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Review of the effect of measles vaccination on the epidemiology of SSPE

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Background When measles vaccines were widely introduced in the 1970s, there were concerns that they might cause subacute sclerosing panencephalitis (SSPE): a very rare, late-onset, neurological complication of natural measles infection. Therefore, SSPE registries and routine measles immunization were established in many countries concurrently. We conducted a comprehensive review of the impact of measles immunization on the epidemiology of SSPE and examined epidemiological evidence on whether there was any vaccine-associated risk.

Methods Published epidemiological data on SSPE, national SSPE incidence, measles incidence and vaccine coverage, reports of SSPE in pregnancy or shortly *post partum* were reviewed. Potential adverse relationships between measles vaccines and SSPE were examined using available data.

Results Epidemiological data showed that successful measles immunization programmes protect against SSPE and, consistent with virological data, that measles vaccine virus does not cause SSPE. Measles vaccine does not: accelerate the course of SSPE; trigger SSPE or cause SSPE in those with an established benign persistent wild measles infection. Evidence points to wild virus causing SSPE in cases which have been immunized and have had no known natural measles infection. Perinatal measles infection may result in SSPE with a short onset latency and fulminant course. Such cases are very rare. SSPE during pregnancy appears to be fulminant. Infants born to mothers with SSPE have not been subsequently diagnosed with SSPE themselves.

Conclusions Successful measles vaccination programmes directly and indirectly protect the population against SSPE and have the potential to eliminate SSPE through the elimination of measles. Epidemiological and virological data suggest that measles vaccine does not cause SSPE.

Keywords SSPE, subacute sclerosing panencephalitis, epidemiology, measles, measles vaccine, MMR vaccine, genotype, vaccination

Introduction

Subacute sclerosing panencephalitis (SSPE) is a progressive neurological disorder caused by persistent measles virus infection. Initial symptoms of SSPE typically occur some years after natural measles infection and are usually subtle, with intellectual decline and behavioural changes, which may only be recognized as symptoms in retrospect. Most patients proceed over months or years to generalized convulsions, dementia, coma and death. Death usually occurs within 1–3 years, although there are reports of prolonged spontaneous remission.[1] SSPE is confirmed when there is a recognized clinical course accompanied by one or more of the following: measles antibody detected in the cerebrospinal fluid; a characteristic pattern on electroencephalography; typical histological findings in brain biopsy material or tissue obtained by post-mortem examination.[2] There is no proven effective therapy for the treatment of SSPE.[3]

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SSPE was originally described as three different neuropathological conditions in the 1930s and 1940s.[4] A viral aetiology was suggested when the condition was first described in 1933, but it was not until 1967–69 that measles viruses were established as the cause. When live measles vaccine became available in the early 1960s, the aetiology of SSPE was therefore unknown. Once the association between measles virus and SSPE was established there were concerns that measles vaccine virus might also cause this condition; particularly as SSPE had been associated with milder natural infection.[5] National SSPE registries were therefore established shortly after measles vaccine introduction in a number of countries.

In this article, we review the impact of measles immunization on the epidemiology of SSPE using comprehensive published and unpublished data. Four areas are reviewed: background SSPE epidemiology world-wide; recent trends of SSPE epidemiology in countries where measles has been eliminated or markedly reduced; available evidence on different theoretical adverse relationships between measles vaccine and SSPE; congenital and neonatal measles and SSPE. Virological sequence information and genotyping[6] are a crucial part of the available data and have been reviewed as part of this study.

Method

Relevant published articles were found using the search terms SSPE and epidemiology and also subacute sclerosing panencephalitis and epidemiology in Pubmed. Abstracts, where available, were used to identify 113 relevant papers, including 23 non-English references. A further 19 papers were found through referenced articles. A review matrix was used to decide which papers contained original data on SSPE epidemiology or risk factors. Papers that did not contain original data, were not of direct relevance, were ad hoc case reports or repeated data in other references were rejected.

A separate literature search was conducted using the search terms pregnancy and measles and SSPE and also pregnancy and measles vaccine and SSPE. In this way, case reports of SSPE onset in pregnant women were identified, together with case reports of neonatal or *in utero* measles exposure leading to SSPE. To identify published viral sequences, a search of GenBank was also conducted using the search terms measles and SSPE.

Available data on national (or regional) SSPE incidence, measles incidence and vaccine coverage was collated to assess the impact of vaccination on SSPE incidence. For inclusion in this analysis, SSPE cases had to have been reported to a sentinel surveillance system that covered a geographical population. Data from the European Sero-Epidemiology Network (ESEN2)[7] was used for measles incidence and vaccine coverage in some countries. This enabled the construction of figures showing SSPE incidence (by onset), vaccine coverage and measles incidence over time. Data from as many different countries as possible were included without applying standardized measures of quality because of the limited availability of these three datasets. Due to the many differences between countries in measles epidemiology, vaccine policy and SSPE registers it was not possible to perform any formal meta-analysis.

The countries were grouped according to the measles control in the available follow-up period:

(i) Good control (long period of low incidence following vaccine introduction);
(ii) Control with outbreak(s) (some small–medium outbreaks);
(iii) Poor control (continued regular large outbreaks).

Comparison of reported SSPE cases relating to 5-year periods with high measles incidence (low vaccine coverage) and low measles incidence (high vaccine coverage) was undertaken for six countries that had good measles control or control with outbreaks. The 5 years of high measles incidence were chosen to correspond to the first 5 years of SSPE reporting. The 5 years of low measles incidence (high coverage) were chosen to correspond to the most recent 5 years of SSPE data available, with the exception of the USA and Bulgaria where different periods were chosen to avoid outbreaks.

In addition to looking at time trends, the vaccination status, measles history and risk estimates per measles case or vaccinated case were sought. Further analysis of the SSPE register for England and Wales was undertaken as this database was available to the authors.

Background epidemiology, demographic data and risk factors

Incidence

Reported SSPE incidence varied greatly from approximately 0.2 to 40 cases per million population per year. Direct comparison of countries is problematic because methods and quality of ascertainment have been inconsistent. UK [8] and, more recently, USA[9] data analyses have calculated true incidence of SSPE to be approximately 4–11 cases of SSPE per 100 000 cases of measles. A higher risk is associated with earlier infection: the risk following measles infection under 1 year of age was 18/100 000 compared with 1.1/100 000 after 5 years of age in the UK. Reported rates in Israel have been even higher reaching 23.2–27.9 cases of SSPE per 100 000 cases of measles between 1964 and 1969; with rates in those infected under 1 year of age cited as 360.3–375.6 cases/100 000 measles cases.[10]

Age at onset and sex ratios

Worldwide average onset ages for SSPE ranged between 6 and 13 years, except Papua New Guinea at 4.9 years[11] (Table 1) and individual ages at onset ranged from 0 to 56 years in the papers reviewed. The average period from initial measles infection to SSPE symptom onset (latency) ranged between 4 and 10 years. A higher incidence has mainly been reported in boys (Table 1); the reason for this is not clear. However, data from South Africa (1984–90),[12] Japan (1999)[13] and Papua New Guinea (1997–2000)[14] indicated more equal distribution between the sexes.

An increase in age at onset once measles transmission has been greatly reduced or interrupted has been observed[22,49,58] together with an apparent lowering of male predominance in some countries.[14,53,59] SSPE cases in Romania exceptionally moved to a slight female predominance.[42] This suggestion of later onset in

Table 1 Summary of data available on age at onset, latency and sex ratios in published reports of SSPE

Ref.	Country	Pub. date	No. of SSPE cases reported on	Mean age at onset (range)	Mean latency (range)	Male : Female
15	Australia	1974	25	9 (4–17 years)	–	2.6:1
16	Belgium	1964	79	9 (3–19 years)	–	3:1
17	Brazil	1999	48	10 (2–27 years)	–	2.4:1
18	Brazil	1967	31	11.7 (3–22 years)	–	2.9:1
19	Bulgaria	2004	40	8.5 (3–16 years)	7 (4–14 years)	2.6:1
20	Colombia	1976	31	9 years	3.75 years	1.3:1
21	Denmark	1981	6	5–11years	–	–
22	E&W	2004	47	12.5[a] (4–26 years)	9.7[a] (2.7–23.4 years)	1.9:1
8	E&W	1992	290	10.5[a] (2–27 years)	8[a] (3M–20 years)	2.8:1
5	E&W	1978	96	9.8 (3–27 years)	6.8 (1.5–18 years)	2:1
23	Finland	1971	20	10[a] (5–21 years) [b]	6[a] (3–14 years)[b]	5.7:1
24	Former Yugoslavia	1989	194	7.7 (3–21 years)	5.5	2.6:1
25	France	1989	157	10 (3–33 years)	8 (2–17 years)	–
26	FR Germany	1978	156	9 (2–21 years)	5.4 (<1–17 years)	2.3:1
27	India	2005	114	9.8 (4–24 years)		3.2:1
28	India	1994	65	(2–24 years)	(2–10 years)	5:1
29	India	1990	47	7.2 (4–18 years)	(2–8 years)	5.7:1
30	Iran	1998	71	11.2 (4–20 years)	–	2.1:1
10	Israel	1983	87	(2.5–19 years)	7.5 (9M–16 years)	–
31	Israel	1976	52	8.5 (2.5–23 years)	5.6 (1–15 years)	2.4:1
32	Italy	1986	207	10.6 (±4 years)	5.6 to 7.1 years	1.8:1
33	Jamaica	1986	12	8 (5–14 years)	4 (3–5 years)	3:1
13	Japan	2003	125	10.3 (0–25+ years)	8.8 (4.3[a]) (2M–23.6 years)	1.1:1
34	Japan	1989	215	(1–29 years)	7 (1–16 years)	1.8:1
35	Kenya	1983	21	7.1 (1.5–14 years)	5.8	2.0:1
36	Kenya	1981	53	9 (4–18 years)	7.2	2.8:1
37	Middle East	1977	99	(2–56 years)	–	–
38	New Zealand	1973	27	(4–21 years)[b]	–	2.4:1
39	Northern Ireland	1986	26	10.8 (3–19 years)	8 (2–15 years)	7.7:1
40	Pakistan	1988	30	–	–	2:1
14	Papua New Guinea	2003	83	7.9 (2–14 years)	6.2 (2–11 years)	1.2:1
11	Papua New Guinea	1992	87	4.9 years	–	1.8:1
41	Poland	1997	249	12.03 ± 4.47 years	9.27 ± 3.9 years	–
42	Romania	1990	112	6.1 years 1978–79, 12.1 years 1988–89	4.5 years 1978–79, 8.8 years 1988–89	2.7:1 1978–79, 0.76:1 1988–89
43	Romania	1988		6.1 years pre-vaccine, 9.63 years post-vaccine		2–3:1
44	Romania	1985	632	6–7 years (2.7–19 years)	4.8 (2–11.3 years)	2.2: 1
45	Romania	1978	33	6.1 (3–11years)	4.5 (1.5–9 years)	3.7: 1
46	Sardinia	1979	20	(4–12 years)	–	4:1
12	South Africa	1992	75	11[a] (2–29 years)	–	0.9:1
47	South Africa	1980	116	9.3 (8.5[a]) (<1–23 years)	6.4 (<1–19 years)	1.5:1
48	South China	2004	10	9.4 (4–14 years)	6.5 (3–11 years)	2.3:1
49	The Netherlands	1992	81	10[a] (2–23 years) increasing over time	–	3:1
50	Turkey	2006	62	7.4 (1–28 years)	5.4 (±2.37 years)	2.3:1
51	Turkey	2001	573	13 pre-1994, 7.6 (1.5–22 years) 1995+	9.9 pre–1994, 5.9 (4[a])1995+	2.3–2.8:1

(continued)

Table 1 Continued

Ref.	Country	Pub. date	No. of SSPE cases reported on	Mean age at onset (range)	Mean latency (range)	Male: Female
52	Turkey	1988	401	10.02 (13.5[a])♂ and 9.4 (10.01[a])♀	7.8 years	2.4:1
9	USA	2005	12	7.7 (1.8–13 years)[b]	6.6 years (1.75–12 years)[b]	0.7:1
53	USA	1985	660 but 85 after 1980	pre-1980 10.31 years, post-1980 13.62 years	pre-1980 7.73 years, post-1980 10.5 years	1.8:1
54	USA	1980	52	12[a] (5–25 years)	–	2.1:1
55	USA	1979	453	9 (1–32 years)	–	2.3:1
56	USA	1977	375	9.5 (2–32 years)	7 (1M–27 years)	2.4:1
57	USA	1972	219	7.2 (2–21 years)	5	3.3:1
Calculated overall median (range)				9.45 years (4.9–13.6 years)	6.7 years (3.75–10.5 years)	2.4:1 (0.7–7.7:1)

[a]Median.
[b]Calculated for this review from data in the published paper.

females is upheld by data from the SSPE Registry in England and Wales, based on 345 cases with onset between 1962 and 2005. The latency using only cases in whom age or date of measles infection was known $n=274$ (and age at onset), in male cases had a different distribution to female cases (Figure 1), which was apparent before puberty. Females had a later age at SSPE onset (10.14 vs 12.21, $P=0.005$ Kruskal–Wallis test) and a longer latency (8.32 vs 9.73, $P=0.03$ Kruskal–Wallis test). Brazilian, US and South African data also supported the suggestion of later female onset.[17,55,60] In two of three published adult onset case series, there were similar numbers of men and women (gender m/f 4/4[61] and 7/6[62]), in the third case series there was a male predominance (25/14).[63]

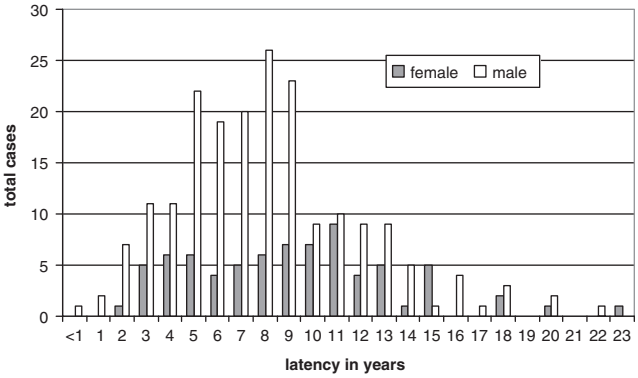

Figure 1 Latency of SSPE: distribution of male and female cases reported in England and Wales between 1970 and 2005 ($n=274$)

History of measles and measles vaccine

A high proportion of SSPE patients have a history of primary measles infection at an early age; many under 2 years.[8,10,13,22,23,27,29,30,32,42,47,48,49,50,52,54,58,64,65] After the introduction of measles vaccine, proportionately few cases were reported to be immunized against measles[8,10,34,41,42,49,50,54,56] as this protects against measles infection with its associated risk of SSPE.

Ethnicity and genetic factors

There is evidence of ethnic differences, including increased risk associated with Hispanic and Asian ethnicity in the USA[59] and UK,[22] respectively. A relatively low SSPE incidence was observed in black Americans.[55] One South African study reported distribution of cases by race roughly proportionate to the racial distribution in the population, but a measles incidence in black babies markedly higher than that for white infants.[12] Other South African studies calculated higher risks of SSPE in the 'coloured' (mixed race or of Indian/Sri Lankan origin) compared with the white population with lowest incidence in the black population.[47,66] In Israel, SSPE was reported almost exclusively in Sephardi Jews (of Afro-Asian origin) and Arabs, and not Ashkenazi Jews (of Euro-American origin).[31] A later Israeli study found differences between Arabic and Jewish populations, but Sephardi and Ashkenazi Jews were not distinguished.[10] Real ethnic differences may exist but this could reflect socio-economic circumstances that affect the likelihood of early measles exposure.

There is no strong evidence of a genetic factor associated with SSPE risk. Where cases have been reported in a twin, the condition has been discordant even in identical twins.[67] Familial aggregation has rarely been reported.[68,69] Two cases in two families have been observed in England and Wales. The probability of two families having more than one case by chance was calculated as under 1 in 10 000, suggesting some genetic tendency.[8]

Other factors

Rural dwelling has been reported as having a higher associated risk than urban dwelling,[16,36,49,53,64,52,65,70] but some studies have found no difference[23,24,32,34,37,38,40,43,55,57] or, unusually, an urban excess.[8] Animal or sick animal contact (more common in rural settings) has been a suggested risk,[16,18,20,54,64,70] but was not substantiated by other studies.[40,70] Close temporal association with another infection, either near the time of SSPE onset or initial measles infection, has also been reported[16,31,64] as has an increased incidence of serious head injury in cases; though this may be due to early undiagnosed disease.[8,42,39,54]

Other suggested risk factors have included larger number of siblings and a later birth order (consistent with increased risk of early disease), lower socio-economic status and more crowded homes.[8,26,31,50,52,54] Uneven geographical distribution has been reported within countries, with a small number of very local clusters,[46,49,70] but no overall geographical pattern has emerged.

Trends in SSPE incidence, measles incidence and vaccine coverage in individual countries

When interpreting trends in each country the following factors should be considered:

(i) When SSPE registers were established, case-finding tended to improve over time. There was also some retrospective case-finding. Therefore, an initial increase in SSPE cases was usually seen.
(ii) Following a drop in measles incidence, an impact on SSPE incidence would not be seen for at least 5 years and it would be over 10 years before large decreases occurred. Even with elimination of measles, cases of SSPE with a longer latency period may be seen 20–30 years after the last measles cases.
(iii) Some changes in SSPE over time may reflect changes in reporting practices and/or case definitions.

Countries with good measles control achieved by vaccination

The Netherlands[49]

Trends. The SSPE register was set up in 1976 when measles vaccine was introduced. Good measles control was achieved with consistent high coverage (Figure 2). There was a small outbreak in 1988, which would not have had time to produce any cases in the period of the published study (1976–90). By 1990, 81 SSPE cases born in the Netherlands had been identified. There was a marked decline in number of SSPE onsets over time.

Measles and vaccine history. Seventy-one of the SSPE cases had had measles, six had unknown measles status and four denied having had measles. All measles was contracted prior to 1975. Three cases had been vaccinated (4%), with no history of measles; they were immunized when aged 4, 8 and 9 years, so there was a high chance of measles exposure prior to this.

England and Wales

Trends. The SSPE register in England and Wales was set up in 1970, 2 years after the introduction of measles vaccine. Between 1970 and 1989, 290 cases were identified (Figure 3).[8] Between 1990 and 2002, 47 cases were identified and a 14% decline in incidence per year was observed.[22]

Measles and vaccine history. Of the 290 cases between 1970 and 1989, nine had vaccine and no history of measles and 10 had both vaccine and measles. The risk due to measles infection was estimated as 4/100 000 using a model that allowed for the distribution of the delay from measles to onset and for 65% notification of measles. The risk was estimated as 18/100 000 in under ones down to 1.1/100 000 for infection at age 5 plus. No change in risk following measles infection over time was found, controlling for age at infection. The risk due to vaccine, assuming all vaccinated cases with no history of natural infection were due to vaccine, was estimated as 0.14/100 000. This is the only article that modelled the data allowing for delay to onset distribution. In the later period, the observed incidence was consistent with a risk of 4 per 100 000 measles cases and no vaccine risk. Four cases had measles vaccine but no history of measles, two of these had wild type measles virus confirmed by biopsy. Observed cases of SSPE continued to decline following the introduction of combined measles, mumps and rubella vaccine (MMR) in 1988 and the mass measles/rubella (MR) school-based immunization campaign in 1994 and was consistent with no cases being vaccine attributable.[22]

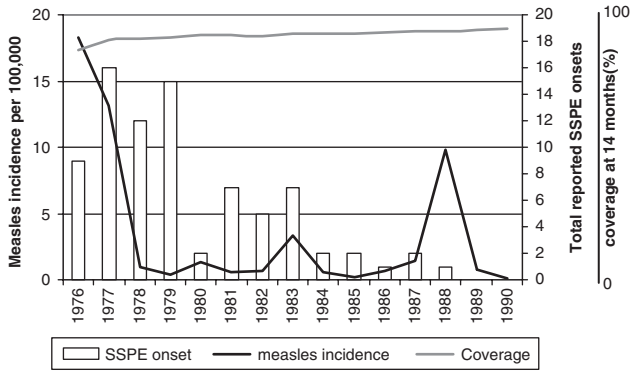

Figure 2 Measles incidence, SSPE onsets and measles vaccine coverage in the Netherlands

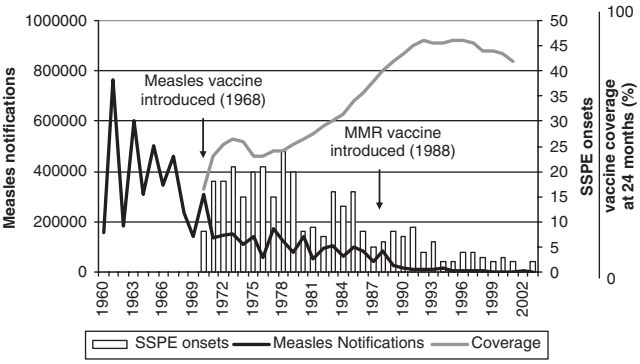

Figure 3 Measles notifications, SSPE onsets and measles vaccine coverage in England and Wales

Countries with periods of measles control where there have been subsequent outbreaks

USA

Trends. The incidence of SSPE in the USA declined from 0.61 per million under 20s in 1970 to 0.35 in 1975 and 0.06 in 1980 (Figure 4).[2]

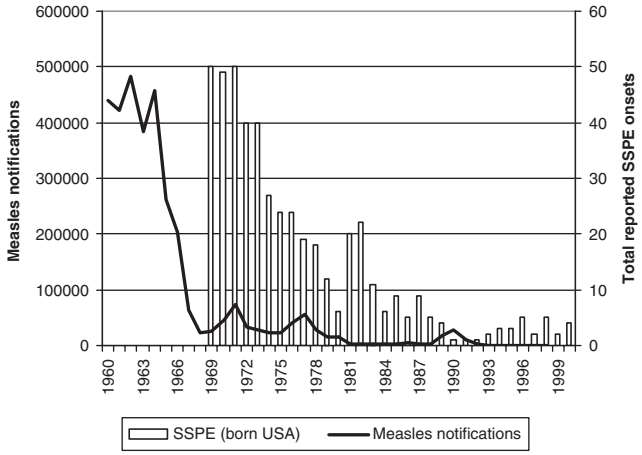

Figure 4 SSPE onsets and measles notifications in the USA

Measles and vaccine history. Risk of SSPE was estimated as 8.5 per million measles cases and 0.7 per million vaccine doses.[2] Bellini *et al*.[9] analysed the 1989–91 measles epidemic. Between 1989 and 1991, there were at least 55 622 (possibly up to 185 000) measles cases. By 2003, 12 SSPE cases could be linked to this epidemic by year of measles/rash and by virus strain identified in brain tissue in those with no history of infection. Risk estimates of SSPE following natural measles infection were calculated at 6.5–22 per 100 000 cases. This risk was much higher than earlier US estimates,[2] suggesting previous under-reporting of SSPE.

Eleven tested SSPE cases reported to CDC had non-vaccine measles strain identified in brain tissue, including six who had no history of measles but were vaccinated.[9]

Israel[71]

Trends. Vaccination began in 1967 with low initial coverage. SSPE incidence dropped from 5.7 cases per million population aged 0–19 years/year between 1968 and 1979 to 1.9 in 1979.[10] An apparent increase in SSPE between 1968 and 1975 was likely to reflect underreporting/diagnosis, whereas the later decline was during a period of intensive surveillance (Figure 5).

Measles and vaccine history. Measles was reported in 79% of SSPE patients born prior to 1965 and 74% of those born 1965 to 1979, despite the large drop in measles incidence. Those born prior to 1965 should have had measles, whereas those born from 1965 to 1979 could be vaccinated. This suggests no vaccine risk because the proportions did not change. For those born in 1965–71, the rate in the unvaccinated was 24.6 per 100 000 births, whereas the rate in those vaccinated with no measles reported was 1.7 per 100 000 births. These rates were likely to be underestimated because not all cases would have been seen by 1979. Of 34 cases born from 1965, 11 were immunized (32%) against an average of 82% in the general population. Of the 11 immunized, seven had subsequent measles documented.

Poland

Trends. SSPE onsets were available from 1974 to 1999 (Figure 6).[58,72] The SSPE registry was established in 1976,

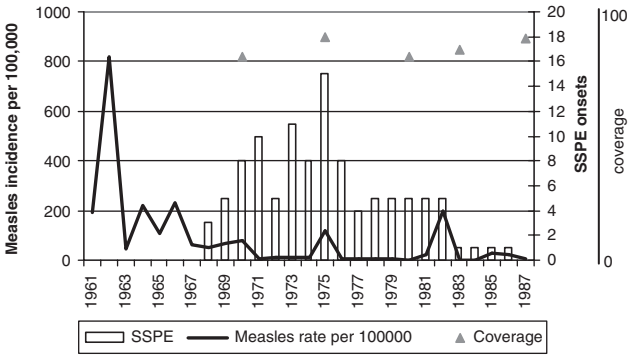

Figure 5 Measles incidence, SSPE onsets and measles vaccine coverage in Israel

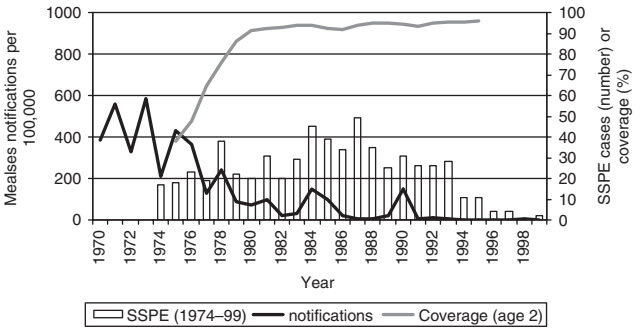

Figure 6 Measles incidence, vaccine coverage and SSPE onsets in Poland

a year after the introduction of obligatory measles vaccination. SSPE incidence was noted as dropping from 3.8 to 0.8 per million in the under 20s from 1984 to 1995.

Measles and vaccine history. No data were available on vaccine status and measles disease in these cases. There was no evidence of a cluster of cases from the measles outbreak in 1990, although, without data on year of measles this would be hard to identify.

Bulgaria

Trends. Routine measles vaccination was introduced in Bulgaria in 1969, with high coverage from 1976. Between 1978 and 2002, there were 40 cases reported to a clinic in Sofia (Figure 7).[65] The number of cases dropped from four per year during 1978–84 to zero in 1985–94 then increased to 1.7 per year in 1995–2002. Half of the cases from 1995–2002 were infected during a 1991–92 epidemic.

Measles and vaccine history. Only two cases were vaccinated of the 40 identified cases of SSPE.

Romania

Trends. Over 1000 SSPE cases were reported in Romania from 1976 to 1988 (Figure 8).[42–45,70] An increase from 1976 to 1985 was partly due to improved case-finding but other factors were

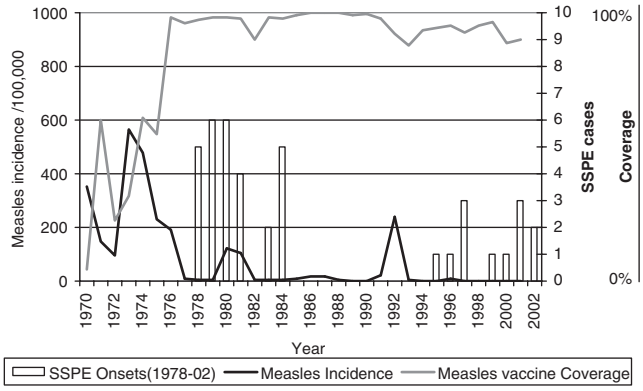

Figure 7 Measles incidence, vaccine coverage and SSPE onsets in Bulgaria

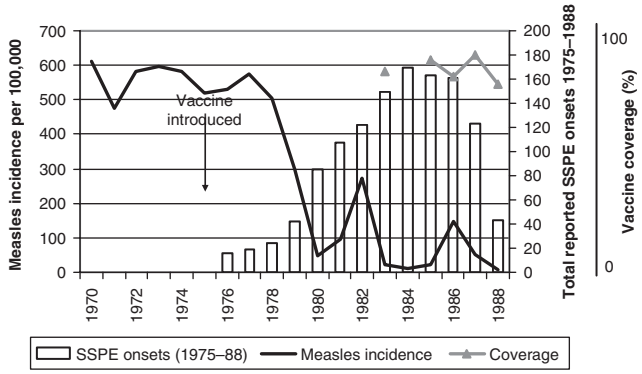

Figure 8 Measles incidence, measles vaccine coverage and SSPE onsets in Romania

also considered to be influencial.[43] The incidence fell from 5.21 onsets per million in 1987 to 1.82 per million in 1988/89.

Measles and vaccine history. The proportion of SSPE cases with known measles under 2 years of age fell from 76% in 1978/79 to 47% in 1988/89.[42] Of the 1988/89 cases, 8/62 (13%) had been vaccinated with no record of natural measles.

Countries with poor measles control

Papua New Guinea (PNG)

Trends. In PNG, 83 cases [57 in the Eastern Highlands Province (EHP)] were identified from February 1997 to November 2000.[14] Vaccination was introduced in 1982 (at 9 months and in 1990 at 6 and 9 months), but coverage remained poor with EHP coverage in under ones of: 55–60% in 1989–91; 19% in 1993; 8% in 1994. Measles outbreaks continued to occur. In the 1998–99 outbreak, the median age of measles was 11 months. The SSPE incidence was reported as 56 per million in under 20s in 1990 (four highland and two coastal regions) and 98 per million in EHP in 1997–98.[11] The continuing high incidence was blamed on low vaccine coverage, with continued measles outbreaks at 3–4 year cycles, and cold-chain problems.

Turkey

Trends. SSPE epidemiology in four time periods was available from Turkey; 1975–84, 1985–89, 1990–94, 1995–99 (Table 2).[51]

Table 2 Comparison of SSPE epidemiology in four time periods in Turkey[44]

	1975–84	1985–89	1990–94	1995–99
M:F ratio	2.5	2.8	2.3	2.4
Age at onset (years)	9.8	11	13	7.6
Latent period (years)	7.0	8.7	9.9	5.9

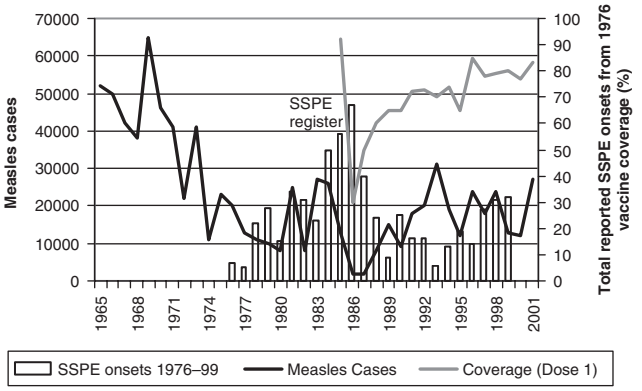

Figure 9 Measles cases, measles vaccine coverage and SSPE onsets in Turkey

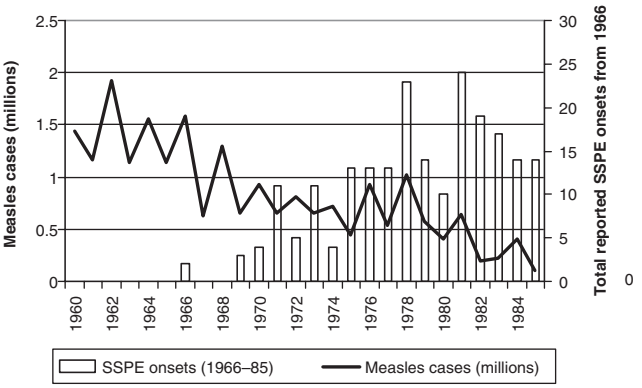

Figure 10 SSPE onsets and measles incidence in Japan

Turkish data were based on newly diagnosed cases since 1984, with earlier cases based on diagnoses from hospital records.

A vaccine campaign was launched in 1985 for all children under 5 with coverage rates rising from 30% to 67% after that campaign. The initial large impact of vaccination on measles in 1985–88 could explain the reduction in SSPE in the early 1990s, however, measles was not controlled and the increase in SSPE cases in 1997–99 was probably due to the subsequent increase in measles (Figure 9).

Japan

Trends. Compulsory measles vaccine was introduced in 1978 (but available before this). Measles incidence declined but remained fairly high. The number of SSPE cases was unchanged from 1975 to 1985. It was probably too early to see a decline in SSPE by 1985. Between 1966 and 1985, there were 215 SSPE cases reported (Figure 10).[34] The SSPE incidence rate for those born from 1968 to 1977 was 16.1 per

million measles cases. The incidence rate for vaccinated cases from 1971 to 1979 was 1.05 per million (eight cases in 7.6 million doses), assuming all vaccinated cases with no known infection were due to vaccine. The follow-up stopped in 1985, so true rates for both groups would be higher.

Measles and measles history. Of 204 cases, where natural measles and measles vaccination history were available, only 11 had measles vaccine and no history of measles. Non-affected siblings were six times more likely to be vaccinated and, when not immunized, were infected with measles at an older age.

Summary of epidemiological trends

In the countries reviewed, the pattern of SSPE reflected the epidemiology of natural measles infection. In countries with good measles control, a decline in new cases of SSPE was seen several years after the decline in measles. In countries where there have been epidemics of measles after periods of good control, cases of SSPE have increased after a delay of several years. Table 3 summarizes SSPE cases in 5-year periods that relate to periods of high measles incidence and low coverage as well as high coverage and low measles incidence. This was possible for data from six countries that had good measles control or control with outbreaks. Vaccination against measles has clearly reduced the incidence of SSPE through protection against measles, with a reduction of 82–96% in the countries in which this direct comparison was possible.

Potential adverse relationships between measles-containing vaccine and SSPE

Potential adverse relationships between measles-containing vaccine and SSPE are considered below. The last three theoretical relationships would be consistent with the identification of wild measles virus, rather than vaccine virus, in the brain of such putative cases.

Theory one: measles vaccine virus can cause SSPE

The decline in SSPE associated with the introduction and increased coverage of measles vaccine has been observed in many countries, as already discussed. This is consistent with a protective effect of vaccine but also a lower risk of vaccine-attributable cases. In the pre-vaccine era, when all children got measles, the risk of SSPE following measles was similar to the total SSPE cases per year divided by the birth cohort (assuming a stable population size). Post–vaccination, this estimate is less straightforward since the number of measles cases each year is required along with total SSPE cases for those infected that year (which is only complete many years later). Modelling by Farrington allowed an estimate of this risk by age at measles infection in England and Wales.[73] The overall risk was four cases of SSPE per 100 000 measles cases. Data from the USA for the epidemic 1989–91 gave a similar risk.[9]

The estimated risk of SSPE after vaccination is often erroneously quoted as 0.14 per 100 000 based on Farrington's 1991 paper.[73] Estimates of the risk from measles vaccination, consistently much lower than the risk from the disease, assume that SSPE came from vaccine if a child had vaccine and no recorded measles, therefore representing the worst case scenario for vaccine risk. Virological evidence does not support the suggestion that measles vaccine virus can cause SSPE. Natural measles virus has consistently been isolated in SSPE brain biopsy material,[74–78] even in cases that were vaccinated and had no history of natural infection.[9,8,79–82] This is in keeping with the fact that natural measles infection can be very mild and is often undiagnosed.[83]

Although measles virus has only one serotype, significant diversity of the genome exists, eight clades (A–H) and 23 genotypes are recognized, based on the sequence of the carboxyl region of the N gene, or the full sequence of the H gene.[6] All measles vaccine strains are genotype A.[84] There have been no cases of SSPE in whom measles vaccine virus has been isolated, and reviewing the published N or H sequences (or with genotype information; Table 4), genotype A has been identified in only two cases (Halle, Horta-Babosa and Mantooth are almost certainly the same isolate passaged in different labs, with the published Halle sequence representing laboratory contamination[85]). No further information is available on Mantooth/Horta-Babosa, but the sequence differs from vaccine strains. Similarly, MVs/Belfast1.UNK/1956-SSPE differs from vaccine sequence and was from a child that acquired clinical measles in 1955 and was never vaccinated.[79]

A total of 23 cases detailed in Table 4 had a history of vaccination, but vaccine strain or genotype A was not identified in any of them. Instead, a wide range of virus genotypes have been identified, reflecting the diversity of wild-type genotypes.

Papers looking at virological features have come from different countries, including North and South America, Western and Eastern Europe, Japan and Papua New Guinea,

Table 3 Comparison of reported SSPE cases relating to 5-year periods with high measles incidence (low vaccine coverage) and low measles incidence (high vaccine coverage) in six countries

Country	High measle/low cover	SSPE period 1 (+7 years)	SSPE cases/year period1	Low measles/high cover	SSPE period 2 (+7 years)	SSPE cases/year period 2	Ratio (period 2/period 1)
Netherlands	1969–73	1976–80	10.8	1979–83	1986–90	0.8	0.07
UK	1963–67	1970–74	16	1992–96	1999–2003	1.8	0.11
USA	1962–66	1969–73	45.8	1984–88	1991–95	2	0.04
Israel	1961–65	1968–72	6.2	1976–80	1983–87	0.8	0.13
Poland	1967–71	1974–78	23	1988–92[a]	1995–99	4.2	0.18
Bulgaria	1971–75	1978–82	4.2	1984–89	1991–95	0.2	0.05

[a]Includes 1 year (1990) with incidence of 148 per 100 000.

Table 4 Summary of viral RNA sequencing of measles virus isolated from SSPE patients

Virus name where given	Alternative name	Country of case	Natural measles infection	Vaccinated	Genotype[a]	Reference
Halle SSPE isolate/USA/1971[b]	Hal[b]	USA			A	85, 86, 87
Horta-Barbosa SSPE strain/USA/1971[b]	HB; ? MA-160	USA			A	86
Mantooth SSPE strain/USA/1971[b]	MA-160 SSPE	USA			A	86
MVs/Belfast1.UNK/1956-SSPE	UK83/56	UK	1955	no	A	79
1P3/USA/early 70s	SIP3A	USA			C1	85, 86
Case A/Germany/mid-80s	S(A)	Germany			C1	85, 86, 88
Case K/Germany/mid-80s	S(K), case K	Germany			C1	86, 89
CDC Case 6		USA	1977	no	C1	9
MF/Europe/early 70s	MF	Europe			C1	86
MVs/Belfast.UNK/1955-SSPE	UK88/55	UK	1955	no	C1	79
MVs/Belfast2.UNK/1956-SSPE	UK85/56	UK	1956	no	C1	79
Osaka-1	Osaka-1	Japan			C1	90
Osaka-2	Osaka-2	Japan			C1	90
Osaka-3	Osaka-3	Japan	1971		C1	90
SMa81/Madrid.SPA/1981/1970	SMa81	Spain	1970		C1	86
SSPE93		Japan	1980		C1	77
Yamagata-1/Japan/mid80s	Yamagata-1, YA	Japan	1970s	no	C1	91
Case B/Austria/mid 80s	S(B), Case B	Austria			C2	85, 86, 92
MVs/Belfast.UNK/1960s-SSPE	UK86/60s	UK	1960s	no	D1	79
MVs/Belfast.UNK/1969-SSPE	UK87/69	UK	1969	no	D1	79
MVs/Bristol.UNK/1980-SSPE	UK157/80	UK	1980	no	D1	79
S33/N.Ireland/1983	S33	UK			D1	86, 93
S81/N.Ireland/1986	S81	UK			D1	86, 93
CDC Case 1		USA		Yes	D3	9
CDC Case 10		Nicaragua		Yes	D3	9
CDC Case 2		USA		Yes	D3	9
CDC Case 3		USA		Yes	D3	9
CDC Case 4		USA		Yes	D3	9
CDC Case 5		USA	1991	Yes	D3	9
CDC Case 9		Puerto Rico	1991	no	D3	9
Kobe-1	Kobe-1	Japan			D3	94
MVs/Goroka.PNG/38.97 SSPE		PNG	No	Yes	D3	80
MVs/Goroka.PNG/39.97 SSPE		PNG	yes	Yes	D3	80
SSPE		USA	1990	Yes	D3	9, 95
CDC Case 8		USA	1991	Yes	D5	9
SSPE Turk./95		Turkey			D5	75
MVs/Buenos Aires.ARG/28.02	SSPE4	Argentina	1998	1999	D6	78
MVs/Buenos Aires.ARG/38.02	SSPE5	Argentina	1998	1999	D6	78
MVs/Buenos Aires.ARG/52.02	SSPE6	Argentina	no	1998	D6	78
MVs/Glasgow.UNK/1990s-SSPE	UK125/90s	UK	1990s	1994, 1997	D6	79
MVs/Zagreb.CRO/08.03/_SSPE		Croatia	Yes	Yes	D6	74, 96
MVs/Zagreb.CRO/47.02/[D6]_SSPE		Croatia	Yes	Yes	D6	74, 96
MVs/Cardiff.UNK/1980s-SSPE	UK99/80s	UK	1980s	1995	D7	79
MVs/Dundee.UNK/82-SSPE	UK585/82	UK	1982	Yes	D7	97
MVs/London.UNK/1980s-SSPE	UK44/80s	UK	1980s	1994	D7	79
MVs/Nottingham1.UNK/1980s-SSPE	UK111/80s; S111/80s	UK	1980s	1994	D7	76
MVs/Nottingham2.UNK/1980s-SSPE	UK98/80s	UK	1980s	1988, 1989	D7	79
CDC Case 11		USA		Yes	E	9
CDC Case 7		USA	1968	Yes	E	9
SMa79/Madrid/1979	SMa79; 791520	Spain	1967		F	86
SMA94/Madrid/1994	SMa94; EV	Spain	1968		F	86

[a]Based on the provided sequence analysis or information in the literature.
[b]These are likely to be the same case.

where different measles vaccine virus strains are used. All measles vaccine strains are genotype A and from the same genetic lineage and, therefore, would be expected to be the same in terms of any theoretical risk of SSPE.

Data from England and Wales showed that the actual number of cases of SSPE between 1992 and 2002 were consistent with the assumption that no cases were vaccine attributable.[22] This period of continued SSPE decline included the introduction of MMR in 1988 and mass MR immunization of school-aged children in 1994. An Israeli study examined the expected number of SSPE cases in vaccinated individuals born between 1966 and 1971 using coverage rates and estimates of vaccine effectiveness.[10] All four vaccinated cases of SSPE observed in this cohort could be accounted for by the fact that the vaccine was not 100% effective.

Theory two: administration of measles vaccine can accelerate the course of SSPE

Dodson *et al*.[98] described a patient who developed SSPE after early measles infection but rapidly deteriorated when immunized against measles 1 year after the onset of SSPE symptoms. They suggested that the vaccine may have led to the acceleration of symptoms (within 3 weeks of immunization) in what would have otherwise been a slowly evolving case of SSPE.

Given the average age at onset of symptoms of SSPE and the age at which immunization occurs in most countries, the situation in which an individual with ongoing symptoms of SSPE is immunized is likely to be relatively rare. In 1978, nine patients on the US National Registry with confirmed SSPE had been given measles vaccine (live and/or inactivated) subsequent to the onset of symptoms of SSPE.[99] Four of the nine had died at an average of 3.6 years (2.4–6.5 years) after symptom onset, whilst the five who were still alive had survived an average of 10.5 years (7.3–12.2 years). This compared with 149 fatal SSPE cases, where average interval from onset to death ranged from 9 to 30 months, depending on age at onset. These data do not support the suggestion that measles vaccine accelerates the clinical progression of SSPE.

Theory three: measles vaccine can trigger SSPE in an individual who would have developed the disease later in the absence of immunization

The possibility that measles-containing vaccine could stimulate the expression of a latent infection was first suggested in 1974.[100] If measles vaccine acted as a trigger for SSPE it would be expected to bring forward the age at which SSPE develops in those immunized before onset compared with unimmunized individuals.

Whilst there are sporadic reports of SSPE onset shortly after vaccination these do not by themselves constitute evidence of a vaccine trigger effect. US data from 1960 to 1974 identified 44 patients, of 292 confirmed cases with a history of measles infection, who had received live measles vaccine subsequent to the natural infection.[56] There was no difference in the mean interval from measles to onset of SSPE for those who received live measles vaccine (6.9 years) and those who did not (7.1 years). Further, there were 58 patients with no history of natural infection of whom 40 had been immunized. Of these, 35 cases had a known date of vaccination and the time period between vaccination and onset of SSPE ranged from 1 month to 9 years (3.3 years mean). Age at vaccination ranged from 12 months to 10 years and there was no apparent association with vaccination at any age.

Table 5 Effect of immunization status on age at onset of SSPE in Turkey (1997–99)[51]

	Children who had measles	
	Immunized	Unimmunized
Number of cases	20	52
Age at onset (years)	6.7 ± 3.2	5.6 ± 3.6
Latency (years)	4.8 ± 3.1	4.6 ± 3.6

In Turkey, there was no evidence that immunization status affected either age at onset or latency in cases with a history of measles (Table 5).[51]

The mean interval between measles infection and onset of SSPE, and the mean age at onset of SSPE in Israel, USA and the UK were virtually identical.[10] In contrast, the mean interval between measles immunization and SSPE onset was longer in Israel than in the USA or UK. Thus, whilst an association between measles infection and SSPE was consistent, there was no such consistency in the relationship between immunization and SSPE. In this Israeli study, it was also found that the median age of onset was 97 months in the 11 vaccinated compared with 99 months in the 23 unvaccinated cases of SSPE among children born from 1965 to 1971.

In England and Wales around 7 million children aged 5–16 years were immunized in the mass MR immunization campaign in November 1994. An increase in observed compared with expected cases of SSPE might have been anticipated from about 1998 onwards if the trigger theory was true but this was not the case.[22]

The 'trigger' hypothesis was further tested using the data available from the SSPE register for England and Wales. Of the 342 cases with onsets between 1962 and 2001, 42 had a history of a measles-containing vaccine, 274 were unvaccinated and the vaccination status of the remaining 26 was unknown. The age at onset in those who had a measles vaccine did not differ from those who were unvaccinated (difference after adjusting for year of birth was 0.14 years younger in the vaccinated with 95% CI 1.82 years younger–1.55 years older). If measles vaccine triggers SSPE then age of onset should be significantly younger in vaccinated cases.

Theory four: measles vaccination in a person who has already established a benign persistent wild measles infection can lead to the development of SSPE where it would not otherwise occur

Wakefield suggested that, based on Japanese studies, persistent infection of the brain with measles virus may not be that uncommon (depending on different variables, e.g. age at infection) but usually without any clinical problem.[101] He theorized that, in the presence of a benign persistent wild measles infection, re-exposure to measles virus via immunization would boost the immune system leading to an attack on

persistently infected cells and the triggering of SSPE in an individual who would not otherwise develop it.

In support of this theory, he cited the increase in SSPE cases in England and Wales and in the USA shortly after the introduction of measles vaccination. Thereafter, according to the theory, a decline would be seen as the protective effect of measles vaccine against wild infection becomes apparent. An increase in SSPE cases shortly after the introduction of vaccination with a subsequent decline has been seen in a number of countries, as already described. However, in these countries, as in the UK and USA, a SSPE register was set up at the same time as measles vaccination was introduced. It is to be expected that improving case ascertainment in the early years of the register with a real reduction a few years later due to prevention of measles infection would result in such a phenomenon.

If SSPE were induced by this 'second hit' mechanism then there should be a higher than expected proportion vaccinated among SSPE cases with a history of measles, and in addition if the effect were acute, a younger age at onset.

An acute effect is not plausible given the consistency in age between vaccinated and unvaccinated cases already discussed.

Looking at SSPE cases in England and Wales in whom measles infection occurred under 1 year of age (before measles/MMR vaccine is offered), the proportion who were subsequently vaccinated was not greater than expected from vaccine coverage figures. In those born since 1970, 9 of 25 had been vaccinated (36%). This compares with an expected vaccine coverage of 55% (calculated using vaccine coverage and number of cases by year of birth).

More recent data have been used to look at cases that have arisen since the MR immunization campaign in England and Wales in November 1994. It was found that 8 of 19 eligible cases (42% coverage) had MR vaccine prior to onset, whereas, overall coverage for the campaign was 92%. A US case–control study showed that measles vaccine was protective; of those who had measles, 11/43 cases were vaccinated (26%) compared with 20/45 (44%) of controls.[54] So, there was no evidence among those who had measles that vaccine provided an additional risk.[102]

Consequences of natural measles infection or SSPE in pregnancy

Measles infection in pregnancy

There are several publications reporting the outcome of measles in pregnancy for the mother and fetus.[103–110] There is general agreement in the literature that maternal measles is associated with a higher risk of complications such as pneumonia and encephalitis than in other adults. There is no convincing evidence of an increased risk of congenital abnormality in the infants of women with measles in pregnancy. Where defects have been reported, no consistent pattern has been seen suggesting that, if the virus does cross the placenta, it is not teratogenic.[105,111–113] There are papers that report an increased risk of fetal loss, intrauterine growth retardation, premature delivery and neonatal death following maternal measles, which may reflect non-specific effects of maternal infection or a specific effect of intra-uterine infection.[105,107,110]

When maternal infection occurs around the time of delivery, however, perinatal infection of the infant may give rise to SSPE with a short onset latency and fulminant course. In three of the five case reports adequately described in the literature,[114–117] the onset of maternal rash (which coincides with the appearance of antibody and occurs as the viraemia is declining), was 1–17 days *post partum*, in one case maternal fever complicated the last 3 days of pregnancy.[118] Under these circumstances, maternal infection could result in transplacental or early neonatal infection of the infant in the absence of maternal antibody. It has been speculated that these circumstances combined with immaturity of the neonatal immune system predisposes towards early onset of SSPE and a fulminant course. In four of the five cases described in the literature, onset of symptoms in the infant occurred under 2 years of age.

SSPE in pregnancy

There is considerable literature reporting cases of SSPE in pregnancy and these have all been confirmed by the usual diagnostic methods.[8,17,22,61,63,119,120] The course appears to be fulminant, for which it is speculated that immunological and hormonal consequences of pregnancy may be responsible. The fetal outcome is often unfavourable due to the obstetric consequences arising from the mother's condition, for example elective premature delivery by caesarean section. No infants who survived subsequently developed SSPE. One report of a 'mild newborn form of SSPE' in an infant whose mother developed SSPE in pregnancy was not subsequently confirmed and the infant was developing normally at 4 years of age.[20] Since viraemia does not occur in SSPE, transmission of measles virus to the infant would not be expected.

Two cases in pregnant women were identified in the England and Wales register with onset between 1990 and 2002.[22] The probability of two cases diagnosed during pregnancy was calculated as only 0.004 based on the age of female cases and birth rate data.

Discussion

Analyses of data from the UK and the USA have shown the true incidence of SSPE to be approximately 4–11 cases of SSPE per 100 000 cases of measles and the risk has been cited as high as 27.9 SSPE cases per 100 000 cases of measles. In many countries, reported rates of SSPE have been much lower, including earlier estimates from the USA. This suggests that there has been substantial under-ascertainment of cases of SSPE. Ideally, national registries should collate information on possible SSPE cases from different sources including neurologists, hospital episodes, laboratories and death certificate data.

With the exception of an increased risk of early measles infection, reduced likelihood of immunization against measles and a higher SSPE rate in boys, risk factors have been differentially described and are based on data of varying quality. The significance of each is thus difficult to assess and may often reflect the chance of contracting early measles infection.

When looking at cases by year of SSPE onset, changes in the mean age at onset (and latency) over time are often seen. In countries with good measles control, where incidence has been

low for some time, the recent cases should be older because they reflect cases infected years ago when measles incidence was higher or because they represent cases infected when older. If measles incidence has not changed then age at onset should not change. If measles incidence declined for some years then re-emerged, then the resulting cases first seen would be young cases. In many countries with good measles control, an increasing age at onset of SSPE (and of latency) has been observed. Even in countries where good paediatric surveillance is in place, cases in older ages may not be detected because there is no routine surveillance of this age group. Whilst the sex ratio is fairly consistently reported with male predominance, there is some suggestion of a different latency (time between infection and onset) by gender. This suggestion comes from the observed differences in sex ratio through time in some countries; with the sex ratio moving towards more equal sex distribution some years after natural measles transmission has been interrupted. Therefore, some years after interruption of measles transmission, cases of SSPE that do still arise are more likely to occur at older ages and a higher proportion of these cases may arise in women than when onset occurs at younger ages.

Patterns of SSPE in individual countries reflected the epidemiology of natural measles infection. In countries with good measles control, a decline in new cases of SSPE is seen several years after the decline in measles. An epidemic of measles after a period of good control leads to increased cases of SSPE after a delay of several years. In the USA such cases were demonstrated to be virologically linked to the 1989–91 epidemic. Vaccination against measles has evidently reduced the incidence of SSPE through protection against measles. Any theoretical risk of SSPE due to vaccination is, therefore, substantially lower than that due to disease. Measles vaccine offers direct protection by preventing measles infection with its associated risk of SSPE. When coverage is high enough there is also an indirect protective effect through herd immunity, which protects the unvaccinated from infection or delays infection until a later age, when risk of SSPE is reduced. However, if coverage is not high enough to eliminate disease, vaccination can result in a resurgence of measles infection in younger children who are at increased risk of SSPE.

Of the four theoretical ways in which measles vaccine could be adversely associated with SSPE none of the available epidemiological evidence is consistent with vaccine virus directly causing (theory 1), accelerating (theory 2), triggering (theory 3) or inducing, through a 'second hit' mechanism (theory 4), SSPE. Some papers do describe cases of SSPE with no history of wild measles infection in immunized individuals. Such cases can be erroneously attributed to vaccine.[121] When individuals with such a history have been examined virologically, only wild measles virus has been found. Before such techniques were available, the estimate of vaccine-attributable risk of SSPE was calculated in England and Wales, in the worst case scenario, to be 0.14 per 100 000 based on a total of nine cases reported with onset prior to 1990.[72] In cases reported since 1990, there were four vaccinated without a history of measles. Brain biopsies were obtained from two of these four cases and in both wild measles virus was identified.[22] Cases of SSPE in which there is no known history of natural measles infection but measles vaccine has been administered should, therefore, not be attributed to vaccine; all available evidence points to such cases being due to undiagnosed or unrecorded natural infection, which can be very mild.

Perinatal infection of the infant, as a result of maternal measles infection around the time of delivery, may give rise to SSPE with a short onset latency and fulminant course. Such cases have been rarely reported in the literature. SSPE arising during pregnancy appears to be fulminant. The fetal outcome is often unfavourable due to the obstetric consequences arising from the mother's condition. However, no infant that has survived has been subsequently diagnosed with SSPE. There is no evidence of a link between measles vaccination in pregnancy and SSPE.

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KEY MESSAGES

- Measles vaccine directly protects against SSPE by preventing measles infection and has the potential to eliminate SSPE through the elimination of measles.
- High vaccine coverage also offers indirect protection through herd immunity, protecting the unvaccinated from infection or delaying infection until a later age when SSPE risk is reduced; it is important to maintain high coverage or measles resurgence may occur in younger groups at higher risk of developing SSPE.
- In many countries with sustained good measles control an increasing SSPE onset age has been observed and in such countries good paediatric surveillance may be in place, but cases in older individuals may be going undetected.
- Evidence does not suggest that measles-containing vaccines can cause SSPE; in individual cases with a history of vaccine and no known natural infection all evidence points to wild virus being the cause.
- Measles-containing vaccines do not appear to: accelerate the course of SSPE; trigger SSPE; or cause SSPE in a person with an established benign persistent wild measles infection.

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