ubacute sclerosing panencephalitis (SSPE) is a rare degenerative disease of the central nervous system causing progressive loss of cerebral function, paralysis, coma, and death. It is the late consequence of measles virus infection, and is associated with viral persistence in brain tissue.¹

When in 1968 routine measles vaccination with attenuated live virus began in the UK, it was hoped that the expected reduction in measles cases would result in fewer cases of SSPE. It was however thought conceivable, though unlikely, that the attenuated virus might be more prone than the wild form to abnormal persistence,² in which case the incidence of SSPE might actually increase. A Register was therefore set up in 1970 to monitor the incidence of SSPE in England and Wales.³ ⁴ A report in 1992 showed a significant decline over the period 1970–89, in line with the partial reduction of notified measles over the previous decades; nevertheless SSPE cases continued to occur. In October 1988, measles, mumps, and rubella vaccine (MMR) replaced measles vaccine with a greatly increased acceptance; this was followed by a massive reduction of annual notified measles. The present report covers the years 1990–2002.

SUBJECTS AND METHODS
The notification methods, criteria for acceptance of cases, and the clinical course have been described previously.⁶ Briefly, cases were ascertained from a variety of sources, including reports from paediatricians through the Surveillance Unit of the Royal College of Paediatrics and Child Health, reports from laboratories to the Communicable Disease Surveillance Centre, and reports from neurologists. The Enteric, Respiratory and Neurological Virus Laboratory (ERNVL) of the Health Protection Agency receives serum and cerebrospinal fluid (CSF) samples from laboratories for diagnostic confirmation. A case is considered confirmed if there is a compatible clinical picture and raised measles antibody titres in serum and CSF, with evidence that the latter is synthesised within the CSF as opposed to serum contamination during CSF collection. All the cases in this report were confirmed by the ERNVL. In March 2002 virology and microbiology laboratories in England and Wales were contacted for reports of SSPE cases diagnosed since 1990; the two reported from this source had already been notified to the Register. Death certificates for relevant categories are received from the Office of National Statistics (ONS); 37 deaths have been reported, all cases being known to the Register.

Information on the age at onset of symptoms, clinical presentation, and progression is sought from the clinician in charge of the case and the general practitioner (GP). The GP is also contacted for a history of measles and/or vaccination (with either measles, MMR, or measles/rubella (MR) vaccine) and date(s) of measles or vaccination. Confirmation of the latter was also sought from the local authority where necessary.

Statistical methods
The significance of the trend in cases over time was assessed using Poisson regression. The adequacy of the Poisson model was checked by comparing the residual degrees of freedom with the deviance. Differences between proportions were assessed using the χ² test. The probability of two pregnant cases was calculated from the Poisson distribution. Cox regression was used for the analysis of time from onset to death. The expected number of cases each year from 1990 to 2002 was calculated from data on measles notifications from 1960 to 2001 as well as the previously estimated age specific risk of SSPE following measles infection (risk per 10⁵ = 18.0,
the gamma (index 3) distribution for the time from measles to SSPE onset as given in the paper by Farrington.7

RESULTS
From January 1990 to December 2002, 58 cases that met the laboratory criteria for confirmation were notified to the Register. Eleven were foreign nationals who returned home after diagnosis and were therefore excluded. The remaining 47 cases are shown in fig 1 according to year of onset and sex. There is a significant (p = 0.0003) downward trend by an average of 14% per year over the period, from about six cases to one or two per year. In the early 1970s when the SSPE Register was established the annual incidence was about 20 per year. The sex ratio was 1.9:1 with 31 male and 16 female cases. No new cases were reported in 2002.

Two female cases, one with onset in 1999 (aged 19 years) and one in 2000 (aged 15 years) were 30 weeks pregnant at the time of onset, one died after five years with a median of 2.7 years. Of the two girls who were 30 weeks pregnant at the time of onset, the other twin in each pair being SSPE cases by year of onset and gender.

SSPE onset and death
The precise age at onset was difficult to define and largely reflected the age at which the patient first sought medical help. The age at onset of SSPE ranged from 4 to 26 years (median 12.5). The mean age at onset increased over the study period by an average of 4.4 months a year (standard error 2.4 months). Although this difference did not reach statistical significance (p = 0.009), 67% of cases with measles onset from 1994 to 2002 were over the age of 12.5 years compared to 1.9 years in those infected under the median age at infection of 1.32 years. In 64% (21/33) cases measles occurred under the age of 2 years, and in 24% (8/33) under 1 year. Measles preceding SSPE occurred at a significantly younger age than in the general population (p = 0.001), in whom only 21% had measles under 2 and 10% under 1 (fig 2). The median interval from measles to the onset of SSPE was 9.7 years; the range was from 2.7 to 23.4 years. This interval did not vary significantly by sex, year of onset, age at measles infection, or ethnicity.

As was seen previously, in those infected with measles at a younger age the course of SSPE from onset to death was longer (p = 0.009). This is shown by a median of 4.2 years in those infected under the median age at infection of 1.32 years compared to 1.9 years in those infected above the median age.

Vaccination with measles containing vaccines
Vaccination was reported in 23 cases (49%); 17 had had a single dose of either measles, MMR, or MR vaccine, five had had two doses of a measles containing vaccine, and one had had three doses. For six patients the vaccination status was unknown; 18 were reported not to have been vaccinated, of whom 14 had recorded measles.

Of the 23 cases with a vaccination history, 18 also had a history of measles; in 12 measles occurred before vaccination, in two after vaccination, in two around the same time, and in two the timing was unclear due to a missing vaccination date. In four vaccinated cases there was no history of measles and in one the measles history was unknown.

Brain biopsy
Brain biopsy was performed on a total of five patients, all of whom had wild strain measles virus identified by nucleotide sequencing of the H and N genes. These included two of the four with a history of vaccination but no history of measles (table 1). All five cases were born between 1979 and 1985 and had biopsy specimens taken between 1997 and 2000; all measles nucleotide sequences were consistent with the wild strains known to be circulating in the 1980s and 1990s.16

Comparison of the observed and expected number of cases from 1990 to 2002 based on the analysis of the 1970–89 SSPE data7
The observed and expected numbers are given in fig 3. This shows a good fit and a total number of 39 cases expected, slightly fewer than the observed total of 47. To examine the
possibility of MMR giving rise to SSPE, the observed number of cases from 1992 to 2002 can be compared to the expected number, which is based on the risk being only from measles infection. The observed number of 31 is very close to the expected number of 29. Note that the period from 1992 to 2002 was chosen because any MMR effect would not become apparent until 1992, given its introduction in October 1988 and the delay to SSPE onset.

DISCUSSION

This study shows that the reduced incidence of measles brought about by vaccination has caused the almost total disappearance of SSPE in England and Wales. From 1968, when measles vaccine was introduced, annual measles notifications fell to about one sixth of the pre-vaccine figures but still exceeded 100 000 in most years. This was due to the poor uptake of measles vaccine, which never rose above 70%. When MMR vaccine replaced it in October 1988, acceptance was quickly reached and, until recently, remained above 90%. Following the national MR vaccination catch-up programme for 5-16 year old children in 1994, enhanced laboratory based surveillance of measles was established and has provided strong evidence that endemic circulation of measles in the UK has been interrupted.11 However, because of the delayed onset of SSPE, a few cases in older children and young adults may occur in the near future as a result of infection acquired in the 1980s and early 1990s. The increase in the age at onset observed over the study period is consistent with the recent cases arising from infection acquired in the 1980s and early 1990s.

While the recent drop in MMR coverage in the UK has not yet allowed the endemic circulation of measles to be re-established, there have been a number of localised outbreaks in 2002 in groups declining MMR vaccine because of safety fears.12 A disturbing feature of these localised outbreaks has been the involvement of infants under 12 months of age. Of the 308 laboratory confirmed measles cases in England and Wales in 2002, 33 (11%) were infants under a year;13 this compares with a total of 40 confirmed cases in infants in the seven years from 1995 to 2001. As in our previous SSPE report,14 measles infection in SSPE cases occurred at a significantly younger age than in the general population. In the current study the last two measles cases preceding SSPE occurred in 1993 and 1994, both in children under 1 year. Current advice is to offer MMR vaccine to infants from 6 months of age in the event of a localised outbreak, with revaccination at 12–15 months of age and again at school age. Infants aged 6-8 months in whom maternal antibody may have waned should be offered post-exposure prophylaxis with normal immunoglobulin if they are household contacts of a confirmed case.14

The good fit of the observed number of cases from 1990 to 2002 to the number expected based on notifications of measles, the previously derived age specific risk estimates, and gamma delay distribution provide validation of these estimates; these gave an overall risk of SSPE following measles of 1 per 25 000 and a delay distribution with a mean of 7.4 years. The risk of SSPE following measles in the first year of life is, however, substantially greater at around 1 in 5500.4 Based on an annual birth cohort of 650 000 and the overall risk of SSPE of 1 per 25 000 measles cases, the expected number of SSPE cases from 1990 to 2002 in the absence of vaccination would have been over 300, compared with the observed number of 47.

The higher than expected proportion of cases who were Asian is consistent with the earlier study which found that 22% of the cases with onset between 1985 and 1989 were Asian.16 The reason for this increased risk of SSPE in this group is unclear but may reflect genetic differences, environmental factors, or differences in measles exposure.

The surveillance shows that the decline in the incidence of SSPE following the introduction of measles vaccine has continued following the change to MMR vaccine in October 1988. Since most cases have an interval of over three years from measles virus exposure to onset of SSPE, any possible MMR vaccine attributable cases would be expected to occur in the period from 1992 onwards. However, the number of cases with onset from 1992 onwards closely fits the number predicted based on the assumption that no cases are vaccine attributable. The virus present in the brain in two SSPE cases without a history of measles disease but who had been vaccinated (one with MR at 11 years and one with measles vaccine at 3 years and MMR vaccine at 4 years) was confirmed as wild-type. In such cases, as in the four cases with neither a history of wild measles nor vaccination, measles infection must have occurred but not been recognised, possibly because it occurred in the first year of life when the disease may be mild and easily missed. The diagnosis of SSPE should therefore still be considered in the absence of a history of measles.

A reduction in SSPE following the introduction of vaccination has been reported from the United States,15 Poland,16 the Netherlands,17 and in the Middle East.18 19 Our study confirms the impact of vaccination and shows that the elimination of SSPE is possible through the use of MMR vaccine. It also underlines the importance of maintaining
high levels of vaccine coverage in order to protect indirectly those most vulnerable to SSPE, namely infants too young to benefit from the direct protective effects of vaccination. Surveillance is continuing in England and Wales in order to monitor the effect of the recent decline in MMR vaccine coverage on progress towards elimination of SSPE.

ACKNOWLEDGEMENTS
We thank Dr Shunmay Yeung for her help with the follow up and virological investigation of the cases. We also thank the general practitioners, paediatricians, virologists, and neurologists who provided information.

Authors’ affiliations
C Miller, M Rush, H Munro, E Miller, Immunisation Department, Communicable Disease Surveillance Centre, Health Protection Agency, 61 Colindale Avenue, London NW9 5EQ, UK
N Andrews, Statistics, Modelling and Economic Evaluation Department Communicable Disease Surveillance Centre, Health Protection Agency, 61 Colindale Avenue, London NW9 5EQ, UK
L Jin, Enteric, Respiratory and Neurological Virus Laboratory, Division of Specialist and Reference Microbiology, Health Protection Agency, 61 Colindale Avenue, London NW9 5EQ, UK

REFERENCES
The epidemiology of subacute sclerosing panencephalitis in England and Wales 1990–2002
C Miller, N Andrews, M Rush, H Munro, L Jin and E Miller

Arch Dis Child 2004 89: 1145-1148
doi: 10.1136/adc.2003.038489

Updated information and services can be found at:
http://adc.bmj.com/content/89/12/1145

These include:

References
This article cites 8 articles, 2 of which you can access for free at:
http://adc.bmj.com/content/89/12/1145#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Drugs: infectious diseases (965)
Immunology (including allergy) (2018)
Vaccination / immunisation (334)
Infection (neurology) (287)
Pathology (248)
Clinical diagnostic tests (1133)
Radiology (976)
Surgery (307)
Surgical diagnostic tests (291)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/