

MFPHM SUBMISSION
THE EPIDEMIOLOGY OF ENCEPHALITIS

IN

ENGLAND AND WALES

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ABSTRACT

AIMS:

These were to describe the epidemiology of encephalitis and to examine the effect of measles vaccine and measles, mumps and rubella (MMR) vaccine and a number of viruses on the incidence of encephalitis.

METHOD:

Information from notifications, Public Health Laboratory data and the general practitioners' sentinel reporting system were used to describe encephalitis in terms of time, place and person, and in relation to certain viruses. An examination was also made of trends in encephalitis before and after the introduction of measles vaccine and measles, mumps and rubella (MMR) vaccine.

RESULTS:

The incidence of encephalitis appears to be decreasing but seasonal and secular trends in notification are difficult to interpret. Reductions in notified cases of encephalitis occur at approximately the same time as the introduction of vaccines but it is not possible to attribute any peaks of encephalitis notifications to reports of specific viruses.

CONCLUSION:

Much of the epidemiology described is speculative so the notification system is not fulfilling one of its objectives, therefore a new system of notification for encephalitis is proposed.

KEYWORDS

Encephalitis
Epidemiology
Measles
Mumps
Vaccination

INTRODUCTION

The control of communicable disease has long been an integral part of the function of public health medicine. Yet two major outbreaks of communicable disease occurred in the mid 1980s which resulted in public inquiries and the establishment of a committee (under the chairmanship of Sir Donald Acheson) to look into the functions of Public Health Medicine, then called Community Medicine ¹. The Acheson Committee published its report in 1988 and made many recommendations on the functions of Public Health Medicine including a strengthening of surveillance systems. It specifically mentioned the importance of the notification system and suggested that the list of notifiable diseases should be regularly reviewed.

The notification of encephalitis was chosen for review in this study for four main reasons:

- a) It is an important disease with considerable potential morbidity and mortality.
- b) A large number of cases of encephalitis are notified each year.
- c) Little is known about notifications of encephalitis, but there is sufficient variation in numbers from year to year which suggests changes in the epidemiology need to be interpreted.
- d) There have been two public health interventions that should have had an impact on the incidence of encephalitis; these were the introduction of measles vaccine and measles, mumps and rubella (MMR) vaccine.

Encephalitis notifications have been collected in their present form by the Office of Population Censuses and Surveys (OPCS) since 1950². They are divided into "infective" and "post-infectious categories" and are published by age, sex and district of origin. There are many causes of encephalitis but most notified cases are thought to be of viral origin even when a causative virus cannot be found.

The primary objective of this investigation was to examine how the notification system for encephalitis fulfills its epidemiological objectives generally. Because of the introduction of measles vaccine, and more recently, MMR vaccine, for diseases which number encephalitis amongst their complications, a more specific, subsidiary study of the effect of these vaccines was made. Laboratory data on the numbers of viruses and information from the Royal College of General Practitioners' (RCGP) sentinel reporting system were also used.

2. AIMS

The aims of this study were:

- (1) To describe the epidemiology of encephalitis in England and Wales by examining notification and mortality data on encephalitis, measles and mumps; public health laboratory data on viruses associated with encephalitis/meningitis; and RCGP sentinel data:
- (2) To study the effects of the following on the incidence of encephalitis:
 - (i) measles vaccine
 - (ii) MMR vaccine
 - (iii) certain viruses normally associated with meningitis and/or encephalitis

3. OBJECTIVES

The objectives of the study were:

- (1) To examine routine notifications of encephalitis in England and Wales for the period 1950-1990 in order to describe trends in time, place and person.
- (2) To analyse available mortality data for encephalitis, measles and measles encephalitis.
- (3) To assess changes in the epidemiology of encephalitis as reflected in patterns of notifications and, where possible, relate them to factors such as the use of measles vaccine and mumps vaccine (as a constituent of MMR), or known trends in reports of other viruses using laboratory reports and RCGP rates of illness between 1975 and 1990.
- (4) To propose improvements in the notification system for encephalitis if necessary.

4. BACKGROUND

4.1 ENCEPHALITIS

In its strict sense, 'encephalitis' means inflammation of the brain. In clinical practice, it is usually taken to mean a cerebral reaction to an invading agent which includes the presence of symptoms and/or signs of cerebral involvement. A wide range of clinical syndromes is covered from a mild illness with pyrexia and drowsiness to a fulminating process resulting in death. It is a disease of all age groups and its incidence is almost certainly greater than that suggested by notifications³.

4.1.1 Aetiology

Encephalitis has many causes. Within the International Classification of Diseases (ICD) 1975, there is an overall code for encephalitis with sub-codes given for the different causal agents (table 1)⁴. These include viruses such as herpes simplex and measles, the slow viruses (e.g. Jacob-Creutzfeld), arthropod born viruses, a number of other organisms and lead poisoning. The recent 1992 revision gives a similar classification. Encephalitis may also result from (and can be classified as) a post-infectious syndrome which may appear after infection with a wild virus such as measles or chickenpox. A post-immunization syndrome occasionally follows immunization with a live vaccine. In Britain and Northern Europe, most cases of encephalitis are thought to be viral, either because a viral cause has been identified or because other causes have been excluded^{3,5}. Studies of patients admitted to hospital with a diagnosis of encephalitis have shown that between 50% and 70% of cases had no evidence of viral infection^{3,5}. Such studies have also found that between 7%

4.1. Diagnosis

A diagnosis of encephalitis may usually be made by a combination of the clinical symptoms and signs, supported by lumbar puncture which should show increased protein and lymphocytes in the cerebro-spinal fluid. Further virological and pathological investigations can be conducted on brain biopsy material. In addition, virological examinations of faeces, cerebrospinal fluid and blood (antibodies) may indicate infection with a virus and hence indicate the cause of the encephalitis. For some encephalitides an electroencephalogram (EEG) can provide evidence of a generalized cerebral disorder even when only minor clinical abnormalities are present. Established herpes simplex encephalitis may cause a typically unique EEG pattern⁵. Computerised tomography (CT) scanning will show some abnormalities but these are not necessarily unique to encephalitis. For example, CT scanning of some patients with post-infectious encephalitis may show the presence of cerebral oedema.

The diagnosis of viral encephalitis is difficult to make, and should only be made after excluding disorders that might be amenable to treatment such as tuberculosis, cerebral abscesses, tumours and bacterial meningitis.⁷ In a study of 120 patients admitted to a Glasgow hospital with a diagnosis of acute encephalitis, nearly half proved to have some other illness such as cerebral abscess ' subdural haematoma etc.³ In addition, encephalitis may include some symptoms of meningitis and primary cases of meningitis may include symptoms of encephalitis. The disease, may be notified as a case of whichever is the primary diagnosis. Difficulties in diagnosis will be reflected by inaccuracies in notification.

4.1.3 Severity

It has been thought that, with the exception of herpes simplex encephalitis, viral infections of the central nervous system (other than the slow viruses and the arboviruses) were uniformly benign⁸. However, in 1990 and 1991, there were 51 and 43 deaths respectively attributed to encephalitis (ICD 323) in England and Wales, and many of these were of presumed viral origin. In a British study of forty-nine children who had had a serologically or microbiologically proven viral infection of the central nervous system as infants, one child had died during the initial illness, three survivors were severely disabled; and the remaining forty five children all attended normal schools, but had lower than average IQs, and slightly more behavioural problems than a control group⁹. A Scandinavian study of 191 adults admitted to hospital with acute encephalitis showed that only about 50% recovered fully (without detectable sequelae), about 22% were left with at least a moderate disability after the acute phase, and over 6% of the group died³. Although most of these studies include only cases of encephalitis severe enough to be admitted to hospital, they show that encephalitis can cause considerable morbidity, as well as mortality.

4.2 MEASLES AND ENCEPHALITIS

It has been suggested that though measles is the cause of troublesome morbidity for children and their families, the main reason for vaccination is the severe (though relatively rare) encephalitis that can occur¹⁰. Complications occur with measles in nearly 7% of all cases and neurological disturbances make up nearly 6% of these. Encephalitis or impaired consciousness has been reported in one of every 1000 cases of measles and a further case in every 1000 will have motor disturbances such as fits¹¹. Other surveys of neurological complications with measles have reported rates of 0.4 % in 1963 and 0.6 % in 1976¹². The rate of neurological complications does not appear to have decreased with the introduction of measles vaccination in 1968 which resulted in a decrease in the total number of cases.

In an American study of those who survived encephalitis associated with measles, 35 % had neurological sequelae at the time of discharge or several months after discharge. Follow-up 2-10 years after discharge showed 57% of these had sequelae, principally mental retardation or behavioural disturbance¹³. Some of the evidence indicates that older children and adults are more likely to have neurological complications with measles^{11,13}.

4.3 MUMPS AND ENCEPHALITIS

Central nervous involvement has been observed¹⁴ in up to 65% of cases of mumps. "Specific brain and spinal cord complications have been reported in up to five per 1000 cases." These CNS complications of mumps have been regarded as benign, a fact which may be true of mumps meningitis but not of mumps encephalitis. In a study of forty-one patients with mumps encephalitis treated in a paediatric department in Helsinki (age range 1.2-13.7 years), ten patients were left with clinical sequelae ranging from concentration difficulties to ataxia and impaired vision; one child who also had congenital toxoplasmosis, died¹⁴.

4.4 VACCINATION

Live measles vaccine has been available in this country since 1968, but uptake of the vaccine hovered at around 50% until the 1980s. The United States (US) has been immunising its population against measles since the early 1960s, and requires all children entering school to have evidence of vaccination. Between 1982 and 1983, 97% of children entering school in the US were shown to be vaccinated against measles. An assessment of 20 years of measles vaccination in the US found that the vaccine had prevented 52 million cases of measles, 5,200 deaths and 17,400 cases of mental retardation¹³. Outbreaks of measles in the US are now thought uncommon enough to be a subject for publication. In these outbreaks of measles in the US, primary vaccine failure, rather than waning of vaccine induced immunity, is thought to have been the main reason for the outbreaks^{15,16}. The United States employ a two dose schedule (15 months and school entry) to reduce the risk of primary vaccine failure.

Measles, mumps and rubella vaccine (MMR) was introduced in Finland in 1982 and the incidence of encephalitis has fallen considerably¹⁷. Since the introduction of MMR, the number of cases of encephalitis associated with the common diseases of childhood (e.g. measles, mumps), has reduced by a third and there has also been a decrease in the number of cases of encephalitis of unknown origin. This decrease in the number of encephalitides has not been accompanied by a decrease in the proportion of cases where the child is severely affected^{12,17}.

The present immunisation policy in England is vaccination with MMR vaccine for children aged between 12 and 15 months, and for all pre-school children who have not previously received it. A massive health education programme was launched with the introduction of MMR vaccine in 1988. In 1990/91, vaccination levels reached 87% (regional range 82-92%); there are however still pockets (particularly in inner city areas) where uptake is relatively low¹⁸.

4.5 NOTIFICATIONS

Doctors are required by law to notify the proper officer of the relevant local authority of all cases of a number of specified infections. Notifications for England and Wales are collated weekly by the Office of Population Censuses and Surveys (OPCS) and the information is published in weekly, quarterly and yearly monitors. A notification may then be categorised by OPCS into subtype depending on the organism, for example a notification of bacterial meningitis will be classified by the causative organism (e.g. meningococcal, pneumococcal or *haemophilus influenzae*). Statutory notification of certain infectious diseases started in 1922¹⁹, a system of surveillance that has the advantage of being nationwide so the information can be analyzed by district, borough, region or nationally. It also gives information on certain diseases over a number of years²⁰. A disadvantage of this system is that only a limited number of diseases are notifiable and clinicians must remember which these are in order to notify them. This may be one cause of under notification. Some diseases tend to cover rather broad diagnostic categories such as acute encephalitis and food poisoning. Because notifications are based on clinical diagnosis, the system is subject to inaccuracy, particularly where a diagnosis may be difficult to make such as with acute encephalitis. Measles has been notifiable since 1940 and mumps was made notifiable in 1988 following the introduction of measles, mumps and rubella vaccine.

Notification of communicable disease is important for a number of reasons:

- (i) Notification enables action to be taken to control the spread of infection. Legal enforcement of these measures is possible.
- (ii) Notification enables monitoring of trends in disease incidence locally and nationally. This may be useful to assess the need for preventive measures. It may also assist clinicians in making decisions about diagnosis and to assess the impact of preventive measures (e.g. measles vaccination), or to detect outbreaks in order to prevent or control them.

- (iii) Notifications allow us to study the epidemiological features and relative importance of different infections.

4.5.1 Notifications of encephalitis and meningitis

Notifications of the infections of the nervous system (apart from poliomyelitis) were initially made either as acute encephalitis lethargica or as cerebrospinal fever, which included the groups of disorders we now know as encephalitis and meningitis. Between 1940 and 1950 encephalitis was notifiable as acute encephalitis. Since 1950, acute encephalitis has been notifiable as acute infective encephalitis which includes all acute viral causes of encephalitis. Acute post-infectious encephalitis (cases of encephalitis which follow known viral illnesses such as measles and chickenpox) has also been notifiable separately since 1950. No further classification of encephalitis is made once notifications are received.

Between 1950 and 1982, notifications of meningitis have been classified into the following categories: meningococcal meningitis; other causes of meningitis; and meningitis of unspecified origin. In 1982, this classification system changed and meningitis notifications are now classified under the following headings:

- i) meningococcal meningitis
- ii) pneumococcal meningitis
- iii) *Haemophilus influenzae* meningitis
- iv) viral meningitis
- v) other, specified causes of meningitis
- vi) Unified causes of meningitis

In addition, meningococcal disease, without meningitis, is notifiable as a 'separate category.

4.6 **OTHER SOURCES OF DATA ON ENCEPHALITIS**

4.6.1 Laboratory Reports

Public Health Laboratories and most NHS (and some private) microbiological laboratories in England and Wales report all viral infections to the Communicable Disease Surveillance Centre (CDSC). The results are collated and published in the Communicable Disease Report (CDR). Reporting laboratories do not usually have a defined catchment population and the geographical distribution of reports is based on the location of reporting laboratories and not the district of residence of the patient. In addition, investigating habits of doctors vary from place to place and over time²⁰. The laboratory reporting system provides useful epidemiological information on diseases where a diagnostic test is usually performed, but it is less useful for diseases such as measles or chickenpox. On the whole, however, laboratory data have been found to be consistent over time and add an important qualitative aspect (e.g. type, subtype of virus) to other sources of information²⁰.

4.6.2 General Practitioner Data

The Royal College of General Practitioners have had a clinical reporting system in operation since 1966. Currently, between 35 and 40 practices report on the diagnoses made within their practices each week. Information on age and sex is also available to determine rates. The practices participate on a voluntary basis and the population covered is not necessarily representative of the whole country (the sample is small and not random). However, data are provided on clinical diagnoses, and information on infectious diseases which may not require laboratory confirmation can be obtained. The

system is particularly useful for rates of non-notifiable disease such as sinusitis, influenza and the common cold.

The main advantages are that, in most areas, a high proportion of the population is registered with a general practice so that reporting rates are provided, and that the information includes non-serious illness.

5. METHOD

Notifications of infectious diseases are collated weekly and reports are published weekly, quarterly and yearly in MB2 monitors by OPCS. An examination of available data on encephalitis notifications was made using the quarterly and yearly monitors. Information in the annual monitors is available by age, sex and place (region) of notification. Quarterly monitors give numbers of notifications by district of residence. Between 1950 and 1981, this data was divided into infective and postinfectious encephalitides. From 1982, annual totals of acute encephalitis notifications were published.

Quarterly and annual MB2 monitors also contain data from the Public Health Laboratory Service (PHLS) on the total number of reports of certain viruses. Data on echoviruses are divided into subtypes if the subtypes are reported in greater numbers than usual. Viruses particularly associated with meningitis and/or encephalitis are reported in a separate section. In addition, monitors contain rates of incidence of a number of infectious diseases from the Royal College of General Practitioners' reporting system. These and PHLS reports were used to look at the epidemiology of mumps virus as mumps has been notifiable only from September 1988.

Vaccination uptake rates were obtained from the Department of Health, who collate Komer Returns on vaccination and immunisation. An attempt was made to correlate measles notifications and uptake of vaccine with encephalitis notifications. Where possible, information was analysed in terms of time, place and person. In some instances ages were examined in three age bands, 0-4 years, 5-14 years and over 15 years, because the age bands used in OPCS monitors changed in the mid-1970s. The age bands displayed are not strictly comparable because each group comprises a different number of years, but they do allow a comparison of the disease in children and adults.

Data from OPCS mortality monitors were used to examine deaths from encephalitis and from measles encephalitis.

Where necessary, data was statistically analysed using the "Confidence Interval Analysis" package by Gardner and Altinan. Specifically, Pearsons Correlation test, and the Z test to detect differences between two proportions were used.

6. RESULTS

6.1 ENCEPHALITIS NOTIFICATIONS

From 1922 to 1940, encephalitis and meningitis were notified as cerebrospinal fever. Some notifications of acute encephalitis were included in the category of acute encephalitis lethargica. The categories of acute infective and acute post-infectious encephalitis and meningococcal meningitis were introduced in 1950. This report examines mainly the notifications from 1950 to 1990.

6. 1.1 Time

The annual number of encephalitis notifications were plotted over time (figure 1) and show some variability from year to year. Notification rates for encephalitis over time show a similar picture. In 1940, when the rubrics changed from cerebrospinal fever to encephalitis, a rapid decrease in notification occurred until 1949. Numbers increased to more than 300 cases a year from 1950 and remained fairly steady at about 250-350/year until about 1965. Since then, there has been a steadily diminishing number of cases notified annually to 1990, although there have been numerous peaks and troughs, notably in 1963-65, 1969-71, 1977-79 and, most recently, in 1987-88.

The trend in the two categories of notifiable encephalitides, infective and postinfectious, show that for the first 10 years, 1950-59, substantially more infective cases than post-infectious were notified (figure 2). From 1960 onwards, the numbers of each of these types of notification became similar. Although the numbers of each did not differ greatly after this, the peaks and troughs rarely coincided; 1978 was the only year when minor peaks occurred at the same time. The decline for both categories started in 1958 with a sharp fall between 1969 and 1972. From 1988, there are fewer annual post-infectious than infective notifications.

The seasonal distribution of notifications shows peaks for both infective and postinfectious encephalitis (figure 3). For post-infectious encephalitis, first or second quarter peaks are apparent between 1980 and 1987 (except 1985); for infective encephalitis, third quarter peaks are seen each year until 1984. From the beginning of 1989, the number of post-infectious notifications per quarter is markedly lower than infective notifications. Previously, any large difference in numbers of notifications did not last beyond one quarter.

6.1.2 **Persons affected**

6.1.2.a **Sex**

The sex distribution of encephalitis notifications (figure 4), consistently shows more reports of disease in males than females until the 1980s when the differences became less consistent. These differences are also apparent in the infective and the post-infectious syndromes (figure 5), differences became marked during peaks of post-infectious notifications (1963, 1966, 1969, 1972 and 1978).

6.1.2. b **Age**

From 1982, data on the age distribution of cases of encephalitis notifications were no longer published by separate category (infective and post-infectious). Between 1950 and 1981 the pattern appears relatively consistent throughout the years, with the highest proportion of cases in the age band, 15 years and over, for infective encephalitis; and most cases of post-infectious encephalitis occurring in the 5-14 year group (figures 6,7, appendix A, tables 1-5,). The proportion of cases in each age group varies with time.

Detailed age distributions for encephalitis are available from 1974. The total age distribution is shown for the years 1974-1980 (figure 8) and separately for 1978 when there was a large peak in notifications (figure 9). Again, the age bands are not all strictly comparable because each comprises a different number of years. From 1974 to 1980 a third of notifications were in the 25 and over age band for infective encephalitis. Most cases however occurred in children under 10 (nearly 45%). For post-infectious encephalitis, most notifications fall into the 0-4 or the 5-9 year bands. In 1978, a similar picture was seen for all encephalitides except for a few minor differences. These were:

- (i) For infective encephalitis, an increase in the proportion in the 5-9 year band and a decrease in the proportion aged 15 to 24, and 25 and over.
- (ii) For post-infectious encephalitis, an increase in the 5-9 year band and a reduction in the proportion aged 0-4 years, 15-24 years, and 25 and over.

6.1.3 **Place**

An examination of rates of encephalitis notifications was made by Regional Health Authority between 1975 and 1989 (table 2). Rates per million varied between zero and seven during this time. Yorkshire and Mersey Region had relatively high rates until 1985 when they declined. Wales had high rates until 1980, and low rates from 1981; North West Thames rates were high until 1978, moderately high between 1979 and 1983 and then low. North Western Region showed the least variability, and Northern Region, Trent, East Anglia, Wessex, Oxford, the West Midlands and South Western Region show wide variation from year to year.

A more detailed examination was made of the place of encephalitis notifications for 1978 and 1988 when peaks of notifications occurred.

6.1.3.a **1978**

Rates for the larger 1978 peak vary from 1.09 (Trent) to 6.44 (North West Thames). Increased rates for this year were observed in Northern Region (5.16), North West Thames (6.44), East Anglia (5.0), South East Thames (3.6) and Mersey Region (6.0). During the 1978 peak, the biggest number of notifications came from North West Thames (29) of which 17 were infective encephalitis and 12 were post-infectious encephalitis; Northern Region (9 infective and 7 post infectious); and Mersey (11 infective and 4 post-infectious). The age distribution during this year showed the greatest proportion of notifications were in the 0-9 year age bands. In this year, there were more than twice as many males as females in the post-infectious category (total 69) and 13 more males than females in the infective group (total 85).

6.1.3.b **1988**

Investigation of the further, smaller peak in 1988, revealed that the biggest number (and rate) of notifications came from Trent Region, particularly from the districts of Rotherham and Sheffield. Almost equal numbers of males and females, mainly in the 25 years and over age band, made up this peak.

6.1.4 **Encephalitis Deaths**

Deaths from encephalitis (ICD code 323) show a decline from 1963 (figure 10). Compared with encephalitis notifications (which fell from about 1965), it can be seen that the fall is most marked from 1972 onwards. These deaths may include deaths from causes other than those notified as infective and post-infectious encephalitis.

6.2 **MEASLES**

An examination of measles notifications shows the well recognised two yearly pattern of peaks and troughs, until 1968 (figure 11). The annual number of measles notifications and measles deaths fell sharply in 1968 when measles vaccine was introduced although deaths from measles had started to decline even earlier (figure 12). Over recent years, the downward trend in measles deaths has continued, though there continues to be at least one or two deaths a year from measles encephalitis (figure 13). A small peak can be seen in 1988 in deaths from measles and measles encephalitis.

6.2.1 **Measles and Encephalitis**

Notification rates for measles show second quarter peaks for measles (figure 14) which coincide with peaks of post-infectious encephalitis notifications during the 1980s (figure 3). A statistically significant correlation ($r^2=0.75$, $p \leq 0.05$, $CL=0.56$ to 0.86) was found to exist between notifications of measles and notifications of encephalitis prior to the introduction of MMR vaccine in 1988 (figure 15).

6.2.2 Effect of Vaccination

Measles vaccine was introduced in England and Wales in 1968 and uptake remained at around 50% until 1980 when it started to increase (figure 16). A negative correlation between measles vaccine uptake and encephalitis notifications (figure 15) was found to be statistically significant ($r^2=-0.71$, $p \leq 0.05$, $CL=-0.88$ to -0.39) prior to the introduction of MMR vaccine. The

6.3 MUMPS

Mumps has only been notifiable since September 1988, so rates of illness based on laboratory reports and RCGP rates in the 1980s were examined (figure 22). Estimates of the incidence of mumps using these sources appear to coincide fairly well. Quarterly laboratory reports of mumps virus (figure 23) show the well recognised three yearly peaks (usually second to third quarter).²⁰ A significant positive correlation ($r^2= 0.73$, $p \leq 0.05$, $CL = 0.37$ to 0.90) between mumps virus reports and encephalitis notifications is observed (figure 24).

6.3.1 Age Distribution of Mumps Notifications

All mumps notifications were combined for 1989 and 1990 and the age distribution calculated (figure 25). Nearly 40% of notifications fell into the 5-9 year band with a further 40% in the 0-4 year age group.

6.4 OTHER VIRUSES

Laboratory reports of other viruses Echovirus, Herpes Zoster and Coxsackie associated with meningitis and/or encephalitis were examined over time (figures 26-28). Some of the encephalitis peaks coincided with Echovirus peaks, particularly in 1975, 1978, 1980 and 1988 (figure 26). Reports of Echovirus II peaked in 1978 and this may have been connected with the peak in encephalitis notifications that year (figure 27). Reports of Coxsackie B also peak in some years when encephalitis notifications peak such as 1978 and 1988 (Figure 28).

6.4.1 Echovirus II

During 1978, a peak in encephalitis notifications was observed which may have been linked to an outbreak of Echovirus type 11, in England and Wales.²¹

The Echovirus 11 outbreak showed a third quarter peak in 1978, as did notifications of infective encephalitis (figure 3) so the place and age distributions of cases of Echovirus 11 infection were compared with the place and ages of notified cases of encephalitis in 1978.

Infection with Echovirus 11 was widespread but greatest numbers were reported from Northern Region, North-Western and South-Western Region.²¹ So severe was this outbreak that 11 reports of neonatal deaths were attributed to it in the first three quarters of the year though less than 5 % of reported Echo 11 infections were in this age group²¹. The specific clinical manifestations most often reported were meningitis and encephalitis.

Our results showed that most of the encephalitis notifications for that year came from North West Thames, Mersey and Northern Region. The age distribution of encephalitis notifications for 1978 varied only slightly from the "norm" (as judged by the combined years 1974-1980).

Table 4 shows a comparison of the age distributions for Echovirus 11 and encephalitis notifications in 1978.

Table 4

Age Distribution of Echovirus11 and Encephalitis Notifications in 1978

| Age Band | Echovirus 11 | Encephalitis | |
|----------|--------------|--------------|-----------------|
| | | Infective | Post-infectious |
| 0-4 | 48% | 23% | 23% |
| 5-9 | 14% | 27% | 49% |
| 10-14 | 8% | 14% | 12% |
| 15+ | 24% | 36% | 15% |
| NK | 5% | 0% | 0% |
| Total | 100% | 100% | 100% |

6.5 SUMMARY OF RESULTS

1. Encephalitis may be notified as infective or post-infectious encephalitis; the incidence of both these categories appears to be decreasing.
2. The annual number of notifications in each category varies with peaks and troughs that rarely coincide.
3. Seasonal and secular patterns for both types of encephalitis are difficult to interpret.
4. More males than females are notified as having encephalitis. This difference is more marked for post-infectious encephalitis.
5. For both categories most notifications were in the under 10 years groups. However, within the age bands displayed, the greatest proportion of infective cases were in the 25 and over group and the largest proportion of postinfectious cases were in the 5-9 year band.
6. A decrease in notifications of measles occurred immediately after the introduction of vaccine which also almost coincides with a reduction in encephalitis notifications. There is a significant negative correlation between measles vaccine uptake and the number of encephalitis notifications and a significantly positive correlation between notifications of measles and of encephalitis prior to 1988.

7. Following the introduction of measles vaccine, there was a significant decline in the proportion of 5-9 year olds who were notified as having measles. The proportion of cases with post-infectious encephalitis, aged 5-14 years, also decreased but this was not a statistically significant change.
8. There is a significant positive correlation between numbers of laboratory reports of mumps virus and of encephalitis notifications.
9. It is difficult to attribute peaks of encephalitis notifications to any peak of reports of specific viruses.

7. DISCUSSION

7.1 ENCEPHALITIS

7.1.1 TIME

7.1.1.a Overall Time Trends

From the results it appears that the incidence of encephalitis has decreased considerably over the last forty years. This may be for a number of reasons; these include:

- i) the true incidence of this group of diseases has changed, reflected in a fall in the number of notifications through the years.
- ii) the incidence has not changed, but fewer cases are being notified. This may be something to do with the notification system itself or because the nature of the disease is changing, for example, cases may be getting milder and therefore notification is less likely; or doctors do not think it worth notifying
- iii) diagnostic techniques have improved so much that those cases thought to have been viral encephalitis, unconfirmed by serological evidence, can now be classified as some other illness.

In a Scottish study of 120 patients admitted to hospital suspected of having viral encephalitis in the late 1960s, nearly 50% proved to have some other illness⁷. Of the 68 cases in whom a diagnosis of encephalitis was made, 70%(48) were really 'presumptive viral encephalitis' and only the remaining 30% (20) had positive pathological or virological findings. Herpes simplex encephalitis was the confirmed cause in 12 out of the 20 (60%) confirmed cases. In a later study of 60 patients admitted to a London hospital with a diagnosis of viral encephalitis over a fifteen year period (1962-78), 32% were thought to have encephalitis following a viral illness (post-infectious), 20% had a known viral infection and 48% were thought to have an acute viral infection of undetermined type (presumptive viral encephalitis).⁵ The smaller percentage of patients with a diagnosis of presumptive viral encephalitis may be related to improvements in diagnostic techniques or there may be bias due to variation in hospital admission practices. It may also show geographically different diagnostic fashions. However, there is no doubt that even today, viral encephalitis can still be a difficult diagnosis to make and many cases may be so mild that they escape detection.

In addition to diagnostic difficulties, notification is probably hampered by doctors forgetting to complete forms, ignorance that notification is required or their personal views on the value of the notification system.²²

All these factors must call into question the accuracy and completeness of notifications of encephalitis. Any one, or combination, of these factors may account for the apparent change in incidence. However, it may be reasonable to assume that there is some consistency to difficulties in diagnosis (particularly on a national scale) and to incomplete notification, i.e. doctors who notify will continue to do so and those that do not will continue not to. In view of this, it seems reasonable to conclude that the incidence of encephalitis has decreased as suggested by our findings.

7. 1. I.b **Trends in Infective and Post-infectious Encephalitis**

As already stated, encephalitis falls into infective and post-infectious categories and notifications of both have fallen over the years. Wide variation is seen in the early years (1950s) of notification, possibly because the new classification was 'finding its feet'. During the 1960s, there were similar numbers in both groups with a decrease in all notifications in 1970. This raises the suspicion that doctors may not be notifying in the "correct" category. Classification may be random giving an equal distribution into both groups. In the London Hospital study, 32% of cases were thought to be post-infectious^{6,7} and the Scottish and Finnish studies did not differentiate any post-infectious cases. These studies suggest that post-infectious encephalitis syndromes are much less common or much less severe than infective ones. It has also been suggested in the literature that the viruses associated with post-infectious syndromes (measles, mumps, rubella, etc) are less likely to cause severe illness,¹⁴ and because milder cases of encephalitis may not be hospitalised (and are also less likely to be notified) the epidemiological picture of post-infectious encephalitis may be less complete than that of infective encephalitis.

7.1.1.c **Trends by Season**

Seasonal variations tell us little about the aetiology of encephalitis. With many viral diseases it is possible to get a clear seasonal pattern; measles for example, had a biennial cycle and mumps a triennial one. Examination of the seasonal distribution of meningococcal meningitis shows first quarter peaks. This investigation shows that though notifications of both post-infectious and infective encephalitis have varied considerably over time, a pattern is not distinguishable. What is apparent though, is that since the introduction of the MMR vaccine in September 1988, the number of post-infectious cases of encephalitis has fallen markedly below the number of infective encephalitis notifications. The incidence of encephalitis in each season is probably subject to the organisms prevalent at the time, e.g. measles or mumps virus, Echovirus or Coxsackie B virus, though it is difficult to show a relationship between peaks of notifications of encephalitis and outbreaks of specific organisms. Vaccination may have an effect on previously apparent seasonal changes. This is clearly seen by the loss of the biennial cycles of measles outbreaks following mass vaccination.¹⁷ (In some other instances, such as whooping cough, periodicity is not lost, but the size of outbreaks may be reduced).

7.1.2 **PERSON**

7.1.2.a **Sex**

When examining the distribution of disease by person, incomplete data may give a biased perspective. However, it is interesting to note that there are consistently more males than females notified as having encephalitis (figure 4). A Finnish study of the effects of MMR vaccine on the pattern of encephalitis in children showed that of 312 children with a known cause of encephalitis admitted to the Children's Hospital in Helsinki, 42% were female and 58% male." in these admissions, the annual incidence of encephalitis was greater for males than females for seventeen of the twenty years studied. Where viruses were identified, mumps, varicella, herpes and enterovirus infections were more common in boys than girls. *Mycoplasma pneumoniae* and adenoviruses tended to affect girls. The

incidence of measles was the same in both sexes. In other studies, also from Finland, mumps encephalitis was found to affect males four times more frequently than females¹⁴. The effects of immunisation may have reduced the sex differences in encephalitis notifications in England and Wales which are not quite so apparent in the 1980s (figure 4).

7.1.2.b **Age**

The exact proportion of cases in age groups has been shown to vary over time (figures 6 and 7). This may represent outbreaks of different organisms causing encephalitis (and thus the susceptibility of different age groups), or it may represent variation (inaccuracies or incompleteness) in notifying disease. Most cases of post-infectious encephalitis fell into the 5-9 age group as expected. The infective encephalitis category showed the greatest proportion of notifications in the 25 and over group, with a fairly large proportion in the 5-9 age group. It is difficult to be certain if this is a true representation of the age distribution of each category because no validation of encephalitis notifications is available. Several factors may influence the age distribution.

- (i) There may be variation in the age distribution between encephalitis notification in the community and patients admitted to hospital with encephalitis. In addition, the notification habits of hospital doctors may be different to those of general practitioners and this may bias notification data. There is some evidence which suggests that general practitioners are better informed of their statutory requirements with regard to notifications.^{23,24}
- (ii) Most encephalitides associated with childhood exanthema (measles, chickenpox, mumps etc), will be classified as post-infectious encephalitis but some of these may really be infective cases. This is because clinicians may not distinguish 'encephalitic type' symptoms that occur in the acute phase of the illness from true post-infectious encephalitis.

In the Helsinki study, nearly 45% of children admitted with encephalitis were under five years and 13% (of total childhood admissions for encephalitis) fell into the 1-2 year age band.¹⁷ Of measles cases complicated by encephalitis or impaired consciousness, the rate was highest for the 15-19 year age band (5.3/1000 cases measles).¹¹ It was 3.8 in the 10-14 year group and 1.3 for children aged 1-2 years. The lowest rates were for children aged 3-9 years and those under 11 months.

The results of this investigation are inconsistent with these Scandinavian studies which have suggested that a greater proportion of notifications of postinfectious encephalitis associated with measles should be expected in the older children and young adults, and in the very young, but not in the 5-9 group. The reason for this is unclear. There is no firm evidence to support the hypothesis that clinicians are incorrectly reporting encephalitis associated with children's diseases in the post-infectious category, but it is possible, as already suggested, that some encephalitides in children that are truly infective may have been reported in the post-infectious category. Differences in age distribution may be because most published studies relate to hospital admissions, and notifications relate to all notified cases of encephalitis in England and Wales. They may indicate that cases of encephalitis are more likely to be admitted to hospital if they occur in the very young or if they are adults. Although it is difficult to be certain, it may be that encephalitis causes more severe illness in the very young and older age groups.

7.1.3 **PLACE**

Although notifications are published by district and region, the numbers per year are usually small, hence even large variations in rates are not significant. Because of this, few deductions can be made about regional trends. One might suspect that encephalitis in AIDS patients in recent years might be recorded within the infective encephalitis group resulting in an increase in notification in this group. However, the most recent peak of

notifications in 1988 (figure 1), though in young adults, came from Trent Region (not London as might be expected) and included equal numbers of males and females.

No attempt was made to correlate notifications by place with laboratory reports but this is a possibility for further study. Areas with good notification habits may have poor laboratory back up (for viral diagnosis) and vice versa.

7.2 **MEASLES AND ENCEPHALITIS**

Our results strongly suggest a link between encephalitis notifications and measles because notified cases of encephalitis started to fall shortly after the introduction of measles vaccine, and there is a significant positive correlation between notifications of measles and encephalitis and a significant negative correlation between uptake of measles vaccine and notifications of encephalitis.

If the rate of measles encephalitis is approximately 1 per 1000 cases of measles,¹¹ it might be assumed that 600,000 notified cases of measles would result in 600 notified cases of encephalitis. This has clearly never been the case (figure 1). It seems likely that once measles has been notified, doctors are unlikely to re-notify the illness as encephalitis even if encephalitic symptoms appear. This is obviously one possible source of error in the notification system. By the time measles, mumps and rubella vaccine (MMR) was introduced in 1988, numbers of encephalitis notifications had already fallen to quite low levels, though there does appear to have been a further fall around that time (figure 1). In general, peaks of measles and encephalitis notifications and deaths coincide (figures 11- 13) suggesting that at least some of the morbidity and mortality from notified encephalitis is caused by measles virus. Vaccination against measles appears to have reduced encephalitis notifications, measles notifications, measles deaths and (to a certain level) measles encephalitis deaths. Even when the vaccination uptake rate of measles was not high, a partial immunity provided by immunised people may have resulted in a fall in the incidence of encephalitis (herd immunity). This seems likely to account for the observed fall in encephalitis notifications from 1970 as measles vaccination uptake was only between 30% and the early 1970s (figures 11 and 15). The results of this study show a 75% fall in measles notifications when vaccination rates were only about 50%.

The complication rate of measles has not decreased following the introduction of measles vaccine,¹² only the total number of cases. The Helsinki study found that MMR vaccine resulted in a decrease in the number of encephalitides but not in a decrease in the proportion of severe cases or the proportion associated with measles.¹⁷ It is therefore necessary to continue to be vigilant about neurological involvement in any cases of measles.

Complete eradication of measles may cause further decreases in deaths from measles and from encephalitis. However in the US, where measles vaccine uptake is very high, eradication of measles has not yet been possible, so even higher levels of vaccination in the UK than those achieved at present may not eradicate measles. In the US, a 90% reduction in the incidence of measles was achieved by 1968, but resources were then shifted to rubella control activities.¹³ The mid 1970s saw a resurgence of measles caused by an accumulation of unvaccinated individuals as well as inadequately vaccinated people (those receiving vaccine before 1st birthday). This experience highlights the importance of continuing surveillance of measles (and encephalitis) and directing resources towards ensuring that high levels of measles vaccine uptake are maintained.

The introduction of measles vaccine does appear to have significantly changed the age groups that get the disease though percentage changes in each age band pre and post measles vaccination are not great. This is in keeping with the findings of other authors.²⁵ Some authors believe that, because older age groups may not have measles immunity, measles is something of a "time bomb" waiting to happen in older, susceptible adults.¹⁰ The age distribution pre and post

vaccination does not suggest this for measles vaccine which started in 1968 (figure 17) or MMR vaccine which started in 1988 (figure 20). The increase in 1989 and 1990 in the proportion of very young children getting measles may be because this group is in the pre-vaccination age (under 15 months).

7.3 **MUMPS**

It may be too early to be certain of effects of MMR vaccine on encephalitis associated with mumps in England and Wales because no notification data on mumps are available prior to 1988 and mumps virus has an unusual three yearly cycle with peaks occurring every spring (second quarter). However, the degree of similarity in the pattern of laboratory reports of mumps virus and in RCGP rates of illness indicate that these do provide a reasonably accurate estimate of the incidence of mumps. These sources suggest that the annual incidence of mumps has fallen quite dramatically. Although the number of encephalitis notifications also fell over the period following the introduction of MMR vaccine, it is difficult to say if this was the effect of immunity to measles or immunity to mumps or a combination of the two.

Mumps is more likely to cause viral meningitis than encephalitis so the introduction of MMR vaccine would be expected to have less of an effect of viral encephalitis than on viral meningitis.

7.4 **OTHER VIRUSES**

Many viral infections show a periodicity which can be used to predict changes in incidence. Some infections show no seasonal variation and herpes simplex virus is typical of this sort of organism. Most cases of severe encephalitis in adults where the organism is known are caused by herpes simplex virus.³ This may be why encephalitis notifications show no clear seasonal trends.

It might be hypothesised that Echovirus 11 was responsible for the 1978 increase in encephalitis notifications but given the differing age distribution of cases (table 4), the geographical variation and the fact that other viruses may have contributed to the encephalitis peak it is difficult to draw firm conclusions.

It is unlikely that with the present notification system we can really ascribe any increase in encephalitis notifications to particular outbreaks of viral disease. Good epidemiological information is easier to obtain with cases of more easily diagnosed diseases such as bacterial meningitis (which is also of greater incidence). However, there are even problems in using notifications to study the epidemiology of meningococcal meningitis. A study in the 1970s showed that only half of meningococcal infections discharged from hospital were notified and Goldacre and Miller had similar findings for all bacterial meningitides investigated.²¹

8. **CONCLUSION & RECOMMENDATIONS**

Much of the epidemiology of encephalitis described in this paper is speculative for the following reasons:

- (i) the term 'encephalitis' covers many disorders.
- (ii) the severity of encephalitis varies and milder cases may not be notified.
- (iii) the diagnosis of encephalitis can be difficult to make.

- (iv) cases of measles encephalitis or mumps encephalitis may be notified as measles or mumps and doctors may not feel it necessary to re-notify when encephalitis occurs.
- (v) it is difficult to identify the effect of measles vaccine or MMR vaccine on encephalitis notifications because so many viral illnesses can cause encephalitis and any effects on the incidence may be caused by more than one virus.

Despite these factors, the incidence of encephalitis does appear to have fallen over the last forty years, and it seems likely that the vaccines have had an effect on encephalitis notifications. Trends examined nationally as well as locally (by region) have proved very difficult to interpret.

The obvious conclusion reached is that the notification system for encephalitis, in its present form, is uninformative.

There are three possible options for the present notification system for encephalitis:

- (1) The status quo
- (2) Deletion of encephalitis from the list of notifiable diseases
- (3) Change the method of notifying encephalitis

The findings of this study suggest that (1) is a poor option because of the difficulties in describing the epidemiology of encephalitis. A change in the system is required because trends are difficult to interpret and all doctors may not be aware that encephalitis is a notifiable disease. It has been particularly difficult to find consistent differences (apart from age distributions) between infective and post-infectious encephalitis.

However, the encephalitides are still important diseases (in terms of health of the public). Specifically, it is useful to have information on the types of organisms that are responsible for encephalitis, encephalitides caused by organisms for which vaccines exist, vaccine-induced encephalitis, the slow viruses and encephalitis associated with human immunodeficiency virus (HIV). Some of the epidemiological information required for this may be obtained from other sources such as the Public Health Laboratory Service and the Royal College of General Practitioners sentinel system but neither of these is likely to be as complete as the notification system for the following reasons:

- a) The RCGP system is not helpful for relatively rare disorders (as some types of encephalitis are).
- b) The laboratory system relies on samples sent for testing, but not all diagnosed cases of encephalitis will have laboratory tests.
- c) Clinicians may not complete diagnostic details on forms requesting virological tests so the association with encephalitis may not be made.
- d) The geographical interpretation of trends may be inaccurate because laboratory sites may not relate to district of residence of patients.
- e) Because many patients admitted to hospital with encephalitis may not have a detectable virological cause, cases of encephalitis may not be notified in other reporting systems.

Therefore, option (2), though preferable to (1), may not be the best way forward as these other systems cannot provide the required epidemiological information. Therefore deleting encephalitis from the notification list means losing the chance to collect this data.

It is suggested that encephalitis, although widely recognised as a diagnosis, should be regarded more as a symptom of disease, as meningism may be a symptom of meningitis or influenza, rather than a notifiable disease in its own right. To improve the system, notifications should include the causative organism. Because clinicians may have difficulty in judging whether encephalitis associated with an illness of childhood is a complication of the disease itself or the post-infectious syndrome, perhaps this distinction should no longer be made. The results of this study lead to the proposal that a new system of recording is instituted to overcome problems of classification and to give better information on the cause of encephalitis.

The following recommendations relating to encephalitis notification are made:

- 1. For purposes of notification, the terms infective and post-infectious encephalitis should be abandoned, and replaced by the simple term 'infectious' encephalitis. When notifying, doctors should be encouraged to classify infectious encephalitis as follows:**
 - i) encephalitis caused by herpes simplex infection**
 - ii) vaccine induced encephalitis**
 - iii) encephalitis caused by childhood exanthema**
 - measles**
 - mumps**
 - rubella**
 - chicken pox**
 - others**
 - iv) encephalitis caused by arthropod borne viruses**
 - v) encephalitis associated with HIV infection, organism specified**
 - vi) encephalitis caused by other organism, specified**
 - vii) encephalitis caused by an unspecified or unknown organism**
- 2. It is recommended that there is better education of clinicians on which diseases are notifiable, particularly where diseases are relatively rare such as encephalitis. Public Health Medicine may play a key role in this task.**
- 3. It is important to continue to support preventive programmes for communicable disease despite quite high level of vaccine uptake in some areas.**

9. OUTCOME AND LESSONS LEARNT

9.1 OUTCOMES

There are two major outcomes of this study:

- (i) A report on the findings of this study will be submitted to OPCS with the recommendation that the notification system for encephalitis is changed.
- (ii) It is essential for any changes in the reporting system to be accompanied by increased awareness amongst doctors that encephalitis is a notifiable illness.

9.2 LESSONS LEARNT & FUTURE RESEARCH

The most important lesson learnt was that routine data may have considerable limitations. Many problems with the notification system became apparent during the course of this study and foremost of these was the difficulty in validating the data. We cannot be certain that...,' cases of encephalitis are notified and secondly, that they are classified in the correct category.

To properly validate the notification system, it is necessary to know the proportion of cases of encephalitis that are not notified and the overall incidence of encephalitis. This can only be done undertaking a special study. Further studies of patients admitted to hospital with a diagnosis of encephalitis may be useful, but they will only provide information on cases admitted, whereas the incidence in the community is important to ascertain. The epidemiology of encephalitis may further change as vaccine uptake improves and changes in the treatment of encephalitis (e.g. use of acyclovir for herpes simplex) have an effect on mortality. Research on the epidemiology of encephalitis in the future may need to concentrate on the outcome of cases and make an examination of cases admitted to hospital with some index of diagnostic accuracy.

Variation in reporting practices between doctors and in the natural history of the disease present serious obstacles for infectious disease surveillance. Generally, it is well documented that some doctors report more disease than others and that some doctors @ that the notification system is unimportant and unhelpful.'," The greater the proportion of the medical profession that subscribe to this view, the less useful the reporting system. Some doctors genuinely forget to notify. Studies in progress are examining the notification habits of doctors to see if there are particular characteristics in doctors who regularly notify diseases and those who do not. These studies may also attempt to correlate notifications with laboratory reports.

It is disappointing that it was not possible to be more confident about the epidemiology of encephalitis, but further research and a change in the system of notification may improve the information available in the future.

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