and B-lymphocyte function – explaining why viruses such as measles, CMV and adenovirus can be as devastating as bacteria and fungi which are often associated only with neutropenia. It has also been suggested that the risk and severity of fungal infection is greater when there is both neutropenia and T-cell dysfunction. This situation is seen most commonly when there is protracted graft-versus-host disease (GVHD) following a bone marrow transplant. In this situation the GVHD itself causes both neutropenia and T-lymphocyte dysfunction and this is compounded by the immunosuppressive treatment necessary to control the GVHD.

Congenital T-cell immune deficiencies such as Wiskott Aldrich syndrome offer a fascinating insight into the importance of T lymphocytes in combating infection caused by the herpes family of viruses. Not only do these children suffer from severe herpes simplex and varicella zoster virus infections, but also chronic Epstein-Barr virus infection of B lymphocytes, which is not fully controlled because of defective T-lymphocyte function, leads almost inexorably to the development of B-lymphoproliferative disease, and ultimately B-cell lymphoma in the majority of patients. HIV infection illustrates the central role played by the CD4+ T helper cell in orchestrating responses, as already mentioned. Infection by members of the herpes virus family can be a particular problem in children on long-term T-lymphocyte immunosuppression to prevent rejection of solid organ grafts. Again, not only is infection with HSV and VZV a significant problem, but EBV driven B-lymphoproliferative disease is now affecting an increasing number of the long-term survivors. Defective antibody production seems to be a problem only when there is long-term immunocompromise, such as seen in congenital B-lymphocyte deficiencies, or due to ineffective T- and B-lymphocyte interactions seen in HIV infection. Bacterial infection of the paranasal sinuses and the chest, as well as skin sepsis, is a particular problem in these conditions. Progressive bronchiectasis due to repeated insidious and often unrecognised chest
infections is a particularly serious problem and must be managed aggressively with physiotherapy and inhaled and systemic antibiotics if early death from respiratory failure is to be avoided.

Conclusion

The increasing recognition of congenital immune deficiency, together with an enormous rise in the number of children immunocompromised as an unavoidable consequence of immunosuppressive treatment, has greatly increased the number of children susceptible to unusual and opportunistic infection. Understanding the nature of the immune defect and the organisms that are able to take advantage of these specific windows of opportunity, allows anticipation of infective problems and planning of the most rational empirical therapy. These children need careful management with meticulous attention to detail, but if this can be maintained, many can be treated successfully and can grow up to lead normal, healthy and active lives.

MANAGEMENT OF CHEST INFECTION IN CYSTIC FIBROSIS PATIENTS

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Survival in patients with cystic fibrosis (CF) has improved dramatically in the last three decades [203]. Although CF is a multisystem disorder, almost all deaths are from respiratory failure. This is the end-stage result of the suppurative lung disease which is characterised by bacterial colonisation and chronic airways infection. Thus, although this improved survival is likely to have been contributed to by a number of different innovations in management, better and more effective treatment of chest infections is likely to have played an important part.

The cellular defect of cystic fibrosis is caused by an abnormality in the cystic fibrosis transmembrane regulator (CFTR), a phosphorylation-regulated Cl− channel located in the apical membrane of involved epithelia. The pathogenesis of lung disease in CF and the precise mechanisms by which defective Cl− transport in the lungs leads to suppurative lung disease are still poorly understood. However, recent studies by Smith et al. [204] have indicated that the high concentration of sodium and chloride in the airway surface lining fluid may inhibit the natural bactericidal activity present in this fluid and thus lead to bacterial colonisation. The organisms that typically colonise the airways of CF patients include Staph. aureus, H. influenzae, Pseudomonas aeruginosa and Burkholderia cepacia. The mainstay of treatment in CF involves the use of chest physiotherapy to clear infected sputum from the airways and appropriate use of antibiotics both to prevent and to treat acute infections. There are several different strategies available for the use of antibiotics and, therefore, these will be considered under separate headings.

Staph. aureus

Staph. aureus is usually one of the first organisms to infect the respiratory tract in CF patients. In a study from Australia [205], untreated CF infants identified by neonatal screening underwent bronchoscopy to establish whether pathogenic bacteria were present in the lower respiratory tract. Around a third of cultures were positive for Staph. aureus. Because of the concern about the acute effects of severe Staph. aureus infection or the long-term consequences of chronic Staph. aureus infection, many units are advocating the use of long-term prophylactic anti-staphylococcal antibiotic therapy. Evidence from randomised controlled trials is at present conflicting. One trial of prophylactic cephalixin conducted in the USA recruited children <2 years old with mild chest involvement. After 4 years the treated children failed to demonstrate any significant clinical advantage [206]. A small trial was conducted in East Anglia in patients identified by neonatal screening, where the prognosis of children treated with continuous oral fluocloxacillin was compared with that of patients treated with antibiotics only when clinically indicated. The number of Staph. aureus isolates and hospital admissions was less in the group treated with continuous fluocloxacillin, but the study failed to show improvement in a number of other clinical outcomes examined. Importantly, the study was not placebo-controlled and there was no intention-to-treat analysis. As yet no systematic review of these trials has been conducted and it may be that insufficient numbers have been included in randomised controlled trials to draw any firm conclusion. In our own institution, the policy is to give regular twice daily anti-staphylococcal prophylaxis in the form of cephradine to all CF patients from the time of diagnosis, to be continued indefinitely. If a child repeatedly grows H. influenzae on cough swab or sputum cultures, then this antibiotic is changed to oral cefaclor.

Ps. aeruginosa colonisation

Colonisation with Ps. aeruginosa does appear to be associated with an adverse outcome in CF patients [207]. Therefore, attempts to eradicate Ps. aeruginosa when it is first isolated are recommended by many centres. There is very little information available from randomised controlled trials about the effectiveness of different methods in eradicating Ps. aeruginosa. A small randomised controlled trial by Valerius et al. in 1991 examined the efficacy of a 3-week course of nebulised colistin combined with oral ciprofloxacin [208]. The results of this trial showed reduction in
colonisation by \textit{Ps. aeruginosa} in those patients who received the treatment and similar regimens are now being used in centres throughout the UK.

**Nebulised antibiotics**

Nebulised anti-pseudomonal antibiotics have been used to reduce bacterial colony counts in the airways and reduce respiratory complications in CF patients since the early 1980s. There are now considerable amounts of data available on the use of this treatment, including a recently published meta-analysis of randomised controlled trials [209]. This meta-analysis has shown that nebulised anti-pseudomonal antibiotics effectively reduce respiratory pseudomonal load, and are associated with improvements in lung function and a reduction in the number of respiratory exacerbations. A question remains about when nebulised antibiotics should be instituted. Many would advocate their use from the time that \textit{Ps. aeruginosa} colonisation becomes established.

**Treatment of acute exacerbations**

Prompt treatment of acute infections is thought to be important in preventing lung damage in CF patients. This treatment may be by an additional course of oral antibiotics to treat the organisms isolated most recently from sputum cultures or cough swab. If the child is acutely unwell, particularly with reduced lung function or chest X-ray changes, a 2-week course of intravenous antibiotics is generally advocated. Most units would now recommend using two intravenous antibiotics in combination, particularly for patients who are colonised with \textit{Ps. aeruginosa}.

**Prevention of cross-infection**

Cross-infection with organisms in CF patients was first established for \textit{B. cepacia}. Infection with a highly transmissible epidemic strain of this organism was associated in some patients with rapid clinical deterioration and death [210]. Molecular biological techniques have now unequivocally demonstrated cross-infection in CF patients for \textit{Ps. aeruginosa} [211], \textit{Staph. aureus} [212] and \textit{Stenotrophomonas maltophilia} [213]. Ten years ago it was usual for CF patients to be nursed together on an open ward and social events including summer camps for children and adults were commonplace and encouraged. The mutual support which derived from these social networks between CF patients and their families was regarded as very beneficial [214]. The recognition of the importance of cross-infection and, in particular, the devastating consequences associated with acquisition of \textit{B. cepacia}, have changed all this. Close association between patients is now discouraged and isolation in cubicles of in-patients is recommended. MRSA, although a relatively uncommon pathogen in CF patients, does colonise the airways in a small proportion and is highly transmissible. It represents a significant risk to certain groups of hospitalised patients, particularly surgical patients. Strict infection control measures should be used if a CF patient colonised with this organism requires hospital admission.

**Viral infections**

Viral infections of the respiratory tract have received relatively little attention in CF patients. Wang and co-workers found that the annual incidence of virus infection was correlated with clinical deterioration [211]. A small study by Ramsey \textit{et al.} found that patients with a high rate of viral respiratory infection deteriorated less than those with fewer such infections [216]. However, recent work from our own unit [217] has demonstrated that viruses which predominantly infect the lower respiratory tract are associated with a decline in forced expiratory volume (FEV\textsubscript{1}) in children with CF. Rhino-virus, which predominantly affects the upper respiratory tract, was not associated with a decline in lung function, but was associated with an increased use of intravenous antibiotics. Clearly viral infections are not amenable to therapeutic strategies in the same way as bacterial infections. However, the implications of this study are that evidence of a viral infection involving the respiratory tract should indicate increased vigilance and early treatment of any associated respiratory deterioration.

The mainstay of management of chest infections in CF patients remains physiotherapy and antibiotics. Better and more effective antibiotics and better methods for their delivery have undoubtedly been associated with improved respiratory outcome in recent years.

**A COMPARISON BETWEEN THE INCUBATION TIME AND CARRIER STATE FOR CLASSIFYING INFECTIONS OCCURRING IN PAEDIATRIC INTENSIVE CARE UNITS**

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**Introduction**

The incubation period for infections caused by high level pathogens, both viral and bacterial, is well-defined. For example, the incubation times for chickenpox and \textit{S. typhimurium} are 14 and 3 days, respectively. Skin rash and diarrhoea, respectively, are produced because of the intrinsic pathogenicity of these two virulent micro-organisms, mostly affecting a
previously healthy individual [218]. In contrast, practically all nosocomial infections occurring in the paediatric intensive care unit (PICU) are caused by potentially pathogenic micro-organisms (PPM) requiring an individual with underlying disease and associated immunodepression to be able to produce disease. The time of onset of the nosocomial infection is related to the severity of the illness [219]. A patient who requires intensive care is, in general, seriously ill and suffers impaired immunity, and this explains why the majority of ICU infections occur in the first episode following admission [220]. Most patients recover and do not develop a superinfection. However, only patients who do not recover, or even deteriorate, need to stay in the PICU for a long time and may suffer a second episode of immunosuppression. This is the subset of patients who develop more than one infection in the PICU [221].

The realisation that the severity of the patient’s illness determines the time of onset of an infection developing in the ICU patient may explain why the Centers for Disease Control and Prevention (CDC) guidelines do not actually recommend a specific time cut-off to determine whether an infection is nosocomial or community-acquired [222]. This definition has been found to meet with many problems in practice, and this experience prompted investigators to introduce an arbitrary cut-off, varying between 24 and 120 h [220, 223–226].

Practically all infections occurring in an ICU are endogenous, i.e., due to PPM carried by the ICU patient in their throat or gut flora, or both [227]. That observation implies that the PPM carried at the time of serious immunosuppression is highly likely to be responsible for the infection. Obviously, the infection is nosocomial, i.e., occurs in the ICU, the epicentre of the hospital where critically ill patients are brought together. However, the PPM involved in the infection occurring on the ICU is not automatically nosocomial, i.e., originating from the ICU’s animate or inanimate environment. A substantial proportion of infections on the ICU are due to PPM imported by the patient requiring intensive care in their admission flora and do not relate to the ICU ecology.

A 1-year prospective study was undertaken in three different subsets of children, requiring minimally 3 days of ventilation on the paediatric intensive care unit, on the oncology unit and following heart surgery, to distinguish infections due to PPM carried on admission from infections caused by PPM acquired in the PICU.

Patients and methods

All children of <16 years admitted to: (1) the medical/surgical paediatric ICU requiring intensive care and expected to need mechanical ventilation for a minimum of 3 days; (2) the oncology unit requiring intensive care and expected to suffer from severe neutropenia of <0.1 \times 10^9 \text{ neutrophils/L} for a minimum of 3 days; and (3) the paediatric cardiac ICU requiring ventilation for at least 3 days following cardiac surgery, were consecutively enrolled in this prospective observational cohort study over 1 year (1995).

Sampling policy

Surveillance samples of throat and rectum were obtained on admission to the PICU and oncology unit, and afterwards twice weekly to distinguish the carrier state of micro-organisms brought into the unit with the patient from carriage of microbes acquired and subsequently carried during their stay on the PICU and oncology unit.

Diagnostic samples of blood, lower airways, bladder and wounds were taken only on clinical indication.

Microbiological methods

Surveillance samples were processed by a semi-quantitative method, i.e., the four quadrant technique combined with enrichment broth [228]. Both swabs were inoculated on to four solid media (staphylococcal agar, yeast agar, MacConkey agar and aesculin azide agar), and placed into 5 ml of brain heart infusion broth. The target micro-organisms were staphylococci (both coagulase-positive and coagulase-negative – CNS), yeasts, aerobic gram-negative bacilli (AGNB) and enterococci. Growth density was classified as very low (equivalent to <10 cfu/ml) where only the enrichment broth gave positive results, low (≥10 <10^3 cfu/ml); medium (≥10^3 <10^5 cfu/ml), high (≥10^5 <10^7 cfu/ml) and very high (≥10^7 cfu/ml) where the plate was completely covered with bacterial growth.

Diagnostic samples of blood for culture were taken from the central venous line or from a peripheral vein, or both, when signs of generalised inflammation were observed. Blood was processed by the Bactec 9240 system (Becton and Dickinson, Diagnostic Instrument Systems, Sparks, MD, USA).

Identification was performed by the ATB system. To differentiate CNS from coagulase-positive staphylococci, i.e., Staph. aureus, the production of DNAase by a DNA agar plate method and a slide-agglutination test (Staphaurex, Wellcome Diagnostics) to detect clumping factor and protein A were used. Staph. aureus was identified by a positive DNAase and slide-agglutination test. If the results were inconclusive, a tube-coagulase test with strain NCTC 6571 as a positive control was performed, and read at 4 and 24 h. A CNS was identified by a negative tube-coagulase test.

Sensitivity patterns were determined by the break
point method [229]. All isolates were suspended in distilled water, then transferred on to a semi-solid growth medium and inoculated on to a plastic strip containing paired wells of standard concentrations of antimicrobial agents. Aerobic gram-negative bacilli were tested against seven antibiotics: cefotaxime and ceftazidime (4 and 32 mg/L); gentamicin and tobramycin (4 and 8 mg/L); netilmicin (8 and 16 mg/L); ciprofloxacin (1 and 4 mg/L); and polymyxin E or colistin (4 and 4 mg/L). Staphylococci were tested against eight antimicrobial agents: oxacillin (2 and 8 mg/L), ceftriaxone (6 and 32 mg/L), cefuroxime (8 and 32 mg/L) and vancomycin and teicoplanin (8 mg/L each). After incubation for 18 h, growth was read automatically by the ATB reader (ATB antibiogram, La Balme, Les Grottes, France). If both wells were clear the isolate was recorded as susceptible, if both were turbid the isolate was resistant and if only the lower concentration well showed growth, the isolate was of intermediate susceptibility.

Definitions

Infection was defined in this study as a microbiologically proven clinical diagnosis of inflammation. The diagnostic sample yielded \( \geq 10^6 \) cfu/ml, supporting the clinical evidence of infection. A septicemic episode was defined by a positive blood culture accompanied by a pyrexia of \( \geq 38^\circ C \).

The identity of micro-organisms was based on antibiotyping by extended sensitivity patterns (CNS, enterobacteria), phage typing (Staph. aureus), serotyping (Str. pneumoniae) and pyocine typing (Ps. aeruginosa).

When an identical micro-organism was isolated from at least two consecutive surveillance samples in any concentration over a period of at least 1 week, the ICU patient was considered to be in a carrier state [228]. If only one surveillance sample was positive for a micro-organism that differed from previous isolates, the patient was considered to have acquired that micro-organism. Thus, carriage referred to the persistent presence of a micro-organism in the oropharynx or gut, or both.

Classification of infection occurring in the ICU

Traditionally, an infection episode occurring \( >48 \) h after admission was counted as a hospital-acquired event [230].

Endogenous infection was an infection caused by a micro-organism carried in either the throat or gut, or both. Primary was distinguished from secondary endogenous infection. Primary endogenous infection was caused by a micro-organism imported by the patient in their admission flora into the ICU. Secondary endogenous infection was caused by a micro-organism acquired while on the ICU. Exogenous infection was an infection not preceded by carriage. According to the criterion of the carrier state, 'true' nosocomial infections comprised exogenous and secondary endogenous infections, because the causative micro-organisms were associated with the ICU ecology. Typical ‘ICU’ micro-organisms were acquired by the ICU patients due to transmission of these particular microbes following breaches of hygiene.

The difference between these two nosocomial infections was that the micro-organism causing an exogenous infection was immediately introduced into the internal organ, e.g., Acinetobacter into the lower airways via a tracheotomy without oropharyngeal carriage, whereas the development of a secondary endogenous infection required the formation of throat or gut carriage, or both, before the infection. For example, the ICU patient first acquired Ps. aeruginosa in the throat and became a carrier. Subsequent colonisation and infection of the lower airways with Ps. aeruginosa occurred following aspiration of the contaminated salivary secretions.

Results

Infection rates

Totals of 110, 101 and 80 children were enrolled over 1 year following their admission to the PICU, oncology and cardiac PICU, respectively.

Of 110 patients, 31 (28%) children developed a total of 47 infection episodes on the medical/surgical PICU. On the oncology unit, the infected patient rate was 37%. Of 101 patients, 37 patients developed a total of 114 infection episodes (3.0 episodes/patient). Of the 80 cardiac surgical patients, 19 (20%) children suffered a total of 34 infection episodes.

Infected organ systems

In the PICU population, more than half of all infections (55%) involved the lower airways, followed by blood and skin infections, each responsible for c. 20%.

In the neutropenic group, 85% of the 114 infection episodes were blood-stream infections. There were seven episodes of stomatitis and two of vaginitis. Three skin infections were diagnosed and there were four central venous line-site infections with or without lymphangitis.

In the children who underwent cardiac surgery, septicemia (27 episodes) and sternal wound infection (three episodes) were the two problems of infective morbidity.

Type of infections

Fig. 20 shows that with the time criterion of a 48-h cutoff, 37%, 48% and 14% of all infections occurring on
Fig. 20. Pie charts comparing the infection rates calculated using the time criterion of (a) 48 h versus (b) the carrier state in the three different subsets of patients: A, paediatric general ICU (n = 47 infection episodes); B, severe neutropenia (n = 114 infection episodes); C, paediatric cardiac ICU (n = 38 infection episodes).
the three different units, respectively, were judged to be community-acquired. However, the carrier state identified 80%, 85% and 80% of all infective episodes as primary endogenous, i.e., caused by micro-organisms brought into the units by the three different patient populations and, hence, had nothing to do with the ecology of the ICUs.

According to the criterion of carriage, 'true' nosocomial infections include both secondary endogenous and exogenous infections due to micro-organisms originating from the ICU. The percentage of nosocomially acquired infective episodes was similar in the three subsets of patients: 20%, 15% and 20% for the PICU patients, oncology and cardiac surgical patients, respectively. In contrast, the 48-h cut-off identified nosocomially acquired infection percentages of 63%, 52% and 86%, respectively.

Causative micro-organisms

On the paediatric ICU, the majority of the primary endogenous infections were caused by 'community' bacteria, including Str. pneumoniae, H. influenzae, Moraxella catarrhalis (lower airways), Staph. aureus, E. coli (blood) and Candida albicans (skin). The nosocomial exogenous and secondary endogenous infections were caused by the typical opportunist aerobic gram-negative bacilli (AGNB) such as Ps. aeruginosa, Enterobacter cloacae and A. baumannii.

In the oncology group, staphylococci were responsible for 60% of all blood-stream infections; coagulase-negative (50%) and coagulase-positive (10%). AGNB and yeasts were involved in 20% and 10%, respectively. Practically all septicaemias and fungaemias were primary endogenous, i.e., were due to micro-organisms that the patient imported into the unit. Candida and Acinetobacter spp. caused exogenous infections of the blood-stream, while secondary endogenous septicaemias were caused by CNS and Ps. aeruginosa.

More than half (11 of 19) of the children who developed an infection after cardiac surgery suffered septicaemia due to CNS and three had sternal wound infections caused by Staph. aureus. Of the 34 infection episodes, 27 were caused by micro-organisms carried by the patient pre-operatively, i.e., primary endogenous. Exogenous infections (10%) were caused by non-aeruginosa Pseudomonas spp. and Staph. aureus, whilst secondary endogenous infections (10%) were caused by C. albicans and Staph. aureus.

Discussion

The main finding of this study is that, of every 10 infections occurring on the paediatric ICU and oncology unit, eight were caused by micro-organisms that the patient carried in their admission flora. In other words, the main infection problem on our paediatric ICUs and oncology unit had nothing to do with the unit ecology.

The application of a time cut-off of 48 h would have led to the opposite conclusion, i.e., a serious nosocomial infection problem of 63%, 52% and 86% on the different units, respectively. Automatically, both medical and nursing staff traditionally would have been blamed for transmitting micro-organisms and hence held responsible for the substantial infection problem during the patients' stay in hospital.

We believe that the introduction of surveillance samples of throat and rectum to detect the carrier state on admission and throughout the ICU stay is a more realistic approach, compared with the criterion of arbitrary time cut-offs.

Not all patients require surveillance samples, only the subset of children who are so ill on admission that they are expected to require intensive care for a minimum of 3 days, i.e., the subset of patients who score a minimum of 6 on the paediatric risk of mortality (PRISM) score [219, 231].

Firstly, the use of a 48-h cut-off has magnified the problem of nosocomial infection. The use of surveillance samples for the detection of carriage enables us to usefully re-classify a substantial number of infections from the unit-acquired group into the imported group. A total of 87 infective episodes (20, 43 and 24 infections in the PICU, oncology and cardiac patients, respectively) were removed from the unit-acquired group into the imported group. In identifying the right population of primary endogenous infections, the classification based upon carriage avoids blaming staff or carers for all infections after 48 h for which they are not responsible. For example, the majority of infections in patients who underwent cardiac surgery (86%) developed after 48 h, delayed because of perioperative antibiotic prophylaxis. Knowledge of the carrier state thus prevents fruitless investigation of apparent cross-infection episodes.

Secondly, the introduction of surveillance samples for the long-stay patients allows the accurate calculation of the 'true' nosocomial infections, comprising secondary endogenous and exogenous infections only. These infections are caused by typical ICU- micro-organisms following transmission via hands of personnel. In other words, that combined figure of secondary endogenous and exogenous infections reflects the level of hygiene and hence a cross-infection problem rather than the total number of infections occurring 48 h after admission to the ICU.

Thirdly, without surveillance samples, exogenous infections, which can occur at any time in the ICU
because of contaminated equipment, are impossible to recognise – at least at an early stage when only diagnostic samples such as tracheal aspirate, urine and blood have been tested [232].

Finally, from an infection prevention point of view, the knowledge of carriage is indispensable for the management of infection in the PICU and oncology unit. The traditional criterion of the time cut-off from 48 h up to 120 h implies that infections that are incubating up to 120 h following admission are not preventable [233]. Handwashing is the generally recommended manoeuvre to prevent nosocomial infections that occur in the ICU after the incubation period cut-off [234]. When the criterion of the carrier state is used, practically all infections occurring in the ICU are preventable apart from the infections on admission. Exogenous infections can be prevented by a high level of hygiene [235]. Parenteral agents control primary endogenous infections [236, 237] whilst non-absorbable antimicrobial agents aim to prevent secondary carriage and subsequent secondary endogenous infections [236, 238]. Selective decontamination of the digestive tract is an infection prevention technique based on the classification using the carrier state, and has been shown to reduce significantly infectious morbidity and mortality by 63% and 20%, respectively [239].

**DRUG METABOLISM AND ANTIBIOTIC THERAPY IN CHILDREN**

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**Introduction**

Infections have always been a problem in children, infants and neonates with significant morbidity and mortality. Antibiotic therapy has undoubtedly resulted in major clinical advances in the treatment of children. However, it is clear that antibiotics have also produced particular clinical problems. A combination of penicillin and sulphamethoxazole resulted in a higher mortality in neonates than those receiving oxytetracycline [240]. This was due to the higher incidence of kernicterus caused by the protein-displacing effect of the sulphonamides [241]. The sulphonamides are highly protein bound and displace bilirubin from albumin.

The grey baby syndrome described newborn infants who developed abdominal distension, vomiting, cyanosis, cardiovascular collapse, irregular respiration and subsequently died following the administration of chloramphenicol [242]. Pharmacokinetic studies showed that newborn infants had impaired metabolism of chloramphenicol and that a reduction of the dosage from 100 to 50 mg/kg/day prevented the development of the syndrome [243].

More recently, there have been case reports of unconsciousness or prolonged sedation following the concomitant use of midazolam with the antibiotic erythromycin [244, 245]. The enhancement of the sedative effect of midazolam is thought to be due to inhibition of its metabolism by erythromycin [246]. This illustrates the importance of having some knowledge of drug metabolism in relation to antibiotic therapy.

**Pharmacokinetics**

Pharmacokinetics is the quantitative study of drug or metabolites, or both, in various compartments of the body in relation to time. This relationship is determined by bioavailability, distribution, metabolism and elimination. Bioavailability describes how much of the drug is available following oral administration in comparison with intravenous administration. In the case of aminoglycosides, with low bioavailability, there is poor absorption from the gastrointestinal tract and, therefore, the drug needs to be given intravenously or intramuscularly. The former route is preferable, especially for newborn infants with limited muscle mass. Drugs do not remain exclusively in the blood, but are transferred into various tissues and blood fluids. The volume of distribution is the theoretical volume into which a drug would need to distribute to achieve a concentration equal to the actual plasma concentration. Drugs highly bound to plasma proteins have a small volume of distribution, whereas drugs extensively stored in extravascular sites have a high volume of distribution. The plasma half-life is the most commonly used pharmacokinetic parameter in clinical practice; it is the time required for the plasma concentration to fall by 50%. Clearance is a quantitative measure that characterises the rate of removal of drugs from the body. It is a more precise measurement of elimination than half-life because it is independent of drug distribution. The formulae available to calculate the above pharmacokinetic parameters are described in detail elsewhere [247].

**Paediatric clinical pharmacology**

It is important to realise that drug metabolism is often different in children in comparison with adults. These changes are most evident in the neonate and the preterm infant in particular. Neonates have impaired renal function and this is especially marked in the preterm infant [248, 249]. During the first 2 weeks of life, renal function dramatically improves and this affects the administration of antibiotics that are excreted renally, e.g., aminoglycosides and cephalosporins [247]. After the first month of life, renal function remains normal. Drugs may undergo metabolism within the liver and this will include oxidation by hepatic cytochrome P450 enzymes or conjugation to
glucuronides and sulphates. The activity of many P450 enzymes is reduced in the neonatal period. The rate by which enzyme activity subsequently increases varies considerably. The metabolism of midazolam is different in children <3 years old in comparison with children aged ≥3 years [250], whereas caffeine metabolism is not affected by age after the age of 12 months [251, 252]. Glucuronidation is usually impaired in the neonatal period and there is enhanced sulphonation [253]. Again, however, the development of these two pathways varies from drug to drug and cannot be accurately predicted [253].

The effect of antibiotics on the metabolism of other drugs

Some antibiotics induce hepatic cytochrome P450 enzymes and this results in enhanced clearance of concomitant medication. One of the most potent enzyme inducers is rifampicin [254] and it is important that if children are receiving other medication (e.g., anticonvulsants, theophylline) the possibility of enhanced clearance of these drugs should be considered. Antibiotics are more likely to be inhibitors of drug metabolism than inducers and this is illustrated by the large number of antibacterial agents that can inhibit the clearance of other drugs (see Table 11). Clinically important drug interactions have been reported with erythromycin [244] and ciprofloxacin [255].

The caffeine breath test

A useful way of studying drug interactions in children is the caffeine breath test. The test uses a non-radioactive stable isotope (13C on the 3-methyl group) of caffeine. The caffeine is given orally and undergoes 3-N-demethylation, which is a cytochrome P450-dependent reaction (CYP1A2). After N-demethylation the labelled methyl group enters the one-carbon pool as it is converted to formaldehyde formate bicarbonate and then exhaled as carbon dioxide. The caffeine breath test was originally used in adults, but has been used successfully in children to study drug interactions [256, 257].

Factors affecting the metabolism and elimination of antibiotics

There are many factors that can affect antibiotic metabolism. The effect of age has been tragically illustrated by chloramphenicol in the neonatal period. It is disappointing that the pharmacokinetics of the cephalosporins that are widely used in sick neonates have not been studied extensively [247]. Another major factor that can affect drug metabolism is the presence of disease. Patients with cystic fibrosis have enhanced clearance of drugs which undergo metabolism in the liver [258] and those which are excreted renally [259]. The mechanism for this is not fully understood. Other disease states such as acute infections or shock can also affect drug metabolism, but this has not been widely studied in relation to antibiotic therapy. Malnutrition generally impairs the elimination of drugs and, therefore, a reduction in dosage is necessary [260]. Again it is disappointing that there have been few studies into the effect of malnutrition on antimicrobial therapy [262], especially if one considers the huge number of children who suffer both malnutrition and infections throughout the world.

Age-specific toxicity

Certain adverse effects only occur in infants or children (including the fetus). Examples of this include the effect of tetracycline on developing teeth and also the possible effect of ciprofloxacin on weight-bearing joints in young children. There are also many aspects of drug toxicity that are not yet understood, e.g., the increased incidence of an allergic response to ampicillin/amoxycillin during glandular fever.

References


Table 11. Antibiotics that affect drug metabolism

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<thead>
<tr>
<th>Enzyme inducers</th>
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<td>Erythromycin</td>
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<td>Ciprofloxacin</td>
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