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Sero-epidemiology of mumps in western Europe

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SUMMARY

Six countries (Denmark, England and Wales, France, Germany, Italy and the Netherlands) conducted large serological surveys for mumps, in the mid-1990s, as part of the European Sero-Epidemiology Network (ESEN). The assay results were standardized and related to the schedules and coverage of the immunization programmes and the reported incidence of mumps. Low incidence of disease and few susceptibles amongst adolescents and young adults was observed in countries with high mumps vaccine coverage (e.g. the Netherlands). High disease incidence and large proportions of mumps virus antibody negative samples in adolescent and young adult age groups was noted in countries with poor vaccine coverage (e.g. Italy). The build-up of susceptibles in older children and adolescents in England and Wales, France, the former West Germany and Italy indicate the possibility of further mumps outbreaks in secondary school environments. To control mumps in western Europe, current MMR immunization programmes will need to be strengthened in a number of countries. Sero-surveillance of mumps is an important component of disease control and its usefulness will be enhanced by the development of an international mumps standard.

INTRODUCTION

The classical symptoms of mumps are unilateral or bilateral parotitis, although many cases exhibit non-specific or primarily respiratory symptoms [1, 2] and approximately a third of all infections are asymptomatic [1, 3]. Infection is considered to provide lifelong immunity, although rare cases of re-infection with mumps virus have been documented [4]. Mumps is often considered as a benign illness with a low mortality, although the burden of disease should not be underestimated [5]. Central nervous system (CNS) complications are common, usually appearing as aseptic meningitis, which occurs in approximately

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5% of patients with mumps [1, 2]. In younger children, mumps was the major cause of acquired sensorineural deafness prior to the introduction of immunization programmes [1]. Although orchitis is a common complication after puberty, occurring in approximately a third of cases, sterility is rare [1].

A number of live attenuated mumps vaccines have been developed and since the 1980s these vaccines have been used increasingly as part of a trivalent combination vaccine for measles, mumps and rubella (MMR). The International Task Force for Disease Eradication identified mumps as a potential target for eradication, and recommended that this should be linked to the policy of combined vaccination against measles and rubella [6]. The World Health Organisation, Regional Office for Europe (WHO/EURO), established a control target of an annual incidence of less than one case of mumps notified per 100000 of the population to be achieved by its member countries by 2010 [7].

The European Sero-Epidemiology Network (ESEN) was established in 1996 with the aim of coordinating and harmonizing the serological surveillance of immunity to several vaccine-preventable diseases in Europe including mumps [8]. In this paper, the standardized mumps antibody levels measured in national serological surveys undertaken in six west European countries are compared. This provides a unique opportunity to compare the results of these mumps sero-surveys, to assess the serological and epidemiological impact of different mumps vaccination schedules, the level of vaccine coverage attained and to determine progress towards mumps control in western Europe.

METHODS

Vaccine programme structure and coverage

A questionnaire was distributed to all participating countries to gather data on the history and the organization of the national mumps vaccine programmes, the current and historical reported vaccine coverage, the structure of the surveillance system for mumps disease and the age-specific incidence of notified mumps cases. Some of these results have previously been reported [11]. On the basis of mean reported vaccine coverage for mumps vaccine in the 3 years prior to the collection of the main serum banks, countries were divided into high (vaccine coverage $>90\%$), medium (vaccine coverage 80–90%) and low coverage countries ($<80\%$).

Serum survey collection

Six countries in ESEN undertook testing for mumps antibody of sera specimens collected between 1994 and 1998 (Denmark, England and Wales, France, Germany, Italy and the Netherlands). The sera were obtained by using the residual sera collected during routine laboratory testing except the Netherlands, where sera were collected by population-based random sampling, and Denmark, where both methods were used [9]. The number of sera collected per country ranged from 2766 to 8303, were evenly distributed between males and females and from a variety of geographical locations within each country to provide a reasonably representative age-specific estimate of immunity to mumps in the general population. Further details of the sera collection have been published elsewhere [9].

Standardization: reference panel distribution and testing

The methodology and the results of the qualitative and quantitative standardization of the mumps virus antibody results has been described elsewhere [10]. In brief, the reference centre (Robert Koch Institute, Berlin, Germany) prepared a panel containing 150 sera that were positive, equivocal or negative as tested using the Behring Enzygost enzyme immunoassay. These panels were then distributed to the national laboratory in each participant country where they were tested with the quantitative enzyme immunoassay normally used to measure levels of serum mumps antibody.

Local titres were converted to standard titres by regressing the results of the panel testing of the national centre against those of the reference centre and thus obtaining standardization equations which could then be applied to the results of the testing of the main serum banks. The standardization of the assays were evaluated quantitatively by determining the fit of the equation using R^2 (the square of multiple correlation coefficients) and qualitatively by assessing the level of concordance in identifying positive, negative and equivocal results.

Main serum bank testing

Each main national bank survey was tested using the same validated assay method as was used for the reference panel. The country-specific standardization equations were then used to convert the local

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quantitative results of the serum survey into standardized reference laboratory units. The reference laboratory cut-offs were used to re-classify qualitatively the standardized quantitative results as negative, equivocal or positive.

Modelled MMR vaccine coverage

A descriptive analysis was conducted in which country-specific sero-profiles were interpreted in the context of that country's mumps vaccination programme history (Fig. 1). MMR vaccine coverage was estimated using modelling techniques in which ESEN serological data at the individual level were used to calculate the proportion of individuals of a given age who had either been vaccinated or infected with each of the three viruses [12]. Reported mumps vaccine coverage was used for age groups targeted by a mumps, but not MMR, immunization programme.

RESULTS

Mumps vaccination programmes

Routine vaccination for mumps was conducted in two countries (West Germany and France) before the introduction of an MMR vaccine (Table 1). In the former West Germany a combined measles–mumps vaccine had been available since 1976. In France, from 1983 a single mumps vaccine was targeted at 12-month-old children until 1986 when MMR was introduced.

By 1991, MMR had been introduced in all countries (Table 1), all of which now have a two-dose schedule. However, in some countries the second dose was introduced either just prior to (France and England and Wales in 1996) or since the completion of this study (Italy in 1999). Following the unification of Germany, a two-dose MMR schedule was introduced in 1991 which replaced a one-dose schedule that had been in place since 1981 in the former West Germany and the absence of any mumps immunization programme in the former East Germany.

In all countries, the first MMR dose is targeted at children in their second year of life (12–18 months) but the second dose is recommended for a wide range of ages. The majority of countries target the second MMR dose to children aged between 3 and 6 years old (England and Wales, France and Germany). However, older children are targeted in Denmark (12 years old) and the Netherlands (9 years old). The Jeryl Lynn and derived strains of mumps virus are now used in most countries, and in Italy it replaced the Rubini vaccine strain which was withdrawn in 2001 [13]. Vaccines using the Urabe mumps strain were withdrawn from routine use in many countries in the 1990s due to an increased risk of vaccine-associated mumps meningitis [14].

Reported mumps vaccine coverage

A reported coverage for the first dose of the MMR vaccine was available for all countries, except Germany, and was calculated using routine data sources except in France and Italy. In France, prior to 1993, mumps vaccine coverage at 2 years of age was reported from routine data sources and, 1993 onwards, from annual surveys of 3–4 year-old children. In Italy, regional cluster surveys using the Expanded Programme on Immunization methodologies were conducted in 1984, 1991 and 1998 [15, 16].

Using the reported mumps vaccine coverage in the 3 years prior to the serological surveys, England and Wales and the Netherlands had high vaccine coverage of greater than 90% and Denmark and France, a medium coverage of between 80 and 90% (Table 2). Italy and Germany were considered as countries with low vaccine coverage. In Italy, the most recent report of mumps vaccine coverage was less than 60%. Reported MMR vaccine coverage was not available for Germany, though modelled estimates of recent MMR vaccine coverage was approximately 60% [12].

Mumps surveillance data

In the most recent years, the annual reported incidence of mumps cases has been less than one per 100000 of the population in Denmark and in the Netherlands (Table 1). In England and Wales, the reported incidence of mumps in 1996 was only just above this target (3·4/100000), although by 2000 the incidence of mumps had increased slightly to 4/100000 [17]. In Italy and France, the incidence of reported disease was very much higher than the target of one case per 100000 of the population. In Italy, the incidence of mumps disease was 113/100000 in 1996. In France, the reported annual incidence of mumps was 84/100000, although since 1996 it has continued to decline and in 2000 the incidence was reported as 29/100000 [18].

Mumps assay standardization

The standardization of the mumps panel was successful with R^2 values greater than 0·85. For the

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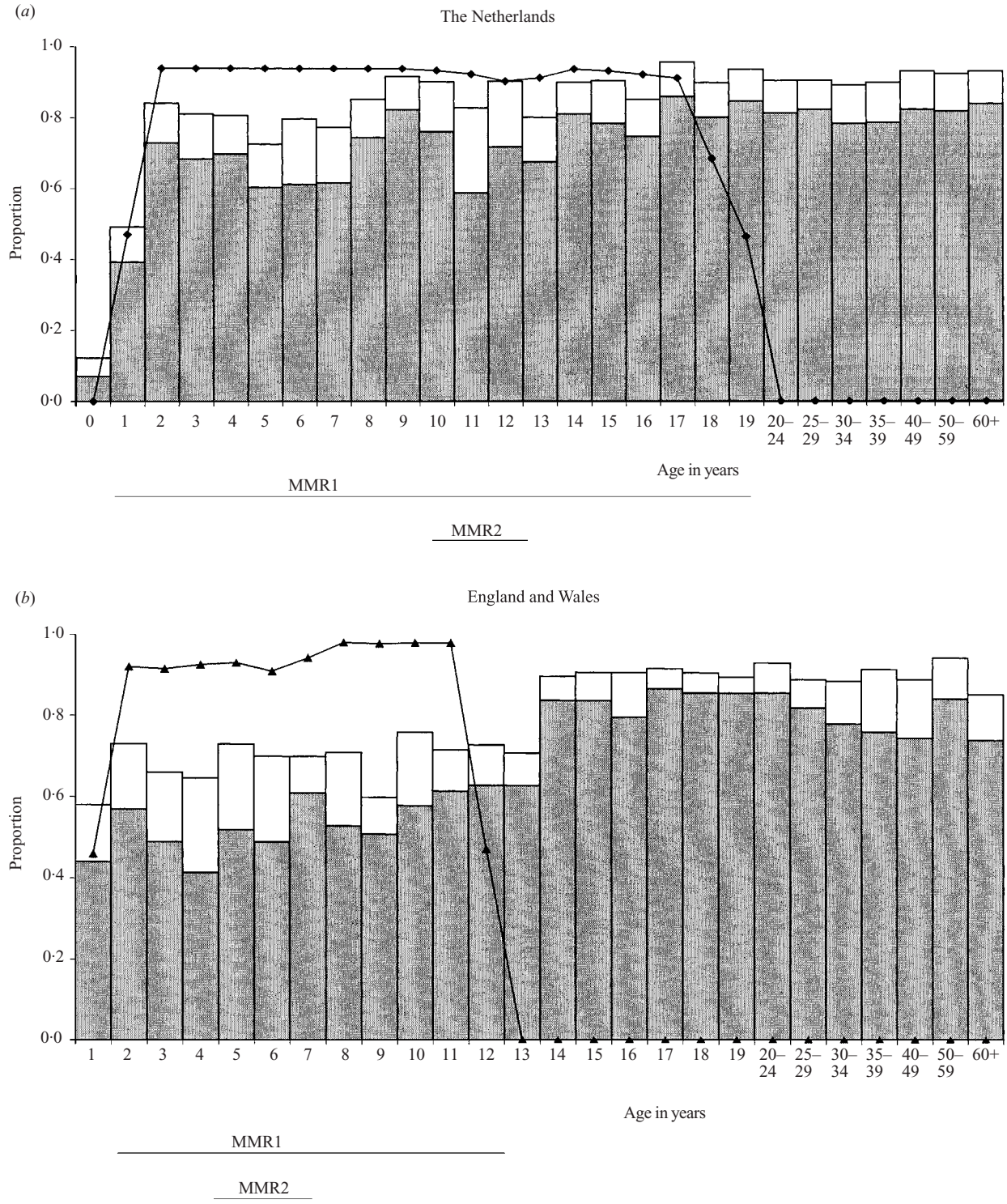

Fig. 1. For legend see page 697.

semi-quantitative comparison after standardization, agreement was very good except for Denmark in which 12 of the 69 positive sera identified by the reference centre were tested negative [10].

Mumps serum bank testing and modelled MMR vaccine coverage

In the Netherlands, despite an MMR vaccine coverage estimated to be consistently above 90%, the

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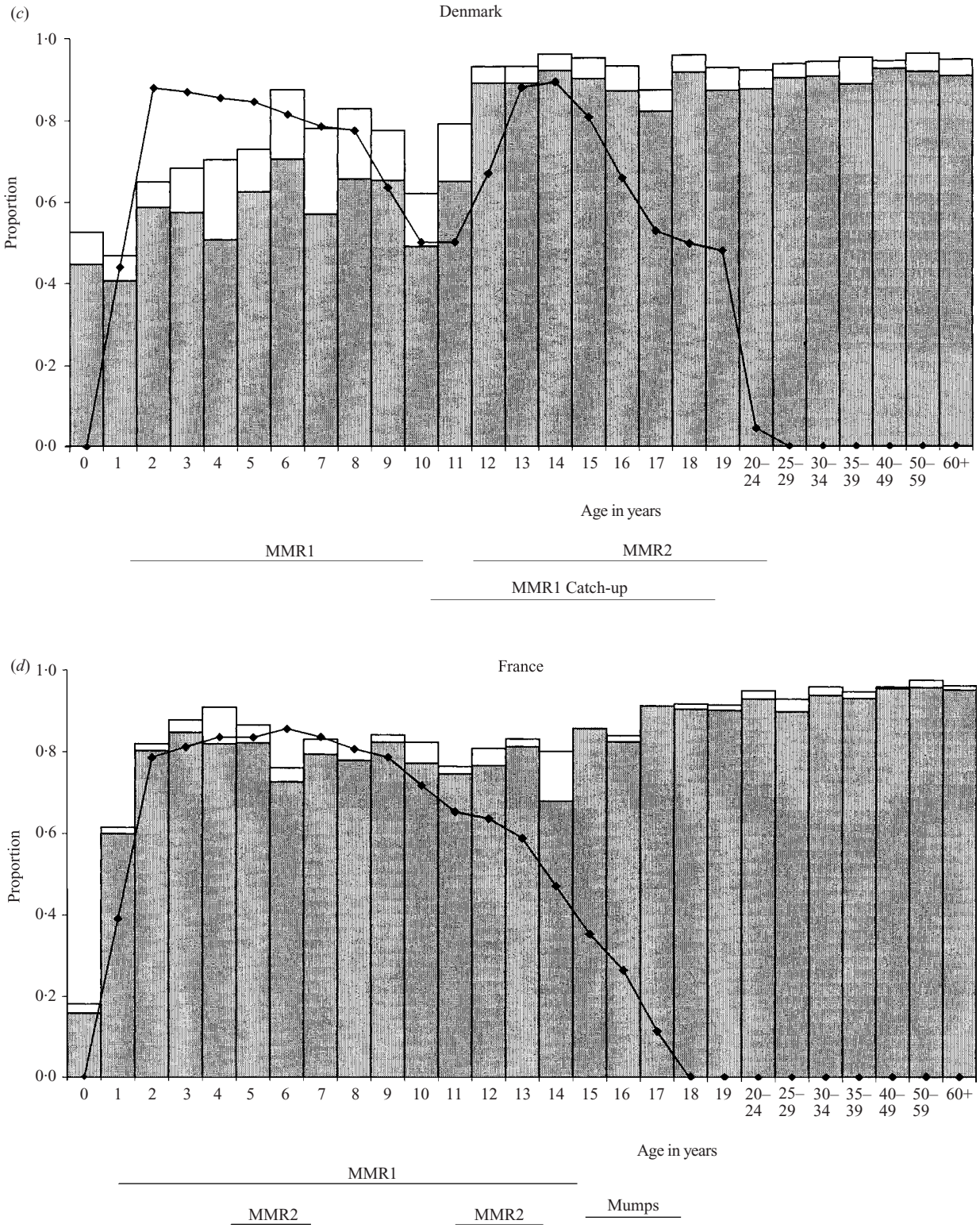

Fig. 1. (*cont.*)

sero-prevalence of mumps virus antibodies in younger children is relatively low (Fig. 1). The sero-prevalence was 81% in younger birth cohorts (2–8 years old) who had received one dose MMR, lower than those who had received a second MMR dose (9–12 years old; 89%, $\chi^2 = 14{\cdot}40$, $P < 0{\cdot}001$). In England and Wales, a sero-prevalence of mumps virus antibodies greater than 80% was only found in samples collected

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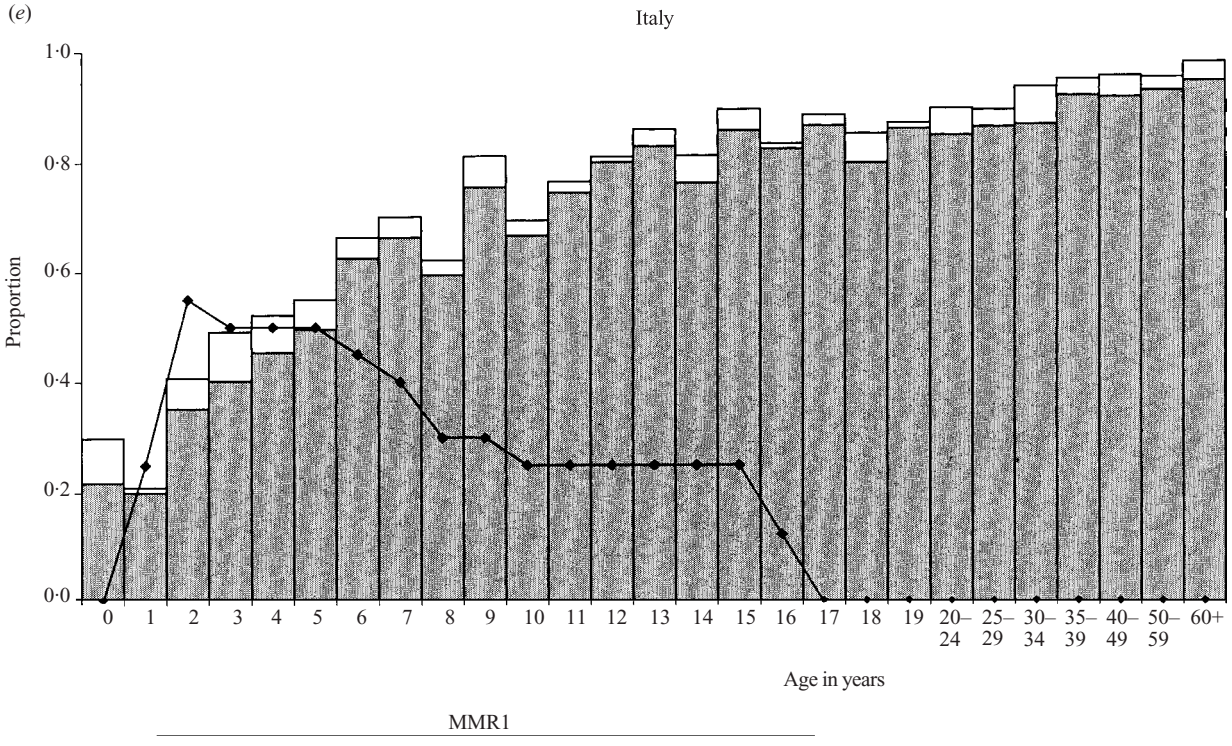

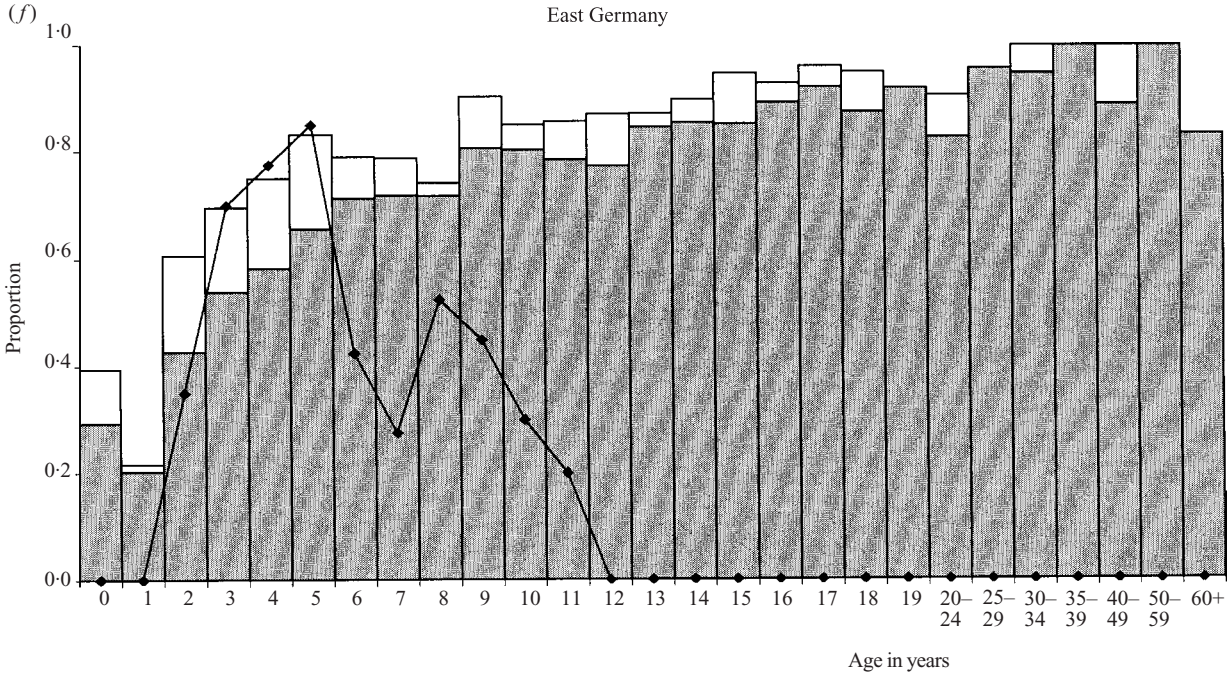

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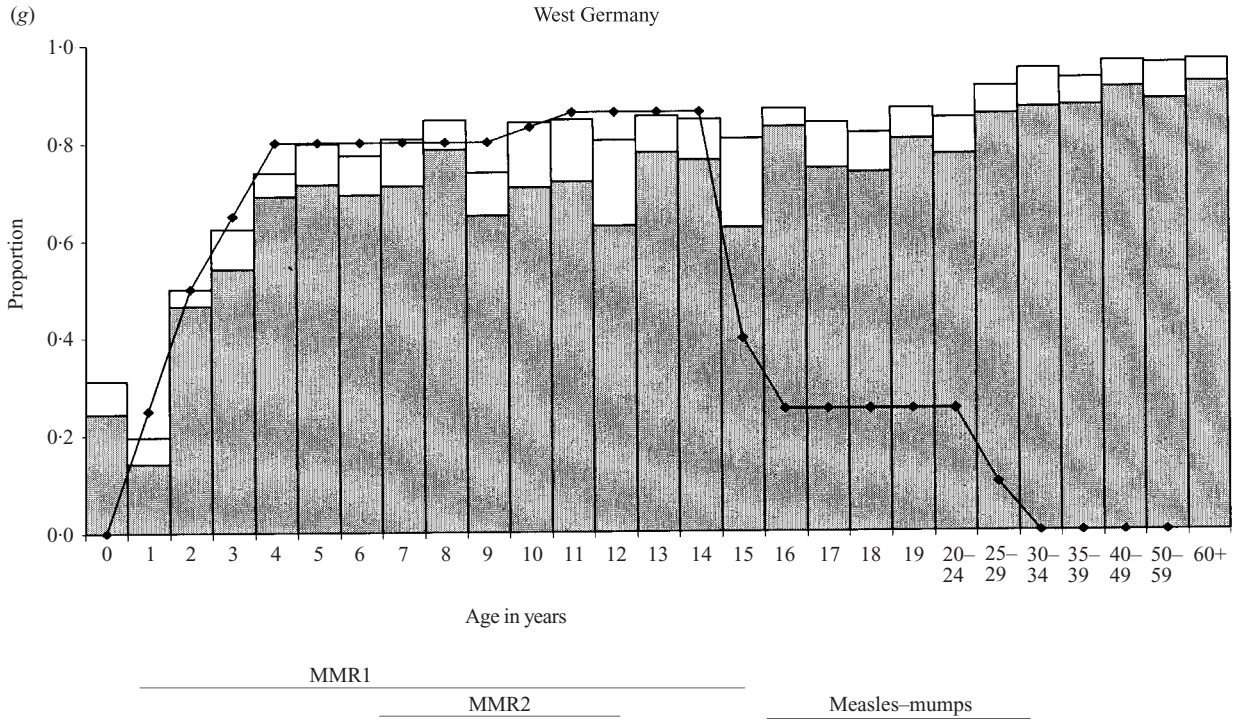

Fig. 1. Seroprevalence of mumps virus antibody for each country (dark bars, mumps virus antibody positive; light bars equivocal). The vaccine coverage in each age group is either estimated from modelling studies (when immunization is with MMR vaccine) or reported data when mumps vaccine is used alone (France in 15–18 year olds) or in combination with a measles vaccine (West Germany in 16–34 year olds). Vaccine history was defined as MMR1 (single dose MMR mass vaccination programme); MMR2 (second dose MMR mass vaccination programme); catch-up MMR: mumps or measles–mumps.

from adolescents or adults (Fig. 1). Amongst young children (2–9 years of age), the sero-prevalence is less than 70% (Table 3), even though in these age groups the MMR vaccine coverage has been estimated at over 90% (Fig. 1).

In Denmark the sero-prevalence of mumps virus antibodies greater than 80% was only found in samples collected from adolescents or adults (Fig. 1). In children aged between 6 and 10 years old, there was a decline with age in the sero-prevalence of mumps virus antibodies (Fig. 1, $\chi^2_{\text{test-for-trend}} = 16{\cdot}00$, $P < 0{\cdot}001$), with a low of 62% in 10-year-old children. In 13-year-old children, the sero-prevalence was over 90%, which coincided with an increase in the estimated vaccine coverage as well as a second dose administered at 12 years old. In those birth cohorts who had received a second MMR dose (aged 12–19 years), both the proportion of equivocal samples was lower (Fig. 1, 4·7% *vs.* 14·5%, $\chi^2 = 22{\cdot}60$, $P < 0{\cdot}001$) and the geometric mean titres were larger (714; 95%CI 655–778 *vs.* 2·308; 95%CI 2·107–2·52580, $P < 0{\cdot}001$) than in those who had received only one dose of MMR (aged 2–9 years).

In France, amongst younger children between 2 and 4 years of age, the sero-prevalence of mumps virus antibodies was nearly 90% (Fig. 1). However, amongst older children and adolescents (i.e. 6–15 years of age), the sero-prevalence of mumps virus antibodies declined to less than 80%, which corresponded with a decline in the estimated vaccine coverage. In Italy, the modelled vaccine coverage of the one dose MMR vaccine programme exceeded 50% only in recent years, an increase from the initial coverage of 25% (Fig. 1). Of all the six countries, the lowest sero-prevalence amongst children was observed in Italy and a sero-prevalence of mumps virus antibodies greater than 80% was observed only amongst those older than 14 years of age (Table 3, Fig. 1).

The sero-profiles of the former German states are presented separately (Table 3, Fig. 1) as only in the former West Germany was a mumps vaccination programme in place until reunion in 1991, even though vaccine coverage was estimated to be low (approximately 30%). The sero-profiles of the former East and West Germany were similar, the proportion of sero-negative samples declined with age, from

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Table 1. *Immunization strategies for mumps in six European countries at the time of the ESEN study, 1998*

	Denmark	France	Italy	England and Wales	Germany	Netherlands
Strategy prior to MMR introduction	None	Yes*	None	None	Yes†	None
Year of MMR introduction	1987	1986	1982	1988	1991	1987
Recommended number of doses of MMR	2	2‡	1§	2‖	2	2
Age groups targeted	15 months 12 years	12 months 3–6 years	12–15 months	12–18 months 4 years	12–15 months 6 years	14 months 9 years
Mumps strains used in MMR	Jeryl Lynn	Jeryl Lynn	Rubini¶ Urabe	Jeryl Lynn**	Jeryl Lynn	Jeryl Lynn

* A one-dose mumps vaccine at 12 months introduced in 1983.
† In the former West Germany, a measles–mumps vaccine was introduced in 1976 and replaced by a single MMR dose at 15 months in 1981.
‡ In 1996 introduction of second MMR dose targeted at 11–13 year olds and then 3–6 year olds in 1997.
§ A second MMR dose introduced in 1999 for children aged 6–12 years of age.
‖ Single dose MMR until 1996.
¶ Rubini strain vaccines replaced by Jeryl Lynn strains in July 2001.
** Urabe strain vaccines withdrawn in 1992.

Table 2. *Incidence of reported mumps disease (/100000) and reported coverage of MMR vaccine by 2 years of age in five European countries, from 1990 to the end of the ESEN study in 1998*

	Denmark		England and Wales		France		Italy		Netherlands	
Year	Incidence (/100000)	Vaccine coverage	Incidence (/100000)	Vaccine coverage	Incidence (/100000)	Vaccine coverage*	Incidence (/100000)	Vaccine coverage	Incidence (/100000)	Vaccine coverage
1990	8·8	84	26·0	86	187·9	54	106·3		0·2	95
1991	6·1	86	20·8	90	221·5	52	71·4	9–53†	0·3	94
1992	3·6	85	15·6	92	242·9	62	51·1		0·3	94
1993	2·9	81	4·2	91	159·9	80	51·0		0·3	95
1994	0·5	88	4·8	91	93·1	84	66·3		0·2	94
1995	0·2	88	3·7	92	84·1	85	115·1		0·2	94
1996	0·8	85	3·4	92	83·8	88	112·9		0·2	94
1997	0·6	84	3·7	91	70·0	89	51·6		0·3	96
1998	0·4	88	3·0	88	45·0	91	25·6	26–87†	0·2	96

* Up to 1992, vaccine coverage was reported for 2-year-old children, and from 1993 for 3–4-year-old children.
† Vaccine coverage estimated using cluster sampling of 2-year-old children.

approximately a third of children aged 2–4 year olds to less than 10% amongst adults. Only amongst 15–19 year olds was a difference in the sero-profiles noted (Table 3) with the proportion of mumps virus antibody negative samples greater amongst those in the former West Germany than in the former East (16% *vs.* 6%, $\chi^2 = 17{\cdot}79$, $P < 0{\cdot}001$).

DISCUSSION

This report describes the comparative sero-epidemiology of mumps infection in six European countries. The aim of the ESEN project was to standardize serum bank testing so that by establishing a common standardized unitage for assay titres, international comparison could be made. In this study, all participant countries used the presence of mumps virus serum IgG antibodies, as measured by enzyme immuno-assays, as a marker of immunity.

In the pre-vaccination age groups, mumps was a childhood illness and most individuals had acquired immunity by early adulthood [19]. The MMR vaccine programmes, introduced in most west European countries during the 1980s, have targeted children. In

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Table 3. *Percentage mumps virus antibody negative by age group for countries participating in ESEN, 1994–98. (n is the number of samples tested).*

	Percentage mumps virus antibody negative by age group											
	12–23 months		2–4 years		5–9 years		10–14 years		15–19 years		20+ years	
Country	%	(*n*)	%	(*n*)	%	(*n*)	%	(*n*)	%	(*n*)	%	(*n*)
Denmark	53·1	(96)	32·3	(269)	19·3	(458)	15·5	(497)	6·8	(340)	5·8	(1409)
England and Wales	42·0	(100)	32·1	(299)	31·2	(500)	23·6	(499)	9·0	(500)	9·4	(1400)
France	38·5	(65)	12·9	(194)	18·0	(294)	19·0	(274)	10·2	(364)	3·3	(1644)
East Germany	88·4	(153)	31·8	(327)	19·1	(634)	13·3	(445)	5·8	(295)	5·6	(144)
West Germany	80·4	(56)	36·6	(227)	20·8	(419)	16·4	(397)	16·1	(429)	6·9	(1373)
Italy	79·8	(100)	52·5	(339)	33·2	(542)	21·3	(520)	12·7	(671)	6·3	(1455)
Netherlands	50·8	(250)	18·0	(573)	18·6	(559)	13·3	(580)	8·8	(455)	7·5	(5261)

some countries, notably Denmark, England and Wales and the Netherlands, the sero-prevalence of antibodies to mumps virus in these age groups was much lower than either reported or estimated vaccine coverage. The discordance between vaccine coverage and immunity in the population may be due to the assay employed, including problems in the standardization procedure, or due to primary or secondary vaccine failure.

The standardization of assay results permitted the comparison of immunity to mumps in several different European countries, although there remained variations in laboratory cut-offs and some residual lack of comparability [10]. For example, despite the standardization of the Danish assay results, a lower sero-positivity was observed [10], which may explain, in part, the discordance between sero-prevalence and vaccine coverage data. The EIA are more sensitive than other techniques [20, 21], probably due to the detection of antibodies involved in complement-mediated immunity [20, 21]. Different EIAs were used in the Netherlands and England and Wales to that of the reference centre, and as mumps antibody titre can vary with the virus antigen used in the assay [22], this may also explain the observed discordance in sero-prevalence and vaccine coverage [10]. The development of an international mumps reference antibody preparation will further enhance the comparability of mumps sero-prevalence data [10, 23].

Failure of the mumps vaccine has been attributed to primary vaccine failure [24]. Sero-conversion rates following mumps vaccination, estimated by modelling ESEN sero-prevalence data, varied in the different countries [12]. For example, in the Netherlands, the sero-conversion rate was estimated to be 82% [12] and this may explain some of the observed discordance in vaccine coverage and sero-prevalence. In Italy, where until recently the Rubini strain was commonly used, modelled sero-conversion rates were very low – approximately 60% [12]. The Rubini strain has been shown not to offer good protection against the disease [25, 26], and the use of this strain in the MMR vaccine, as well as the poor vaccine coverage, may have contributed to the low mumps virus antibody positivity observed.

The administration of a second MMR dose has been shown to boost serum IgG antibody levels [27, 28], although it remains unclear whether waning antibody levels represents secondary vaccine failure or if other mechanisms of immunity exist [24, 28]. In Denmark and in the Netherlands, an increase in mumps virus antibody positivity was observed in those birth cohorts in whom a second MMR dose had been administered. However, no consistent trend was observed, although, at the time of the study, three of the six countries had only just implemented a two-dose MMR immunization strategy. In countries with well-established vaccine programmes, the lack of circulating wild virus may not boost immune responses, resulting in waning immunity. In contrast, there would be circulation of wild virus in countries with poor vaccine programmes. This may partly explain the discrepancy between vaccine coverage and mumps virus antibody prevalence noted in Denmark, Netherlands, England and Wales, but not in Italy and Germany.

The level of population immunity required to block transmission of mumps has been estimated using mathematical models to be between 85 and 90% [19, 29, 30]. In countries with high vaccine coverage, such

as the Netherlands, the proportion of older children and adolescents with antibodies to mumps virus was above these levels. In contrast, in countries with poor vaccine coverage, such as Italy, large proportions of susceptibles were noted in these older age groups, although almost all individuals had become immune by early adulthood due to the continued circulation of the wild virus. We noted large proportions of susceptibles amongst older children and adolescents in England and Wales, France, the former West Germany and Italy, and it is in older age groups that the sequelae of mumps are more serious [31]. Recent outbreaks of mumps in secondary educational establishments [32, 33] demonstrate the continuing possibility of outbreaks in these older age groups [30].

Denmark and the Netherlands have achieved the WHO/EURO target of less than one case of mumps annually per 100000 of the population. England and Wales are close to achieving this target, although this is not the case in France or Italy. These discrepancies in incidence of disease between countries with similar vaccine coverage may be due to different histories of immunization programmes. However, the use of surveillance data for either setting targets or to compare disease epidemiology between different countries is fraught with difficulties [11]. For example, in France, unlike other countries, the mumps incidence data is extrapolated to account for the incompleteness of mumps notifications [34]. Although laboratory confirmation of mumps cases has been recommended, especially in countries with a low incidence, to minimize the poor sensitivity of clinical case definitions [5], only in England and Wales is this practiced using salivary samples [30].

To control mumps in the countries involved in this study, MMR immunization programmes will need to be either strengthened or maintained by ensuring that a two-dose immunization schedule is employed and that vaccine coverage of the first dose is greater than 90%. Alongside the enhancement of the MMR vaccine programmes, measures to improve the surveillance of both the mumps immunization programme and disease, such as routine vaccine coverage, age- and sex-specific incidence data including the laboratory confirmation of cases, will need to be introduced in many countries. Sero-surveillance of mumps is an important component in the monitoring of disease elimination targets as, unlike reported surveillance of disease, a clearer picture of population susceptibility is obtained and these data are less open to biases. In future, the sero-surveillance of mumps will be enhanced by the development of an international standard [23].

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