

Meningococcal disease in siblings caused by rifampicin sensitive and rifampicin resistant strains

SJ Dawson, RE Fey, CA McNulty

Summary: Two brothers presented with meningococcal infection in a five day period, the first with a rifampicin sensitive strain and the second, who had received rifampicin chemoprophylaxis, with a resistant strain. Secondary cases of meningococcal disease can occur despite chemoprophylaxis, and may be rifampicin resistant. Close contacts should be informed of the early symptoms of meningococcal disease and of the need to seek medical advice urgently if they occur.

Commun Dis Public Health 1999; 2: 215-6.

Introduction

National guidelines recommend that close contacts of cases of meningococcal disease are given chemoprophylaxis, and vaccination if appropriate (serogroup A or C infections)¹. Rifampicin is currently used for chemoprophylaxis as it eradicates carriage in 85% to 90% of contacts² and resistance is rare (<1% of meningococcal isolates in a recent survey in England and Wales)³. Prophylaxis is known to fail,, however, and we report a case of failure due to the acquisition of a rifampicin resistant strain in a sibling.

Incident report

A 5 year old boy was admitted to hospital with a history of fever and headache for 36 hours, but no rash. Blood cultures taken on admission grew *Neisseria meningitidis* serogroup C after 36 hours incubation. Disc sensitivity testing by Stokes method showed that the strain was sensitive to penicillin, cefotaxime, ciprofloxacin, and rifampicin. Cerebrospinal fluid obtained on admission contained less than 5 x10⁶/L white blood cells and normal levels of protein and glucose; bacterial culture was negative after 48 hours. The patient was treated with intravenous (IV) ceftriaxone and recovered.

Household contacts were given chemoprophylaxis in line with national guidelines¹. Contacts included two adults and seven children living in the same house, and prophylaxis was also recommended for a nearby household of two adults and two children who were part of the extended family. Rifampicin (10 mg/

kg twice daily for two days) was prescribed for children, and ciprofloxacin (500 mg as a single dose) for those aged over 12 years. Household contacts were advised to attend their general practitioner to be given meningococcal polysaccharide (A + C) vaccine when the grouping was confirmed by the PHLs Meningococcal Reference Unit (MRU).

Five days after the admission of the index case, his 30 month old brother was admitted to hospital. He had been unwell since the previous day, become feverish, vomited, but had no rash. Blood cultures grew *N. meningitidis* after 24 hours. Like his brother the second case was treated with IV ceftriaxone and made a full recovery. On the morning of the day before admission he had completed a two day course of rifampicin chemoprophylaxis. His mother reported full compliance.

As a close contact had developed meningococcal infection despite prophylaxis, throat swabs were taken from household contacts as the two cases, and a repeat course of chemoprophylaxis was recommended.

The second isolate, identified as serogroup C by MRU, was sensitive to penicillin, cefotaxime, and ciprofloxacin but resistant to rifampicin on disc sensitivity testing. No further chemoprophylaxis was recommended as none of the throat swabs taken from the family contacts before the second course of chemoprophylaxis had yielded meningococci. Throat swabs from the same family contacts two weeks later also yielded no meningococci.

Subsequent typing by MRU showed that both isolates had the same phenotype – serogroup C serotype NT serosubtype P1.5 P1.2 – and were indistinguishable by pulsed field gel electrophoresis (PFGE). The minimum inhibitory concentration of rifampicin was 0.06 mg/L (sensitive) for the first isolate and 10 mg/L (resistant) for the second isolate.

Discussion

The risk of infection in close family contacts of patients with meningococcal infection is about 500 to 1200 times greater than in the general population^{4,5}, and is highest in the first seven days⁴. Chemoprophylaxis with rifampicin reduces this risk by eliminating nasopharyngeal

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carriage from the network of close contacts¹.

Prophylaxis can fail for a number of reasons: because of co-primary cases (those incubating the disease when given prophylaxis)⁶; failure to take the prophylaxis^{7,8}; reinfection⁶; or, as reported here, the development of a rifampicin resistant strain^{7,9,10}.

Several possible mechanisms may explain how this occurred. Resistance to rifampicin develops rapidly by a spontaneous one step point mutation of the *rpo B* gene^{11,12}. As the incubation period for meningococcal infection varies from two to 10 days (usually three to four)¹³, both siblings could have been infected with the same strain. This could then have mutated before the second sibling completed prophylaxis, with the resistant strain then surviving in preference to the sensitive one. Alternatively, the resistant strain could have been acquired from another carrier (within or outside the family), but this is less likely as both isolates were indistinguishable by PFGE, and none of the throat swabs from close contacts grew meningococci.

Rifampicin resistant meningococcal infections after chemoprophylaxis have been documented^{7,9,10}. A three year survey of secondary cases found that one in 17 (6%) cases was rifampicin resistant⁷. A higher resistance rate has also been found in nasopharyngeal isolates obtained after rifampicin prophylaxis^{8,14,15}. Rifampicin given to carriers of *N. meningitidis* during an outbreak in naval recruits failed to eradicate pharyngeal carriage in 26% of recipients. Eight per cent of the recipients were found to be carrying a rifampicin resistant strain after prophylaxis⁸. The American Public Health Association consequently does not recommend rifampicin for use as mass prophylaxis and suggests limiting its use to close contacts, who are most at risk, so minimising development of meningococcal resistance¹³.

When rifampicin resistance is detected in meningococci, consideration should be given to alternative chemoprophylaxis, such as ciprofloxacin or ceftriaxone (although neither is currently licensed for this purpose) for close contacts. It has been suggested that these two new agents are better than rifampicin and should be used as first line prophylaxis¹⁶. Both are given as a single dose, which ensures compliance, and meningococci have not acquired resistance. Ceftriaxone has to be given by intramuscular injection, however, and ciprofloxacin is not currently recommended for use in children or pregnancy¹⁷ and has been associated with allergic reactions¹⁸. Alternatively, previously favoured agents such as sulphonamides or minocycline could be given.

Clinicians and epidemiologists need to be aware that secondary cases of meningococcal disease occur after chemoprophylaxis, and close contacts should be informed of the early symptoms of meningococcal disease and told to seek medical advice urgently if they occur. Rifampicin resistance may occur in secondary cases who have received this agent for prophylaxis. It is therefore important to obtain the results of serogrouping and sensitivity tests of isolates from secondary cases quickly. If rifampicin resistance

is found a repeat course with an alternative prophylactic agent such as ciprofloxacin or ceftriaxone should be considered for contacts. Collection of this data for national surveillance of antibiotic resistance will enable the best chemoprophylactic agents to be chosen at a national as well as a local level.

Acknowledgments

We thank Dr David Hunt for providing details of the prophylaxis of cases, Dr David Stevens for allowing us to report them, and MRU for typing the isolates.

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Leptospirosis in the South-Eastern Health Board region of the Republic of Ireland: 1990 to 1996

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Summary: *The South-Eastern Health Board (SEHB) has the highest annual incidence of leptospirosis in the Republic of Ireland (12.3/million according to hospital inpatient enquiry data; 10.4 /million by serology). Discharge diagnosis correlates strongly with numbers of cattle, but not of other livestock, which may indicate a true association with leptospirosis or may reflect an increased clinical suspicion in areas where livestock are prevalent.*

Commun Dis Public Health 1999; 2: 217-8.

Introduction

We recently published data on the incidence of leptospirosis in the Republic of Ireland from 1990 to 1996¹. Hospital In-Patient Enquiry (HIPE) data, which are derived from diagnoses recorded when patients are discharged from hospital, yielded 121 episodes, equivalent to a mean annual incidence of 4.9/million. There were 147 serologically confirmed cases of leptospirosis over the same period, equivalent to a mean annual incidence of 6.0/million. The incidence of leptospirosis varied significantly between the eight health board regions. We decided to investigate more fully and looked for associations with cattle and other livestock.

Methods

Regional incidences of leptospirosis derived from HIPE data were examined using various statistical models. We reviewed and cross-referenced serological and HIPE data from the South-Eastern Health Board. Data on population and livestock were obtained for 1991^{1,2}. Spearman rank correlation was used to measure the association between leptospirosis incidence and the numbers of cattle, sheep, pigs, and horses and also the combined total.

Results

Using a Poisson distribution model¹, with the North-

Western Health Board (nearest to the median) as a reference, the only significantly different incidence of leptospirosis was for the South-Eastern Health Board, with an incidence rate ratio of 3.6 times that of the North-Western Health Board. (95% confidence interval (CI)=1.4-9.2, $\chi^2 = 44.2$).

There was a strong correlation between the mean annual incidence of leptospirosis according to HIPE data and the natural logarithm of the number of cattle in the various health board regions ($r = +0.85$, $p \leq 0.006$). There was no evidence of association between disease rate and the numbers of sheep, pigs or horses. A positive correlation with total livestock numbers was not significant ($r = +0.64$, $p \leq 0.09$).

Further examination of the HIPE data showed that the 33 hospital inpatient episodes recorded in the South-Eastern Health Board represented 28 patients with a clinical diagnosis of leptospirosis, some of whom had been admitted more than once. Only 17 of these episodes were for seropositive acute leptospirosis (16 patients, one re-admission). A further 12 seropositive cases from identified laboratory data were not included in HIPE data, presumably because these results had not been available at the time of discharge.

The annual incidence of leptospirosis in the South-Eastern Health Board based on serological diagnoses was 10.4 cases/million. This laboratory based method is more reliable than the HIPE figure. Based on the binomial distribution model¹, the incidence rate ratio for the South-

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TABLE Cases of leptospirosis (1990 to 1996) and numbers of livestock (1991) in health board regions of the Republic of Ireland

| Health board | Number of cases | Mean annual incidence (per million) | Number of cattle | Number of sheep | Number of pigs | Number of horses |
|---------------|-----------------|-------------------------------------|------------------|-----------------|----------------|------------------|
| Eastern | 18 | 2.1 | 311120 | 944660 | 50084 | 9802 |
| Midland | 5 | 3.5 | 731502 | 666507 | 230362 | 4662 |
| Mid-Western | 16 | 7.4 | 999916 | 375283 | 89740 | 8614 |
| North-Eastern | 9 | 4.3 | 811792 | 721295 | 307404 | 6529 |
| North-Western | 5 | 3.4 | 411747 | 1087326 | 44062 | 2364 |
| South-Eastern | 33 | 12.3 | 1254646 | 1775660 | 276128 | 15698 |
| Southern | 20 | 5.4 | 1393411 | 1130517 | 260669 | 9264 |
| Western | 15 | 6.2 | 997841 | 2186956 | 45246 | 6181 |
| Ireland | 121 | 4.9 | 6911975 | 8888204 | 1303695 | 63114 |

(HIPE Data 1990 to 1996; all animal numbers from 1991 Census of agriculture)

Eastern Health Board compared with the rest of Ireland was 1.93 (95% CI=1.23-2.93). The higher incidence of disease was attributable to infections with *L. hardjo* and to serovars other than *L. icterohaemorrhagiae*.

Discussion

Discharge diagnoses of leptospirosis recorded in health board regions were found to correlate with the numbers of cattle in the regions. The positive predictive value of HIPE diagnosis was 52% and its sensitivity was 57%. Serological data could not be examined for correlation with livestock because regional data were available only for the South-Eastern Health Board. The South-Eastern Health Board has the second largest numbers of cattle, sheep, and pigs, the largest number of horses, and the largest number of livestock overall. The higher incidence of serologically confirmed leptospirosis in this region

may be due to a true differential in disease occurrence but the numbers of samples screened from each of the regions were unknown so we could not comment on the possibility of referral bias. This study identified a need for serologically based diagnosis for accurate determination of the incidence of leptosporosis.

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Survey of neonatal hepatitis B vaccination in Leicestershire

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Summary: *Some 121 390 live and still births were recorded in Leicestershire between June 1986 and May 1995. All mothers were offered antenatal screening for hepatitis B and 161 were positive for hepatitis B surface antigen. Examination of case notes from 113 mother and baby pairs identified 70 infants who fulfilled criteria for vaccination in place at the time, 47 of whom (67%) had received the three doses of hepatitis B vaccine then recommended for prevention of neonatal infection.*

Commun Dis Public Health 1999; 2: 218-9.

Introduction

Hepatitis B may be transmitted in the perinatal period from chronic carrier mothers to their infants. A large proportion of these infected infants will develop chronic infection which – if acquired in infancy – carries a 25% risk of serious sequelae: liver cirrhosis and hepatocellular carcinoma¹. Perinatal transmission of infection is preventable, in at least 90% of cases², by active and/or passive immunisation of 'at risk' infants identified through antenatal screening. Trent region has had a policy of antenatal screening for hepatitis B for 20 years

(PA Nuttal, personal communication).

This survey sets the context in which Health Service Guidance urging health authorities to implement antenatal screening for hepatitis B in all pregnancies by April 2000³ was issued.

Methods

We reviewed the management of infants born to hepatitis B surface antigen (HBsAg) positive women in Leicestershire by examining the case notes of pregnant women with a positive HBsAg test at antenatal screening from June 1986 to May 1995 and the case notes of their offspring. The main outcome measure sought was the number of doses of vaccine per infant, according to the recommendations for prevention of neonatal infection in place at the time.

Until December 1991, vaccination was only offered if HBsAg positive women were also considered to be of high infectivity – that is, if they were hepatitis B e antigen (HBeAg) positive or if neither HBeAg nor antibody to HBeAg (anti-HBe) was detected. Thereafter vaccination was recommended for all infants born to mothers who were HBsAg positive, irrespective of e antigen or antibody status⁴.

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Results

The local virology laboratory identified HBsAg in serum in 161 pregnancies from June 1986 to May 1995, a period during which 121 390 live and still births occurred in the district. This was equivalent to a rate of 1.33 positive results per 1000 live and still births.

Forty-eight (30%) positive results were excluded from the study, leaving 113 mother and infant pairs available for analysis. The commonest reason for exclusion was the inability to trace infant's case notes (31), followed by booking in another or unknown district (10), miscarriage, fetal death or still-birth (5), and removal to another district or country (2).

Sixty-one (54%) of the 113 mother and infant pairs were of south Asian (Indian, Pakistani, Bangladeshi) ethnic origin, 30 (27%) Chinese, 16 (14%) white, 2 (2%) black Caribbean, 1 (1%) black African, and 3 (3%) other.

Seventy infants fulfilled criteria for vaccination: 47 (67%) received all three doses of vaccine; 20 of them within an acceptable time scale (0 to 72 hours for first dose, 3 to 5 weeks for the second dose, and 20 to 24 weeks for the interval between second and third doses). Seven received two doses, 13 one, and three none. There was recorded evidence of contact tracing of immediate household and sexual contacts in 35 of the 113 cases (31%).

Discussion

This survey showed that not all infants at risk of hepatitis B were being vaccinated. It has provided a baseline level for Leicestershire, which may be reviewed later, in line with recommendations recently published³. Our results are comparable with those of a similar survey conducted in the West Midlands⁵, where 66% of infants completed three doses, 43% within an acceptable time scale. In both surveys it was clear that most infants at risk received the first dose of vaccine and that the main problem was to ensure that the second and third doses were given.

The local service has been improved as a result of

sharing the survey results with local clinicians and virologists. There is now a designated paediatrician for follow up of infants born to HBsAg positive women and a clinic nurse responsible for structured call and recall of patients in the follow up programme. The virology laboratory now sends the consultant in communicable disease control copies of all newly identified HBsAg positive results from the antenatal clinic. An antenatal midwife counsellor for HIV now includes counselling for hepatitis B and hepatitis C in her remit. Communication with general practitioners and other health professionals to ensure that both mother and immediate household/sexual contacts are followed up has been coordinated. Follow up of infants with incomplete vaccination histories identified by the survey has begun.

Acknowledgements

We thank the Virology department at Leicester Public Health Laboratory, hospital paediatric departments in Leicester hospitals. Jane Whitehouse, Janine Milligan, and the records departments of Leicester Royal Infirmary (LRI), Leicester General Hospital, and the LRI Children's Hospital.

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Hepatitis B vaccination for occupational risk: an audit in general practice

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Summary: *Surveys of hepatitis B vaccine coverage among patients at risk of infection in an urban practice in north west England in 1992 and 1998 showed that the proportion of patients ascertained to be at risk had increased from 4% (194) to 5% (258) and coverage (with a full course of hepatitis B vaccine, with or without confirmed immunity) from 46% to 78%. The contribution from occupational health departments was poorly documented, identifying a need for increased communication.*

Commun Dis Public Health 1999; **2**: 219-21.

Introduction

Hepatitis B vaccination has been available for over a decade and is probably the main reason for the fall

observed in occupationally acquired infection^{1,2}. General practitioners are in an ideal position to vaccinate their patients at risk since they maintain long

term records, are a recognised source of advice, and may be able to start vaccination before occupational training begins. They have been encouraged repeatedly to do so³.

We audited the hepatitis B vaccination programme in one general practice surgery to draw lessons for primary care and occupational health.

Method

Our practice cares for 8000 patients in urban South Lancashire. There is an annual turnover of between 7% and 8% of patients. In late 1998 the list included seven drug users being prescribed methadone. We examined our computerised data on hepatitis B vaccination in patients aged 16 to 64 (the main age group at occupational risk) in 1992 and 1998. In 1998 we also examined the full paper records of patients at risk of hepatitis B.

To identify unrecorded hepatitis risk we questioned 200 consecutive, patients aged 16 to 64 years who attended the surgery in April and May 1998.

Results

The results of the two surveys are shown in the table. There were 4926 patients aged 16 to 64 years in 1992 and 5258 in 1998. At the time of the 1998 survey, patients had received 649 doses of hepatitis B vaccine, three quarters of which had been given in this practice, a fifth (165) by occupational health departments, 3% (27) in a previous surgery, and 3% (23) in other or unknown settings.

Our survey of 200 consecutive attenders identified one new patient who needed to start a course of immunisation, which suggests that we knew of 91% (95% confidence interval: 77-100) of patients at risk.

Discussion

This audit provides a snapshot of an unending, major task. If our population is representative then about 5% of adults of working age need hepatitis B vaccination. Although the work is partially offset by vaccinations carried out by occupational health departments our records showed no correspondence from such departments, nor do we inform them in return. Perhaps sharing information would be worthwhile.

Our practice population was better protected in 1998 than in 1992, although the number known to be at risk had increased by 33%. We estimate that between 6% to 29% of people may be unprotected at

work: 6% had not completed a course of vaccination (despite all being reminded); we may not know about the potential exposure of a further 0% to 23%.

The doctors in the practice attributed the increased level of protection to greater awareness of the need; financial incentives were a weaker motivation. Although there were two distinct periods of data collection, we set standards informally by recognising the need to protect as many patients at risk as possible, rather than by setting explicit targets.

Vaccination against hepatitis B, like other adult vaccinations (such as rubella)⁴, requires continued vigilance and much effort in contacting defaulters, especially for serological testing. Indeed, the need for serological testing remains controversial and secondary to the achievement of high vaccine coverage since 'it is failure to vaccinate, not vaccine failure, that poses the greatest risk'⁵. Epidemiological data show that occupational protection against infection is now well established^{1,2}. It is therefore likely that our figures are representative, and that few people at high risk of infection are completely unprotected. Meanwhile people who inject or might inject drugs are the main group currently at risk^{5,6} and general practitioners should consider making them a priority.

Acknowledgements

We thank all the practice staff for their help and cooperation in running the hepatitis B programme and retrieving numerous records, and the general practitioners for permission to publish this audit.

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TABLE Patients of the practice recorded as being at risk of hepatitis B in 1992 and 1998 and their immunisation status

| Immunisation status | 1992 number (%) | 1998 number (%) |
|--|--------------------|--------------------|
| Serologically immune after vaccination | 48 (25) | 157 (61) |
| Primary vaccine complete but needing serology | 42 (22) | 44 (17) |
| Part way through a primary course of vaccination | 46 (23) | 15 (6) |
| Had some vaccinations but no longer at risk | - (-) | 9 (3) |
| Occupational health departments supervising immunisation | no record | 23 (9) |
| Serologically immune in past; booster now more than 1 year overdue | - (-) | 15 (6) |
| Persistent low immunity | - (-) | 3 (1) |
| At risk but vaccination status and/or immunity unknown | 58 (30) | 1 (0) |
| Total | 194 | 258 |

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Letters and corrections

Inadvertent use of time-expired yellow fever vaccine should be followed by revaccination

Editor: K W Allen and colleagues described what was perhaps the most timely way of managing a problem created by the inadvertent use of time-expired vaccine¹.

However, the authors failed to mention the best way to manage such an incident if time and patients allow – revaccination of the patients with in-date vaccine. The authors conceded that an antinflavivirus antibody test is not specific for immunity to yellow fever, and another weakness of their approach is that the antibody response to 17D vaccine takes about 10 days to appear and then can be poor so that revaccination would anyway be indicated. Strictly speaking, a neutralisation assay would be needed to demonstrate the presence of protective antibody. Furthermore, only immunisation with a satisfactory vaccine preparation can justify the issue and use of an International Certificate of

Vaccination.

While the authors may have dealt with the situation with which they were confronted in the way most convenient to the recipients of the out-dated vaccine, such circumstances demand a re-vaccination to guarantee protection against yellow fever, both for the individuals and for the communities that they visit.

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Authors' reply

Editor: Philip Mortimer states that revaccination with in-date vaccine represents an alternative strategy for managing such an incident. In practice, however, this would not have obviated the need for an early 'hands-on' response. Our recipients of time-expired yellow fever vaccine potentially fell into four categories:

- 1) people who had already travelled and returned, having potentially exposed themselves to yellow fever infection on the assumption that they were 'safe' through vaccination;
- 2) people abroad, who may have been exposing themselves to yellow fever infection, based on the same assumption;
- 3) people about to travel;
- 4) people due to travel at some time in the future.

The first step in managing the incident was to identify how many people fell into each category. Having

done this, people in categories 1 and 2 (the vast majority) required advice about seeking early medical attention for any febrile illnesses and about warning the attending physician about a theoretical risk of yellow fever. From the point of view of their recent holiday, it was already too late for revaccination. Mortimer also makes the point that the antibody response to 17D yellow fever vaccine takes about 10 days to develop; thus people in category 3 also might not have benefited from revaccination in terms of their immediate holiday plans, and the reinforcement of a 'bite-avoidance' message remained paramount.

We believe that most people in Doncaster who attend for yellow fever vaccination do so on the basis of planning 'one-off' expensive holidays to exotic destinations and that few are habitual travellers to the tropics. Thus for many people, revaccination would have been of theoretical benefit only and we suspect that many would have refused.

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Here comes *The Sun* – sensationalism and CDPH

Editor: I read volume 2 number 1 with great interest but the sensational quotations on the cover suggested that you were trying to attract *Sun* readers!

"it is feared that 446 000 infected animals entered the human food chain before control measures were introduced..."

Given the enormous transformation that the beef industry has had to undergo, the relatively few cases of variant Creutzfeldt-Jakob disease (vCJD) and their apparent stability over time, the

Advice to authors

Letters in response to articles in *Communicable Disease and Public Health* are welcome and should ideally be sent by email or on disk to the editor (shandysi@phls.nhs.uk). Letters should not exceed 400 words, cite no more than five references, and include no more than one table or figure. Please include the name and address of each author, and a telephone, fax, or email address for the corresponding author. Letters will be edited, and may be shortened.

relevance of the fact that 446 000 infected animals may have entered the food chain now seems limited since vCJD is likely to have a much shorter incubation period than classical CJD. With hindsight we can all throw bricks at the authorities for not having insisted on better monitoring and more efficient advertising at an earlier date but the system now seems to be running well. In public health and other terms, it would be interesting to calculate what the cost per life saved has been given that there are 10 to 12 cases of vCJD per year in the United Kingdom.

"Farm visits are popular, but the educational and entertainment benefits need to be balanced against potential

risks of zoonoses..."

This is the sort of statement that I would expect from a group visiting tropical Africa, where the likelihood of acquiring a serious zoonosis is far greater. I think that most children see too little of rural life already and are therefore ignorant of its value. Life in and visits to the country provide valuable opportunities to appreciate birth, life, development, and death as a complete cycle, now rarely observed by children with the decline of the extended family.

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Editor's reply

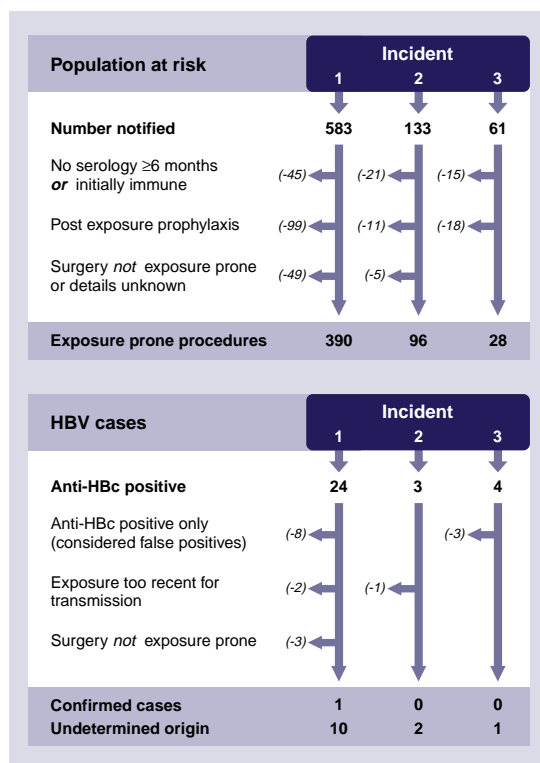
The quotes on the cover of Communicable Disease and Public Health are certainly intended to attract readers; what else they read is up to them! Numerous scholarly and popular publications compete for attention. The success of a new journal depends on its getting noticed. The brief statements from the papers inside, abbreviated titles, and subject headings used on the cover aim to catch the eye and enable the structure of the journal and the topics covered in a particular issue to be seen at a glance.

Stuart Handysides
Communicable Disease and Public Health

CORRECTIONS

SE Oliver, et al. Lessons from patient notification exercises following the identification of hepatitis B e antigen positive surgeons in an English health region. *Commun Dis Public Health* 1999; 2: 130-6 (June)

FIGURE 1 Establishing denominators and numerators for estimates of transmission risk



In table 2, the 'HBIG offered' row of the 'incident 3' column should have read 'Yes (from 0 to 2 weeks)', rather than 'months'.

In the 'HBV cases' section of figure 1 the row labelled 'exposure prone procedures' should have been labelled 'confirmed cases'. The corrected figure is reproduced to the right.

DS Tompkins, et al. A study of infectious intestinal disease in England: microbiological findings in cases and controls. *Commun Dis Public Health* 1999; 2: 108-13 (June)

TABLE 5 Frequency of multiple organisms in faecal specimens (percentage)

| Organisms identified | GP component cases (%) (n=2893) | Community cohort (%) cases (n=761) | Controls (%) (n=2819) | Total (%) (n=6473) |
|----------------------|---------------------------------|------------------------------------|-----------------------|--------------------|
| 0 | 1305 (45.1) | 480 (63.1) | 2296 (81.4) | 4081 (63.0) |
| 1 | 1261 (43.6) | 232 (30.5) | 478 (17.0) | 1971 (30.5) |
| 2 | 276 (9.5) | 48 (6.3) | 41 (1.5) | 365 (5.6) |
| 3 | 48 (1.7) | 1 (0.1) | 4 (0.1) | 53 (0.8) |
| 4 | 3 (0.1) | - | - | 3 (0.1) |

In table 5, row 3 of column 5 (headed **Total (%) (n=6473)**) should have read 365 (5.6) instead of 365 (5.6). The corrected table is reproduced.