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The sero-epidemiology of diphtheria in Western Europe

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SUMMARY

Seven countries in Western Europe collected large, representative serum banks across the entire age range and tested them for diphtheria anti-toxin (sample size ranged from 2991 to 7715). Although a variety of assays were used, the results were all standardized to those of a reference laboratory and expressed in international units. The standardization process, and the availability of similar, large data sets allowed comparative analyses to be performed in which a high degree of confidence could be ascribed to observed epidemiological differences. The results showed that there were large differences in the proportion of adults with insufficient levels of protection amongst different countries. For instance, roughly 35% of 50- to 60-year-olds were found to be seronegative (titre $\leqslant 0{\cdot}01$ IU/ml) in Finland compared with 70–75% in the United Kingdom. Furthermore, the proportion of seronegative adults would be expected to increase in some countries, notably Italy and the western part of Germany. In those countries with vaccination of military recruits there was a marked sex-related difference in the proportion of seropositive individuals. All countries have high levels of infant vaccine coverage ($> 90\%$) but the accelerated schedule in the United Kingdom appears to result in lower anti-toxin titres than elsewhere. In Sweden, booster doses are not offered until 10 years of age which results in large numbers of children with inadequate levels of protection. Although the United Kingdom and Sweden both have higher proportions of seronegative children than elsewhere the likelihood of a resurgence of diphtheria in these countries seems remote.

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INTRODUCTION

Before the introduction of active vaccination, diphtheria was endemic in most European countries. It was a childhood infection, with roughly 80% of the population immune by the age of 15 years [1, 2]. The disease was characterized by periodic epidemics, with the last major European epidemic occurring during the 1940s (as described below). With socio-economic improvement and the introduction of mass infant immunization during the 1940s and 1950s, there was a remarkable reduction in the incidence of infection in Europe. The near elimination of diphtheria from Europe at, in some countries, relatively modest coverage, demonstrates that mass immunization leads to herd immunity even though vaccine induced immunity is not directed against the diphtheria bacterium but its toxin.

With an all-time low number of reported cases of 623 in 1980 [3], the WHO seemed within reach of its target of diphtheria elimination in Europe by the year 2000 [4]. However, in 1990, epidemic diphtheria re-emerged in the Newly Independent States (NIS) of the former Soviet Union after several decades of control. The outbreak began in the Russian federation, and quickly spread to all 15 of the NIS [5–7]. In 1994, nearly 40000 cases were reported in Russia alone [5, 6]. As many of these cases occurred in adults [7], most of which would have been previously vaccinated, it seems that immunity as well as antibody levels [8–10] may decline with time since vaccination.

It is now critical to assess whether there is a potential risk in other European countries of large epidemics and/or sporadic cases due to travel of unprotected individuals to endemic or epidemic areas. Hence it has become crucial to document the levels of susceptibility in Western Europe and compare the effectiveness of the different vaccination programmes. Although a number of studies have shown that the proportion of susceptible adults might be high [1, 10–22], some of these were conducted a number of years ago, and, if waning vaccine induced protection is the cause, then the levels of susceptibility might be expected to have increased over time. In addition, as the various studies used different tests and methods of sera collection, observed differences between countries which might imply differences in epidemic risk could be artefacts of different methodologies or small or biased samples. For instance, many of these studies were of blood donors (which might not be representative) or were undertaken using methods which have poor sensitivity and specificity at low anti-toxin concentrations [1]. Vero cell culture toxin neutralization assay [1] and the recently described double antigen techniques [23, 24] have been shown to have a high specificity. Hence there is an urgent requirement for up-to-date, large, representative samples to be tested with sensitive and specific methods.

We report the results of recent, large, population-based serum surveys from seven different European countries, tested for antibodies to diphtheria toxin. Although the laboratories used a variety of tests, the results were standardized to the designated reference laboratory in Finland. As results could be expressed in equivalent units any observed differences between countries is likely to represent real epidemiological variation.

METHODS

Sera collection

Seven member countries of the eight European Sero-Epidemiology Network, ESEN (Italy, Germany, Finland, France, The Netherlands, England and Wales, and Sweden) undertook collection of several thousand sera specimens between 1995 and 1998 and tested them for diphtheria antitoxin. The minimum number of sera to collect per age group was determined from power calculations using age specific estimates of sero-prevalence of antibody to various vaccine preventable infections including diphtheria toxin. The target number of samples were 100 from yearly age classes 0–19 years of age, then 200 samples from 5-yearly age classes to 35–39 years, then 200 from 10-year age classes to 50–59 years and 200 samples from those over the age of 60 years.

Two sources of sera were used: prospective, population based random sampling (The Netherlands and Sweden) and residual sera colleted during routine laboratory testing (the remaining countries). In The Netherlands a two-stage sampling technique was used (8 municipalities selected with probability proportional to their size in each of 5 regions). Within each municipality 380 individuals were randomly selected, from the population register. Approximately half of those invited to participate provided a serum sample [25]. In Sweden, adult samples ($>$ 19 years of age) were randomly selected by a similar two-stage sampling plan from each county except Stockholm [26]. Children were selected randomly from within parishes previously chosen as pertussis vaccine trial sites [27, 28]. Age groups were sampled immediately before

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booster doses are given in the Swedish schedule. Samples in the United Kingdom were collected from residues sent to 18 laboratories around the country for microbiological or biochemical investigation [29]. Italy and Germany followed similar sampling regimes. In Italy samples were collected from 19 of the 20 regions, and in Germany from each state, via seven non-randomly selected laboratories. Samples in France were collected from a network of laboratories set up as part of the project: at least one laboratory was in each region, with no more than 200 samples taken from each laboratory. Samples were also taken from the emergency or outpatient departments of paediatric hospitals. In Finland, samples were taken from individuals visiting 15 health centres around the country for a general medical examination, or were taken from samples sent to laboratories for diagnostic purposes. In all cases samples were collected from a wide range of geographical locations within each country, and, to avoid systematic bias, sera likely not to be representative of the population were excluded (i.e. sera from patients known to be immunocompromised, or with known recent blood transfusion).

For each serum specimen, a minimum data set including age, sex and year of collection was gathered. Some laboratories also recorded the geographical region from which the sample was collected. This allowed an analysis of German samples to be stratified according to whether the sample originated from a laboratory in the former East Germany or not, as East German individuals may have experienced very different histories of exposure and vaccination [22].

Testing and standardization

Each country undertook diphtheria anti-toxin testing (and also testing for mumps, measles, rubella and pertussis antibody) in a designated national laboratory. The assays were performed according to well described procedures [23, 24, 30–32]. Finland, France and Germany used the Vero cell neutralization test; the United Kingdom and Germany used double antigen delayed time resolved fluorescence immunoassay (DELFIA); The Netherlands used a toxin-binding inhibition test (ToBI); and Sweden used a single-antigen enzyme-linked immunosorbant assay (ELISA). Although the French laboratory tested their serum bank using both a double antigen ELISA and Vero cell assays the results presented here are those of the latter (chosen as it measures functional antibodies).

To achieve quantitative comparability of assay results between countries, the results of diphtheria toxin testing were standardized using a methodology developed as part of the ESEN project, which is to be described in detail elsewhere [33]. The results were calibrated to the Finnish neutralization test (chosen as it gave intermediate results compared with the other neutralization assays). Briefly, the process involved the distribution of a panel of negative, low positive and positive sera to all participating countries. The panels were tested using the local assays. Standardization equations were developed by regressing the local results against those of the reference laboratory. These equations were then used to convert the local quantitative results of the main serosurveys into standardized results. All quantitative results were expressed in international units.

The internationally accepted reference laboratory cut-off range was used to classify these standardized quantitative results [1]. Antitoxin concentrations, as measured by the neutralization test, of $\leqslant 0{\cdot}01$ IU/ml are referred to here as being seronegative. Antibody concentrations of 0·01–0·1 IU/ml are referred here as low positive, and antitoxin concentrations equal or greater than 0·1 IU/ml are termed here positives.

Vaccine programme structure and coverage

As part of ESEN, country specific data were gathered on diphtheria vaccine programme structure, historical vaccine coverage and reported incidence of diphtheria infection. Data were collected by means of a questionnaire distributed to the project co-ordinators in each of the eight countries. Details of the questionnaire and many of the results have already been reported [34]. We highlight here those aspects of this work which are important for interpreting the observed patterns of serological markers.

RESULTS

Table 1 provides a summary of the current diphtheria immunization schedules and recommendations in the eight ESEN countries, as well as the year of introduction of infant immunization and recent changes to the schedule. All countries give 3 or 4 doses over the first year of life starting at either 2 or 3 months of age. The scheduling of the booster doses in children is highly variable across the different countries: the number of boosters scheduled for children varying between one in Denmark and Sweden to four in France. Italy, Germany and Finland

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Table 1. *Current diphtheria vaccination programmes and recommendations in ESEN member countries*

	Germany	Denmark	Finland	Italy	France	The Netherlands	Sweden	United Kingdom
Year introduced	1934	1930s	1943	1939	1938	1952	1951	1940
Primary series	3, 4, 5 mo	3, 5, 12 mo*	3, 4, 5 mo	3, 5, 11 mo	2, 3, 4 mo*	3, 4, 5 mo	3, 5, 12 mo	2, 3, 4 mo*
Lf of toxoid (infant dose)	> 30 IU	50 Lf < 1997 25 Lf now	19 Lf	25–30 Lf	30 Lf	15 Lf	> 30 IU	30 IU
Age of boosters	12–15 mo 6 yr 11–15 yr	5 yr*	24 mo 11–13 yr* 10 yr intervals	5–6 yr	16–18 mo 6 yr 11–13 yr 16–18 yr	11 mo 4 yr 9 yr	10 yr	3·5 yr 15 yr*
Target populations	10 yr booster	1. Travel recommendation	1. Travel recommendation	1. 10 yr booster 2. Travel recommendation	1. Health professionals 2. Travel recommendation	1. Travel recommendation to young unimmunised children 2. Refugees	1. Travel recommendation 2. Socially disadvantaged	1. Case contacts 2. Travel 3. Lab workers
Military recruits			Yes*		Yes	Yes	Yes	
Age shift for infant (D) to adult dose (d)	6 yr	D only	11 yr	7 yr	19 yr	4 yr	D only	15 yr

* Following changes:
France: prior to 1986 primary course was 3, 4, 5 months. **Denmark**: prior to 1996 primary course was 5, 6, 15 months, no 5 yr boost. **United Kingdom**: prior to 1991 primary course was 3, 5, 10 months; prior to 1994 no Td booster at 15 years. **Finland**: prior to 1989 no booster at 11–13 yr, no 10-yearly booster; 1990, reintroduced for men in military service; 1994, campaign targeted > 40 yr olds.

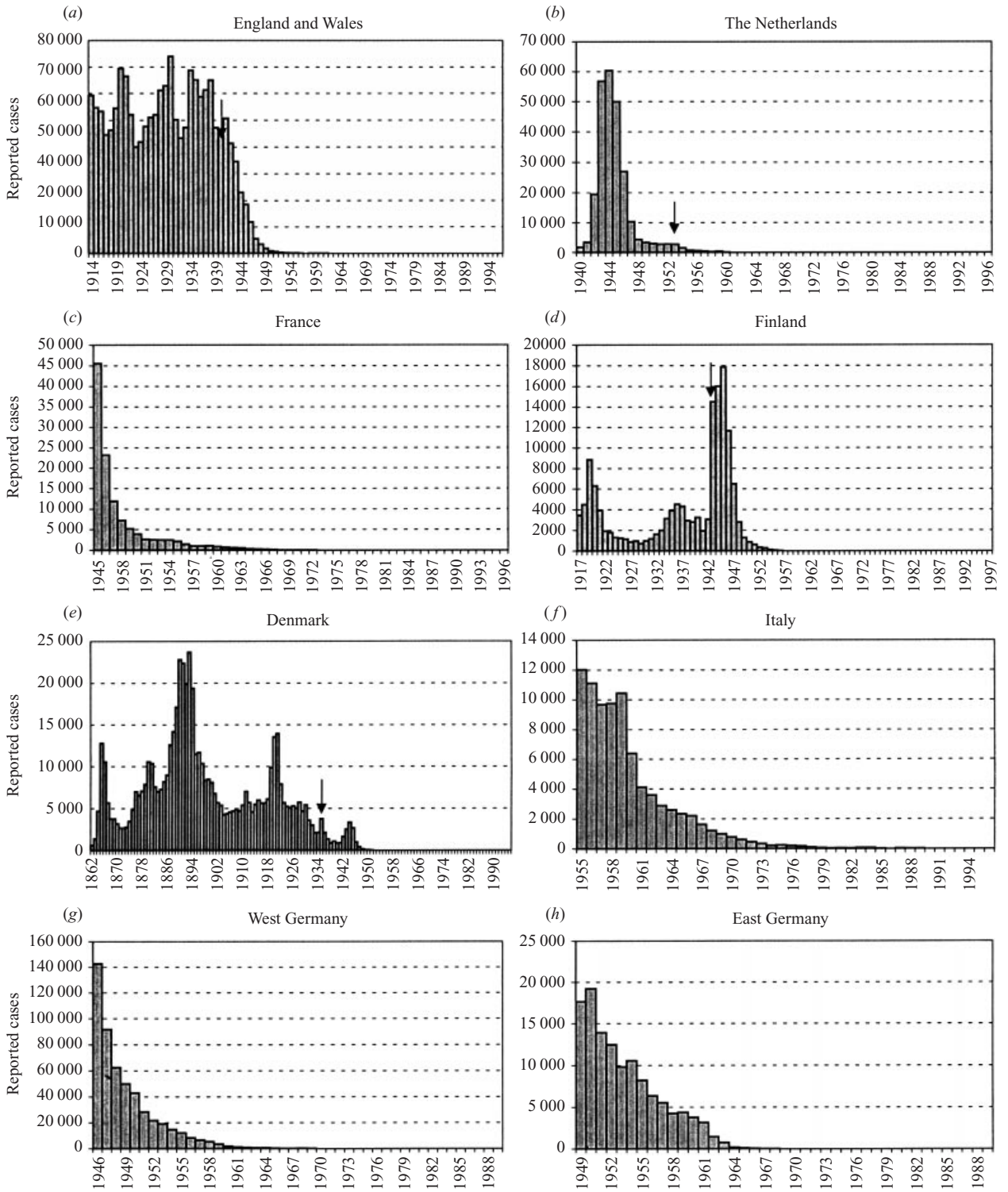

Fig. 1. Annual notifications of diphtheria from (*a*) England and Wales, (*b*) The Netherlands, (*c*) France, (*d*) Finland, (*e*) Denmark, (*f*) Italy, (*g*) West Germany and (*h*) East Germany [35]. Note the differences in scales. Arrows indicate the year in which mass diphtheria vaccination was introduced (see Table 1). In Italy, France and Germany vaccination was introduced before the available time series.

recommend a 10-yearly booster dose be given to adults. All countries recommend that travellers to endemic/epidemic areas receive a booster.

Figure 1 shows time trends in case notification data from a number of the study countries. There was a decline in the incidence of diphtheria in Northern

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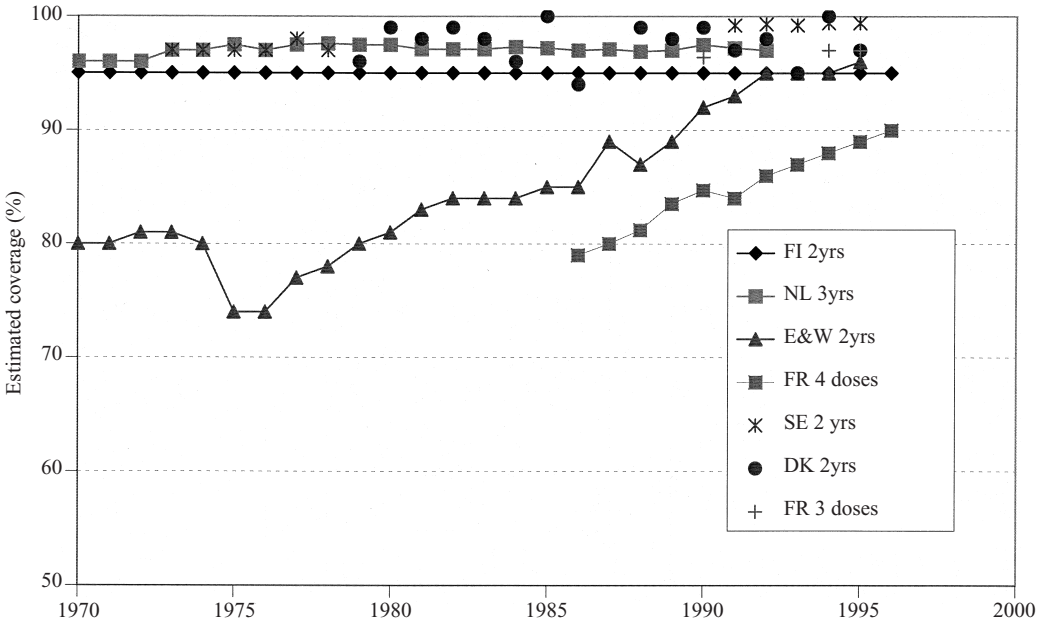

Fig. 2. Estimated coverage of primary immunization course in six of the ESEN countries. The age at which coverage was estimated is given in the legend. Data from France are also presented on the estimated coverage for the first booster (at 16–18 months), as few data were available on the primary course coverage.

Europe during the 1920s and 1930s presumably as a result of improvements in socio-economic conditions. In The Netherlands, Finland and Sweden, this decline in incidence was followed by an epidemic during the Second World War. (In Finland this was preceded by a smaller epidemic in the mid-1930s). Although mass vaccination was introduced in Germany in 1930s it had little effect until the mid to late 1950s (DPT was licensed for use in West Germany in 1959 and became compulsory in East Germany in 1961). Taking results together suggests that birth cohorts born after the late 1940s in The Netherlands, United Kingdom, Sweden and perhaps France, are very unlikely to have experienced natural infection, whereas in Germany those born after the late 1950s are unlikely to have been infected. Older individuals (those born before the Second World War) in The Netherlands and the participating Nordic countries are less likely to have experienced natural infection than in Germany and the United Kingdom.

Figure 2 depicts the estimated coverage of primary course diphtheria vaccination in seven of the eight study countries. Only three data points are available for primary course coverage from France, hence, the estimated first booster coverage is also presented (where boosters are given at age 16–18 months). Finland, The Netherlands, Denmark and Sweden have maintained high (approximately 95 % or greater) levels of coverage since at least the 1980s. In the early 1970s the United Kingdom had 80 % coverage, which fell to below 75 % in the mid-1970s probably as a result of vaccine refusals in relation to fears over whole cell pertussis vaccine safety. Since then the level of coverage has improved steadily, and has been above 90 % since 1990. Recent surveys from France suggest that the primary course coverage is currently above 95 %. As the booster dose coverage has been steadily increasing since the mid-1980s it is likely that the primary course coverage has followed a similar trend (that is primary course coverage was lower a decade or so ago). In Italy, cluster surveys showed a primary course coverage ranging from 77–99 % in 1991 [36] and 89–99 % by region in 1998 [37]. Although regular national data are lacking from Germany a study in Berlin in 1992 found that 69 % of East German and 88 % of West German children had at least three doses of diphtheria vaccine by their second birthday [38], and a recent study of over 600000 individuals found that 87 % had vaccine history documentation and 95·5 % of them (East 94·2, West 95·8) had basic immunization against diphtheria by the age of 6 years (G. Rasch, personal communication).

Figure 3(*a–g*) shows standardized age-serological profiles to diphtheria anti-toxin in the seven European countries for which results are available (the data are available from the authors on request). The proportion in each age group who have antibody levels

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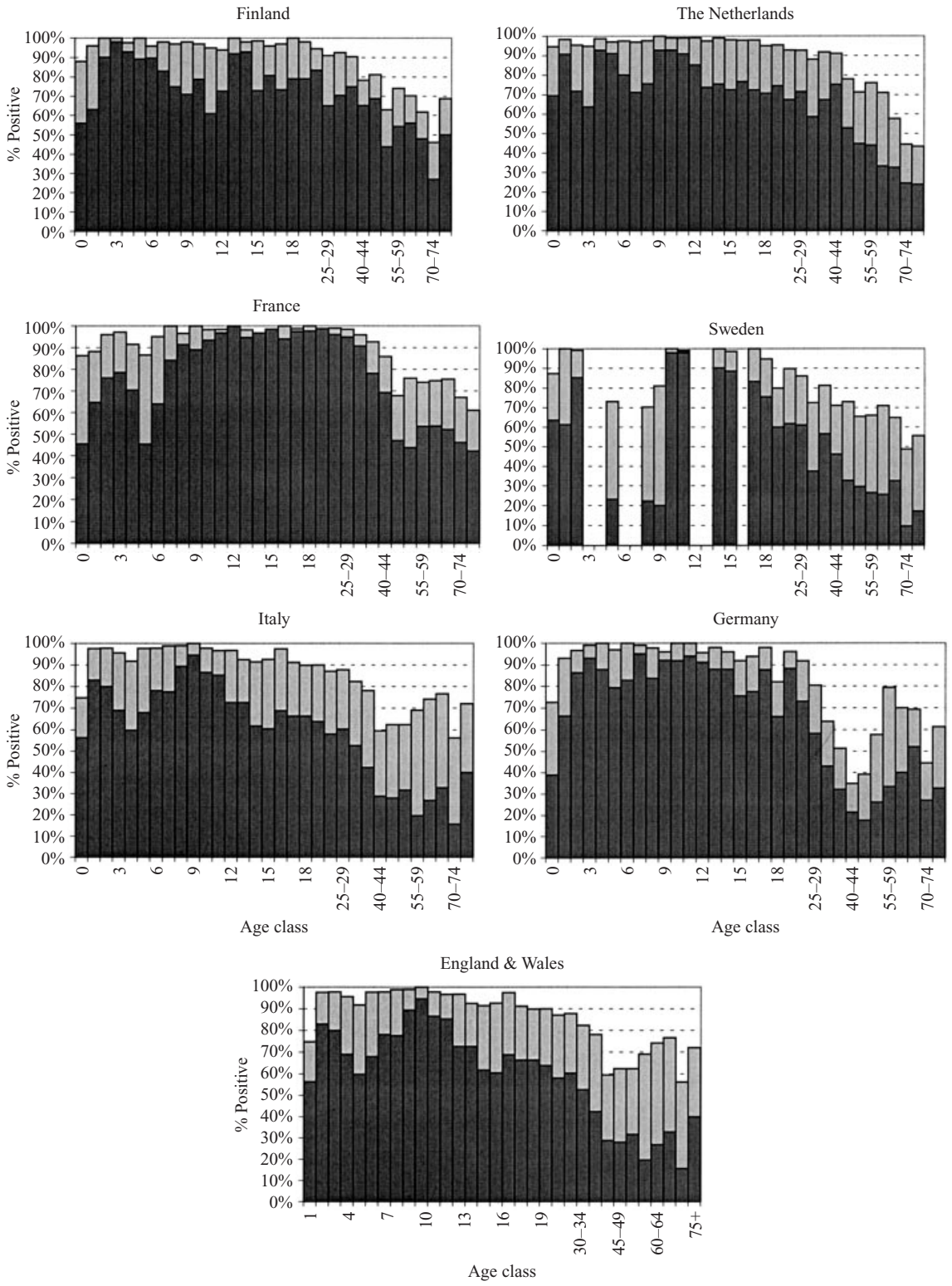

Fig. 3. Standardized age serological profiles. Dark bars represent the proportion with antitoxin concentrations $\geqslant$ 0·1 IU/ml, and light bars represent the proportion in each age group with antibody titres of between 0·01 and 0·099 IU/ml. Each bar represents an age class (yearly age classes for 0–19 years, 5-yearly age classes up to 70–74 years then 75+ years).

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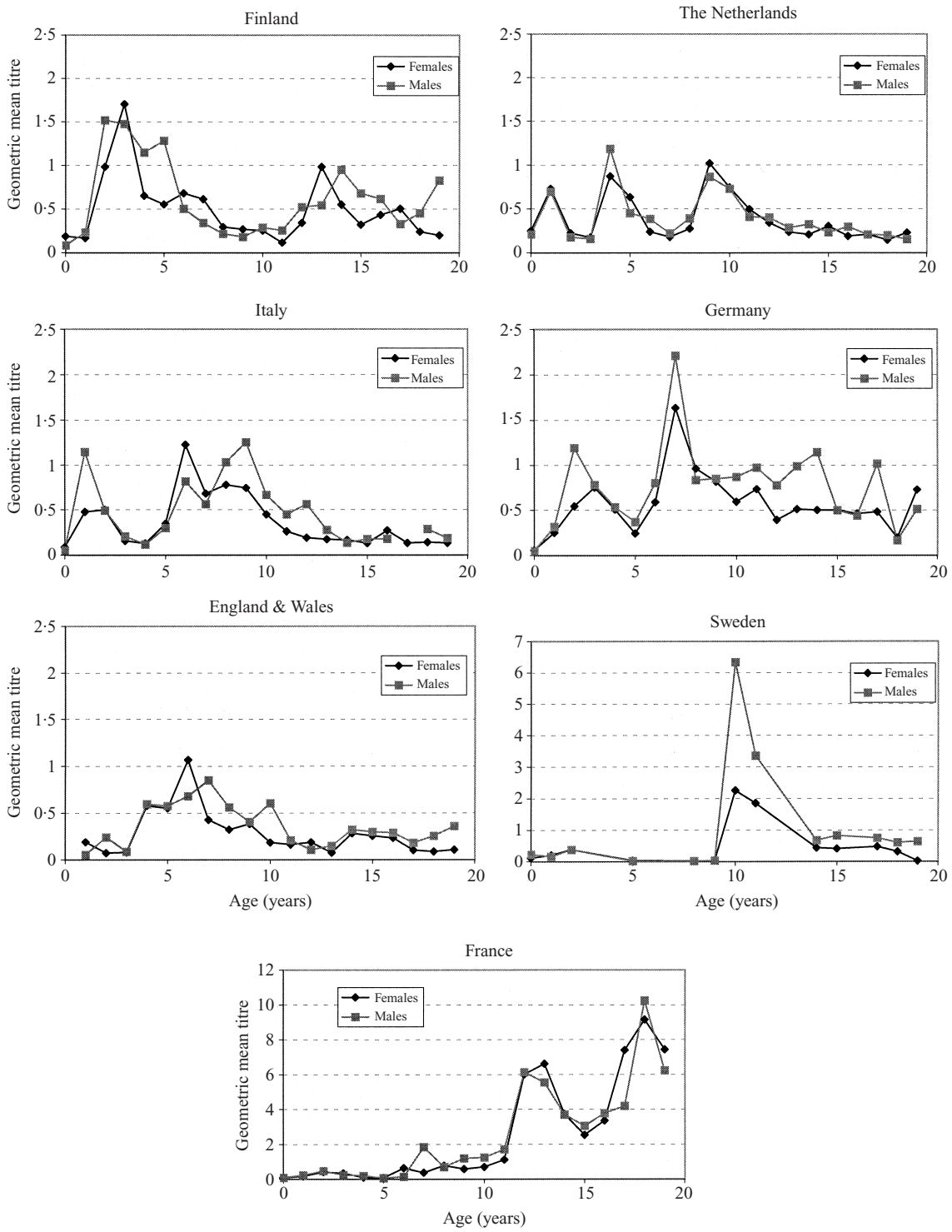

Fig. 4. Geometric mean antibody titres (GMT) in each sample by sex and yearly age class 0–19 years of age inclusive. Note that the denominator to calculate GMT is the sample size in each age class, not those who are deemed positive ($\geqslant$ 0·01 IU/ml). In practice the GMT in positives and the overall GMT are very similar over the age range 1–19 years in all countries except Sweden, as the vast majority of individuals have antibody titres greater than 0·01 IU/ml.

equal or above 0·1 IU/ml (dark bars) and between 0·01 and 0·099 IU/ml (light bars) are shown for each of the countries. It is clear from Figure 3 that the proportion with serum antibodies to diphtheria toxin rise rapidly with age, so that in each country, except the United Kingdom, more than 90% of 1-year-olds

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are seropositive. The apparently lower levels of seropositivity in young children in the United Kingdom is not as a result of low levels of coverage (see Fig. 2), but may be attributed to the change, in 1990, to an accelerated DPT schedule [39–41].

The quantitative antibody results, in particular the change in the proportion of high ($> 0{\cdot}1$ IU/ml) positives, demonstrate the boosting of antibody levels provided by revaccination of children and adults, and the decline in antibody levels which occurs after vaccination. For instance, in The Netherlands booster doses are given at 4 and 9 years of age. This can clearly be discerned in the serological profile as an abrupt rise in the proportion of infants with levels of antibody $> 0{\cdot}1$ IU/ml. With the exceptions of Sweden and the United Kingdom, Figure 3 shows that almost all individuals between the ages of 1 and 20 have serum antibodies against diphtheria toxin above the putative lower protection threshold of 0·01 IU/ml. In these countries revaccination of children tends to boost existing detectable antibody levels, the proportion of seronegative individuals hardly changing.

The serological profile for Sweden is quite different to the other countries, although care should be exercised in interpreting the results at low titres as the Swedish laboratory used an ELISA test with a lower detection threshold of 0·02 IU/ml. After standardization samples below the detection threshold were all classified as being negative, thus the proportion of seronegatives may be overestimated if there are significant numbers of individuals with titres of between 0·01 and 0·02 IU/ml. Nevertheless, there appears to be high levels of seronegativity (or at least a high proportion of very low positives) in children: only 70–80% of 5- to 9-year-olds were estimated to be seropositive and the majority of those have low titres (70–75% of the positives have a titre below 0·1 IU/ml). However, Sweden has high levels of infant vaccination coverage which is evident by the high proportion of 1- and 2-year-olds who are seropositive. Furthermore, roughly 99% of 10- to 11-year-olds are seropositive (a booster is given at age 10). It seems, therefore, that the Swedish vaccination programme may result in low antibody titres after primary vaccination which subsequently decline resulting in large numbers of children below the putative protection threshold. Indeed, further inspection of the Swedish results revealed that those children who received an accelerated schedule (i.e. 2, 4, and 6 months, as opposed to the usual 2, 5, 12 months) as part of the first Swedish DT/DPT vaccine trial performed in the early 1990s [27] – there were 54 of these children in this sample – had even lower titres at the age of 5 years: only 50% were positive, 85% of which were low positives. These children were removed from the analysis presented in Figures 3–5.

Figure 4 plots the geometric mean titre (GMT) of antibody by yearly age class from 0 to 19 years of age, from each of the study countries. It also clearly demonstrates the rise and fall in antibody levels which occur after primary vaccination and boosting. Note the differences in scale, remembering that these reported titres are all standardized to those of the reference laboratory. It seems that geometric mean titres in Swedish children less than 10–11 years of age are lower than in most other countries. In Sweden a high dose booster is given at age 10, and in France a high dose booster is offered at 11–13 years and again at 16–18 years (other countries switch to low-dose boosters before this age; see Table 1). These boosters (in both Sweden and France) appear to result in geometric mean titres in children orders of magnitude higher than in most other countries. Figure 4 also suggests that females may have somewhat lower titres than males, though the boosting evident in 18- to 19-year-old Finnish males is almost certainly due to vaccination during military service.

It is evident from Figure 5 and Table 2 that all of the countries studied have substantial proportions of seronegative (antibody concentrations $< 0{\cdot}01$ IU/ml) individuals in the adult age groups. In each country roughly 40–80% of the oldest age group (70 years of age or greater) lack serological makers to diphtheria toxin. However, it is also apparent that there are large differences in the proportion of seronegative adults between the countries (Fig. 5). For instance, approximately 60–70% of 40- to 50-year-olds appear to be seronegative in West Germany, more than twice the proportion in East Germany (Fig. 5). Although 10-yearly boosters are recommended for adults in Germany and Italy [33], the serological evidence presented in Figure 5 suggests that these recommendations are poorly implemented.

As is evident from Table 2 significantly fewer adult men (over the age of 30 years) are seronegative than women in The Netherlands, Finland, Sweden and France. Note that Table 2 should be interpreted with some caution as it represents the prevalence of negative individuals in the *sample* not in the population (to obtain the population prevalence the proportion seronegative in each age group would have to be weighted by the proportion of the population in

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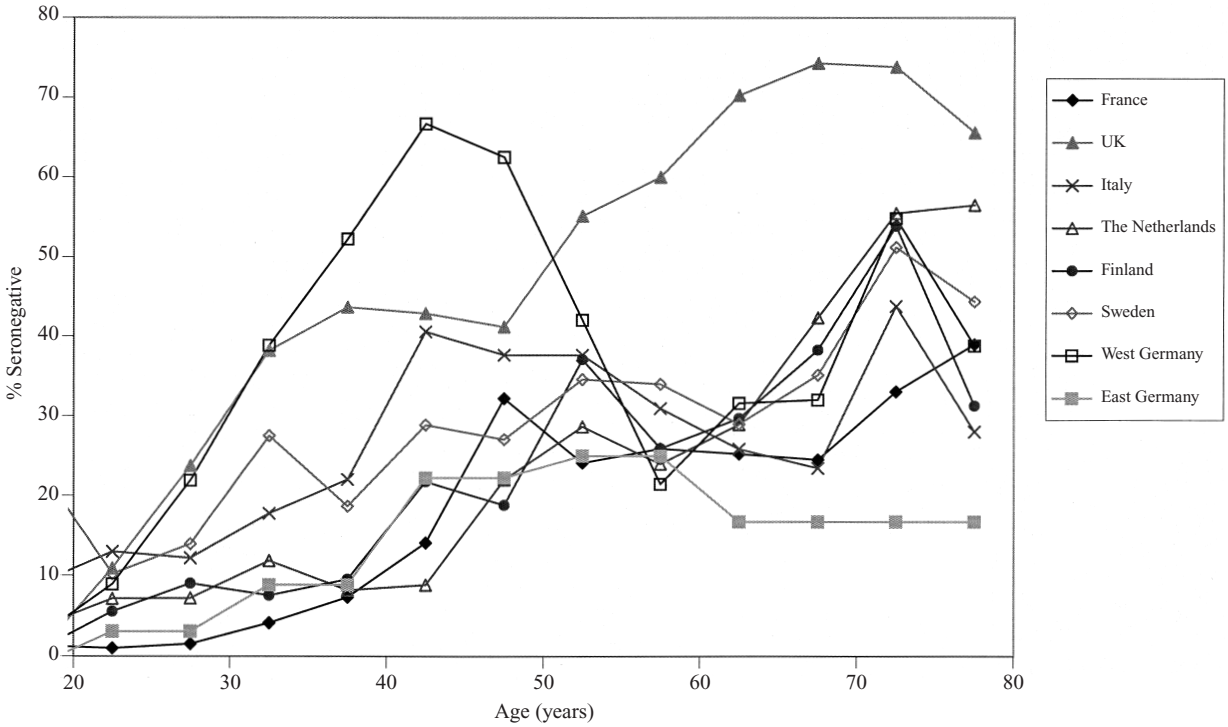

Fig. 5. Proportion of seronegative (titre < 0·01 IU/ml) adults by age in each of the study countries. The midpoint of 5-year age-classes are shown. Due to insufficient sample sizes 10-year age groups were used for East Germany.

Table 2. *The prevalence of seronegative adults (⩾ 30 years) by sex*

	Females (%)	Males (%)	*P*-value
The Netherlands	33	21	< 0·0001
France	27	14	< 0·0001
Sweden	37	28	< 0·0001
Finland	29	16	< 0·0001
Germany	45	42	0·19
Italy	28	29	0·68
United Kingdom	50	50	0·55

each age group). Nevertheless it demonstrates the sex-related difference in prevalence which occurs in some countries. This difference is likely to be as a result of vaccination during compulsory military service. In the United Kingdom compulsory military service was abolished around 40 years ago; in Italy diphtheria vaccine is not given to military recruits; and in Germany either single antigen tetanus or Td is used.

In addition to the total proportion who are seronegative, the patterns of serological markers in adults differs between the countries. The serological profile in The Netherlands, Finland, and Sweden demonstrate high levels of seropositivity in adults below about 40 years of age, after which the proportion seropositive declines steadily. Both Germany and Italy, however, have a markedly different pattern in adults. In both these countries there appears to be a significant peak in the proportion seronegative in middle-aged adults which is not discernible in the other serological profiles (Figs. 3, 5). The United Kingdom and France appear to display intermediate patterns.

DISCUSSION

We have undertaken large serological surveys across a wide age range in seven countries of Western Europe to document the current patterns of immunity to diphtheria. The results of the surveys have been standardized to those of a reference laboratory, and, as the sample sizes are large, any observed differences in the patterns of serological markers across the different European countries are likely to reflect epidemiological differences.

Although all assays were internally calibrated against the WHO reference preparation, there remained differences between the laboratory results when the same reference sera were tested (details are given elsewhere). Clearly these differences would have affected the comparability of the results had they not been subsequently accounted for. This comparability

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is one of the key strengths of the current study though it is important to bear in mind that statistical standardization, as used here, is unlikely to give as comparable results as testing in the same laboratory.

The comparatively high proportion of adults in Western Europe with anti-toxin titres below the putative threshold for protection has been reported previously [1, 10–22]. This study updates and confirms these results and extends them to countries for which data were lacking or poor. In addition we were able to demonstrate large differences in the patterns of serological markers across different countries. For instance, approximately 40% of 40- to 50-year-old UK adults were found to have titres below the putative lower protection threshold, about twice that found in Finnish adults of the same age. The most striking differences were between the former East and West Germany, which probably reflects the use of a compulsory booster dose at 8 years in the former GDR [22] and perhaps higher uptake rates of adult booster doses in East Germany.

Additionally, different patterns of serological markers were found amongst adults in the various countries. Age-serological profiles from Finland, the Netherlands and Sweden showed a gradual decrease in the proportion of adults seropositive with age, such that the highest proportion of 'susceptibles' occurred in the oldest age groups. In Germany and Italy, however, there were two peaks in adult susceptibility – one occurring in middle aged adults (40–50 years old) and the second occurring in the oldest age group. France and the United Kingdom showed an intermediate pattern. A possible explanation for these different patterns is that the peak in seronegativity observed in middle-aged Italian and German adults coincides with the first age cohorts which were unlikely to have experienced natural infection (see Fig. 1). Older individuals probably experienced natural infection stimulating longer lasting antibody titres. In the former group of countries (The Netherlands and the Nordic countries) the incidence of diphtheria had been declining for a number of years before the Second World War (see Fig. 1), which might negate the expected rise in seropositivity in age groups born in the 1920s and 1930s. It is worth noting that if the above explanation for the peak in seronegativity is correct, then the level of adult susceptibility in Germany and Italy (and to a lesser extent France and the United Kingdom) is likely to increase in the future unless adult booster doses are administered.

This survey was the first population based serological survey in the United Kingdom covering all ages since the change from a 3-, 5-, 10-month to a 2-, 3-, 4-month DPT schedule in 1990. As previously shown [38–40], the accelerated schedule appears to result in lower titres. Supporting evidence for this is presented here as the primary course in France (also a 2-, 3-, 4-month schedule) seems to produce comparatively low titres (Fig. 4) and Swedish children who received the accelerated DT/DPT schedule [27] had significantly lower titres than their counterparts. (Partly as a result of this study, the tracing and vaccination of these children is under consideration.) The adoption of a school-leaving boost in the United Kingdom appears to have been necessary to ensure adequate antibody titres.

Several factors related to the break-up of the former Soviet Union seemed responsible for the outbreak in the NIS during the 1990s: a highly susceptible childhood population, partly as a result of using low-potency TdP vaccine; an unprotected adult population due to waning of vaccine derived immunity; poor infection control measures to prevent secondary transmission; and large population movements facilitating spread [5, 6]. Do any of these risk factors occur in Western Europe, and are any countries at a greater risk than others? Clearly most countries have significant numbers of adults below the putative protection threshold, although most of the adults seemingly lacking protective immunity occur in the oldest age classes, who are probably at a low risk of exposure. The high number of seronegative middle-aged adults in the United Kingdom, Germany and Italy, however, appear to pose a greater epidemic risk. In addition to having a relatively high proportion of seronegative adults, Sweden also appears to have a high proportion of children who may have inadequate levels of protection. The joint occurrence of inadequately protected children and adults would suggest that Sweden is at a greater risk of epidemic diphtheria than many other Western European countries.

In response to the epidemic in the former Soviet Union many of the countries of Western Europe have revised their immunization policies. For instance, many countries now recommend 10-year booster doses in adults, and Finland implemented a campaign in the over 40s (see Table 1). However, the results presented here show that, with the possible exception of Finland, there are still significant numbers of adults below the supposed protection threshold in each of

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the study countries, suggesting that in most countries few adults have actually been vaccinated as a result of these measures. It is worth noting that if the conditions for an epidemic exist (that is there is an adequate density of susceptibles) then the vaccination of travellers to endemic areas can only be expected to delay, not prevent an epidemic. Ensuring adequate levels of population immunity is the only reliable method for preventing epidemics.

So do the countries of Western Europe have adequate levels of population immunity? The lack of epidemic diphtheria in Western Europe would suggest so, although significant numbers of adults appear to be susceptible. There are a number of possible explanations for this paradox. First, the levels of individual protection are, in fact, adequate. That is, the internationally accepted threshold titres of 0·1 IU/ml for 'full protection' and 0·01 IU/ml for 'basic immunity' [1] do not, in fact, correlate well with immunity to diphtheria, perhaps because the ability to mount a rapid immune response (i.e. immunological memory) may be more important. Second, the available evidence from the pre-vaccination era in Europe seems to suggest that the basic reproduction number, R_0, for diphtheria (a measure of the maximum transmissibility of the pathogen in a given population) was low compared with other common childhood infections. A comparatively long inter-epidemic period (5–10 years in England and Wales; see Fig. 2), and a relatively low age-specific prevalence of past infection (about 80% by 15 years [1, 2]) are both indicative of a low R_0. This would have been expected to fall due to improvements in socio-economic conditions (as was observed in the Nordic countries during the 1920s and 1930s). There is an inverse relationship between R_0 and the critical density of susceptibles required for an epidemic. Furthermore, R_0 is a weighted average of the invasive potential among and between different (age) groups in the population. For many close-contact infections the transmission potential amongst children is the most important determinant of the overall transmission potential largely due to school-related mixing patterns. Thus the number of susceptible children is likely to be a critical determinant of the epidemic potential. In all the countries studied with the possible exception of Sweden the level of susceptibility in children is extremely low. Herd immunity might be protecting the populations of Western Europe from diphtheria.

Although the epidemic in the NIS appears to have largely abated [6], there is still a need for vigilance in Western Europe. Susceptibility needs to be closely monitored, particularly in those countries, such as Italy and Germany in which levels of susceptibility are likely to increase. It is important that public health authorities remain vigilant to the risk of diphtheria. Sensitive surveillance mechanisms need to remain in place with rapid reporting and investigation of possible cases coupled with immediate antibiotic prophylaxis and vaccination for contacts of cases. Active immunization, however, remains the most important means of prevention. Improved coverage of travellers to endemic or epidemic areas as well as immunization of susceptible age groups should be considered, possibly by replacing adult tetanus boosters with Td.

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