Cross-sectional antibody prevalence studies were originally used as research tools to investigate acquisition of various infections in different populations. For example, in the early 1950s many surveys of antibody to poliomyelitis were conducted in different countries. These contributed greatly to the understanding of the epidemiology of the infection.1,2 Extensive surveys also clarified the epidemiology of other infections including measles, rubella,3 hepatitis A4–6 and hepatitis B. The need for continuing serological surveillance following the introduction of vaccination has been highlighted by mathematical models of disease transmission, which have demonstrated that gradual accumulation of susceptibles could lead to resurgence of disease after many years of low incidence.7,8 Studies that monitor changes in the prevalence of antibody following the introduction of vaccination programmes demonstrate their epidemiological impact.9,10

The first age-stratified serological survey of antibody to measles, mumps and rubella (MMR) in England and Wales was conducted in 1986/87 prior to the introduction of MMR vaccine into the immunization programme. Serum collection and testing have continued annually, allowing trends over time to be monitored. These sera have also been available for ad hoc surveys of other infections.

The first age-stratified serological survey of antibody to measles, mumps and rubella (MMR) in England and Wales was conducted in 1986/87 prior to the introduction of MMR vaccine in 1988. We describe the development of the serological surveillance programme over the following ten years, presenting its main results and their implications for disease control.

Methods

Serum collection and storage

The Public Health Laboratory Service (PHLS) integrates microbiology and epidemiology at every level within its national organization comprising a network of 50 public health laboratories (PHL), the Communicable Disease Surveillance Centre (CDSC), and the Central Public Health Laboratory (CPHL). The number of PHL participating in the serological surveillance programme has increased from five in 1986/87 to fifteen in 1996 (Figure 1). Three London based NHS (National Health Service) laboratories were also included in 1996, to address the under-representation of London in previous years. It is planned to continue to improve the geographical coverage, by recruiting PHL in the areas not currently represented.

Participating laboratories are asked to provide aliquots of serum (minimum 0.2ml) from residues remaining following the completion of microbiological and/or biochemical investigations.

Background

The first age-stratified serological survey of antibody to measles, mumps and rubella in the UK was conducted in 1986/87 prior to the introduction of MMR vaccine into the immunization programme. Serum collection and testing have continued annually, allowing trends over time to be monitored. These sera have also been available for ad hoc surveys of other infections.

Methods

Residual sera are collected in participating laboratories and sent to a central store where they are irrevocably unlinked from identifying data. A unique identity number is assigned to each serum and details of age and sex are collated on a database. The sera are accessed for testing as required.

Results

The results of recurring and other surveys performed over the last ten years are presented. These demonstrate that opportunistic serum samples are an ideal resource for serological surveillance programmes.

Conclusions

The serological surveillance programme has provided past exposure profiles for many infections. These data have resulted in a number of national policy changes and have been instrumental in shaping the UK vaccination programme.

Keywords

Serological surveillance, immunization, vaccine preventable diseases, mathematical modelling, MMR

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Ten years of serological surveillance in England and Wales: methods, results, implications and action

Kate Osborne, Nigel Gay, Louise Hesketh, Peter Morgan-Capner and Elizabeth Miller

Background

The first age-stratified serological survey of antibody to measles, mumps and rubella in the UK was conducted in 1986/87 prior to the introduction of MMR vaccine into the immunization programme. Serum collection and testing have continued annually, allowing trends over time to be monitored. These sera have also been available for ad hoc surveys of other infections.

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Sera from immunocompromised people are excluded. Those submitted for testing for antibody to HIV and hepatitis B infection were excluded until 1996. Since then, to provide as complete a sample as possible for a viral hepatitis survey, laboratories have been asked to include these sera, flagging them appropriately. Laboratories are also asked to exclude recent repeat sera from the same individual.

For each serum, the age (or date of birth if available), sex, date of specimen and laboratory number are entered on a data sheet in the collecting laboratory. Sera and the accompanying documentation are forwarded to Preston PHL where each serum is assigned a unique identity number and the laboratory numbers removed so that the patients are no longer identifiable. This irrevocably unlinks the serum from any patient identifying data. Sera are stored at −20°C in dedicated freezers at Preston PHL. The data sheet is then forwarded to CDSC where the information is entered onto a central database.

Each year target numbers of sera (stratified by age and sex) are collected in the age groups 0–24 years. Every five years (1986/7, 1991 and 1996) sera are collected across the entire age range (although any sera provided in the intermediate years from older age groups are not discarded). Figure 2 shows the number of sera collected each year by age group. For each survey the required number of samples for each stratum (e.g. age group) are randomly selected from those available. The identification numbers are sent to Preston PHL where the majority of the testing (largely automated since 1994) is performed. Results are downloaded directly from the auto-analyser and sent to CDSC in computer files, where they are incorporated into the database and analysed.

Laboratory tests

Until 1992 sera were tested using haemagglutination inhibition (HI) (for measles) and radial haemolysis (for mumps and rubella),
with enzyme immunoassays (EIA) being used to resolve sera giving a low concentration of specific IgG. Plaque reduction neutralization would be the test of choice for measles and mumps, but it is not suitable for testing large numbers of sera as it is time-consuming and relatively expensive. Moreover, measles haemagglutinating antigen and primate red blood cells became increasingly difficult to obtain. Since EIA had commercially produced reagents and benefited from automation, they became the most attractive option. It was therefore necessary to identify sensitive and specific EIA, which also enabled quantitative assessment of antibody levels. This was to provide discrimination at low concentrations of antibody, which may not provide complete protection. In 1993, suitable assays were selected following evaluation of many EIA and comparisons with previously used tests (measles; mumps and rubella [unpublished results]). These were: measles, Rubella-IgG, Gull Laboratories, Utah; mumps, Mumps IgG, Human, Weisbaden; and rubella, Captia Select Rubella G, Trinity Biotech, Dublin. Quantification is achieved by calibrating the optical density reading for each test serum against a standard curve, which is calculated from dilutions of a standard serum included on every test plate.

Results

Four tables describe the surveys, their results and implications, and the resulting actions. The latter may be further surveys or investigations or, as has happened on a number of occasions, changes in the UK national vaccination policy.

Measles, mumps and rubella

The measles, mumps and rubella surveys have been performed every year since 1986/87 (Table 1). The results have played a crucial role in shaping the UK national vaccination policy, most notably in identifying the need for a national vaccination

Table 1 Surveys of measles, mumps and rubella

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. sera</th>
<th>Year collected</th>
<th>Results</th>
<th>Implications</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles, Mumps &amp; Rubella&lt;sup&gt;11&lt;/sup&gt;</td>
<td>8716</td>
<td>1986/87</td>
<td>Prevalence increased with age 60% of 1 year olds were susceptible to measles and &gt;85% to mumps and rubella At age 4 years 15%, 37% and 67% were susceptible to MMR respectively</td>
<td>Suggests that vaccinating children early in second year of life is necessary to eliminate measles, mumps and rubella</td>
<td>Catch-up MMR dose given at 4 years of age for first four years of MMR programme (1988–1991) Surveillance to assess necessity for two dose vaccination schedule—see below</td>
</tr>
<tr>
<td>Measles&lt;sup&gt;12&lt;/sup&gt;</td>
<td>&gt;10 000</td>
<td>1986–1991</td>
<td>Susceptibility in 7–14 year olds rose from 6% (1986) to 9.2% (1991) with a peak of 11.2% in 8–10 year olds Susceptibility in pre-school children fell between 1986 and 1991</td>
<td>Mathematical models predicted that by the mid 1990s the increase in susceptibility in schoolchildren would be sufficient for an epidemic to occur</td>
<td>Mass campaign to immunize all children of school age&lt;sup&gt;13&lt;/sup&gt; Enhanced surveillance by the PHLS to evaluate the effect of this campaign&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>Measles&lt;sup&gt;13&lt;/sup&gt;</td>
<td>4496</td>
<td>1994–1995</td>
<td>Proportion of 5–16 year olds with antibody levels &lt;50 mIU/ml fell from 8.4% to 2.1% and those with &lt;100 mIU/ml from 15.7% to 6.6% Both before and after campaign 13% of 2–4 year olds had levels &lt;100 mIU/ml</td>
<td>Vaccination campaign had a significant impact on the prevalence of measles antibody in target cohorts High susceptibility in 2–4 year olds shows the need for a routine second dose of vaccine</td>
<td>Addition of a second dose of measles (at 4 years as MMR) to the vaccination schedule in 1996&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mumps&lt;sup&gt;31&lt;/sup&gt;</td>
<td>3535</td>
<td>1993</td>
<td>Data compared with 1986/7 survey&lt;sup&gt;1&lt;/sup&gt;; the proportion in whom no antibody was detected fell at 2–6 years of age due to vaccination but rose at 9–20 years as a result of reduced exposure to infection</td>
<td>One dose vaccine reduces the number of infections, but reduced circulation of virus causes many who are not protected to remain susceptible into adult life</td>
<td>The second dose of vaccine offered to pre-school children (see above) should eliminate mumps infection (and all its complications, particularly in adults)</td>
</tr>
<tr>
<td>Rubella&lt;sup&gt;22&lt;/sup&gt;</td>
<td>1750, 1846</td>
<td>1994, 1995</td>
<td>In 5–10 year olds the proportion without antibody fell from 17.5% to 3.0% In 11–16 year olds the proportion fell from 6.2% to 1.0% in females and from 24.5% to 6.9% in males</td>
<td>Vaccinating target groups leads to decreased susceptibility which in turn should lead to a decrease in CRS Sex difference in prevalence shows effect of previous selective vaccination</td>
<td>MR campaign should prevent future outbreaks in adults; without it susceptibility in males aged 18–20 years would have risen above 20%</td>
</tr>
</tbody>
</table>
campaign in 1994 to prevent a potential measles epidemic.\textsuperscript{13,14} As a result 7 million children aged 5–16 years were vaccinated in November 1994, 92% of all children in this age group. The impact on immunity to measles and rubella in the target populations was confirmed by surveys using samples taken before and after the campaign.\textsuperscript{15} Following this, and the subsequent introduction of a second dose of MMR vaccine in 1996, the incidence of measles, mumps and rubella is low. It will be important to continue serological surveillance to monitor antibody prevalence, particularly in cohorts not vaccinated in the campaign (young adults and young children).

**Other vaccine preventable diseases**

Table 2 provides details of serological surveys of other vaccine preventable diseases. The survey performed for diphtheria demonstrated the speed with which the sera can be accessed, tested and the results analysed in response to emerging and re-emerging disease threats (in this case diphtheria in the former Soviet Union). The hepatitis B surveys are an example of sero-prevalence studies that complement disease incidence data and improve the understanding of disease epidemiology. These confirmed the low prevalence of hepatitis B infection in the UK,\textsuperscript{16,17} and informed the decision not to implement a universal hepatitis B vaccination programme at present.

### Table 2

<table>
<thead>
<tr>
<th>Disease</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria\textsuperscript{27}</td>
<td>2862</td>
<td>1991</td>
<td>67% had antibody concentrations considered to be protective (conservative cutoff); however proportion declined with age in both sexes</td>
<td>Proportion of total population with protective levels of antibody is below the 70–75% considered to confer herd immunity to diphtheria</td>
<td>A booster dose for school leavers of low dose diphtheria vaccine combined with tetanus toxoid introduced October 1994\textsuperscript{28}</td>
</tr>
<tr>
<td>Varicella\textsuperscript{29}</td>
<td>9000</td>
<td>1991</td>
<td>Results supported an increasing susceptibility to VZV in young adults (10–20 years)</td>
<td>This increase in susceptibility may lead to an increase in the number of infections in pregnancy and adults</td>
<td>Further studies to investigate the causes of the changing epidemiology</td>
</tr>
<tr>
<td>Hepatitis A\textsuperscript{30}</td>
<td>7196</td>
<td>1986/87</td>
<td>Steady increase in prevalence with age</td>
<td>A vaccine giving long-lasting protection with modest coverage could eliminate hepatitis A transmission</td>
<td>A repeat survey to be performed (on sera collected in 1996) enabling the incidence of infection to be estimated (paper in preparation)</td>
</tr>
<tr>
<td>Hepatitis A and B (in children aged 13 &amp; 14 years)\textsuperscript{16}</td>
<td>2025</td>
<td>1986/87–1995</td>
<td>Hepatitis A antibody was detected in 16.2% of 1986–1991 sera compared to 10.6% of 1992–1995 sera</td>
<td>Hepatitis A incidence declining Childhood infection with HBV is rare. Perinatal transmission and immigration (from endemic countries) could account for the observed prevalence</td>
<td>Universal HBV\textsuperscript{3} immunization of infants would therefore prevent few childhood infections</td>
</tr>
<tr>
<td>Hepatitis B\textsuperscript{17}</td>
<td>3781</td>
<td>1996</td>
<td>Low prevalence of past infection, 3.9% and chronic carriage, 0.4%</td>
<td>Implications for universal versus selective vaccination policy</td>
<td>Incidence estimates used in cost effectiveness analysis of universal and selective vaccination policies\textsuperscript{31}</td>
</tr>
</tbody>
</table>

\textsuperscript{3} Hepatitis B virus.
in participating countries (Table 4).20 Once survey results are directly comparable, the impact of different national vaccination programmes on the respective populations may be assessed. This enables the strengths and weaknesses of the different vaccination schedules across the European Union to be identified.

Another current survey is assessing the extent of hepatitis C infection outside of known risk groups in England and Wales. Other proposed projects will exploit the serum archive to investigate changes in the prevalence of antibody to hepatitis A, Helicobacter pylori and Toxoplasma gondii between 1986 and 1996. The incidence of infection over this period in different age groups will be estimated by comparing the prevalence in equivalent birth cohorts (e.g. 30–34 year olds in 1986 with 40–44 year olds in 1996).

Discussion

Collection of sera

The sera used in this programme are not a random sample of the population, rather they are derived from residual blood samples obtained for diagnostic and screening tests. Women tend to be over-represented, presumably because of attendance for antenatal care. However, this over-representation is controlled for when selecting samples for testing from those available. It is also possible to use other data to estimate the sera’s representativeness. For example, the prevalence of antibody to measles, mumps and rubella observed in 2–4 year olds by serological surveillance is that expected from coverage data and vaccine seroconversion rates.15,21,22

The UK has a well-developed NHS with free access to health care for all. This limits the selection bias for UK residual sera, which is likely to be less than that for residual sera obtained in countries where access to health care is more limited. Furthermore, the sera have the advantages of being cheap and easy to obtain. Importantly they also avoid additional patient discomfort, particularly in young children. In view of the comprehensive diagnostic service that each laboratory offers, substantial differences in the reasons for which sera were submitted are unlikely, either over time or between laboratories. Therefore valid regional

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and temporal comparisons can be made. Regional comparisons have been facilitated by the increase in the number of participating laboratories.

In other countries (e.g. the Netherlands,23 the US24) surveys have been conducted using sera specifically donated by people randomly sampled from the population. This has the advantage of allowing detailed risk factor information to be obtained, but any gain in the representativeness of the sera comes at considerable financial cost. There is also no guarantee that the sera will be representative because of the potential for participation bias. Even follow up of non-responders cannot completely eliminate or correct for this bias.

The major limitation of the programme in England and Wales is the lack of any data on ethnic group or country of birth. This is particularly problematic when studying diseases that are far more prevalent in other countries, e.g. hepatitis B. One solution would be to conduct occasional cross-sectional surveys on a smaller scale in which the requisite demographic information was collected.

The relatively simple methodology of the serological surveillance programme in England and Wales makes it transferable to other populations and countries. In countries with less developed health care infrastructures, alternative sources of sera could include those taken in accident and emergency departments.

Interaction with mathematical modelling

The interaction of serological surveillance with mathematical modelling has been particularly fruitful: surveys have provided better baseline data for mathematical models, which have been used to interpret the results of later serological surveys. The force of infection (the rate at which susceptibles acquire infection)18 can be estimated from the age-specific antibody prevalence in an unvaccinated population, provided there is no long term trend in the incidence of infection. Contact rates between age groups, which can be estimated from the age-specific force of infection in an unvaccinated population, are fundamental parameters of mathematical models of disease transmission,25 and reflect the potential for transmission of infection within the population.

Introduction of vaccination will change the prevalence profile (the age-specific prevalence of antibody) and the force of infection in a population, but not the contact rates (although, over long periods of time, contact rates may be affected by social changes within a population). Contact rates derived from pre-vaccination prevalence profiles can therefore be used to interpret the profiles obtained after vaccination is introduced.14 Each serological profile can be summarized by a single parameter: the reproduction number, \( R \). \( R \) is the number of secondary cases produced by a typical primary case; thus potential for an epidemic exists if \( R \) is greater than one. \( R \) is determined by the level of susceptibility in each age group and the contact rates within and between age groups. The sensitivity of \( R \) to the contact rates can also be explored. This method was applied to the serological results for measles, predicting a potential measles epidemic14 that was prevented by the 1994 national vaccination campaign.

Interaction with other surveillance programmes

Comprehensive surveillance of vaccine preventable infections requires data from several sources. Serological surveillance complements but cannot replace surveillance of vaccine coverage and disease incidence (both clinical diagnoses and laboratory confirmed cases). For example, serological surveillance cannot rapidly detect changes in vaccination coverage, which can only be achieved by direct monitoring of coverage itself. Similarly, it cannot identify disease outbreaks or short term trends in disease incidence. However, disease incidence data yield little information on the epidemiology of infection if many infections are asymptomatic (especially if the proportion asymptomatic changes with age) or are clinically misdiagnosed. Furthermore, the absence of cases in a population reveals little about the potential for cases in future. Therefore, serological surveys are an important element of the surveillance of vaccination programmes.

Influence on vaccination policy

Serological surveys provide baseline data on the distribution of immunity to infection within a population. They are particularly valuable for evaluating the need for and the planning of new vaccination programmes and supplementary measures such as mass vaccination campaigns. Identifying the cohorts most susceptible to infection enables the intervention to be targeted to achieve maximum effect with the available resources.

The serological surveillance programme in England and Wales has directly influenced national vaccination policy. Examples include the 1994 measles and rubella campaign; the introduction of a second dose of MMR at 4 years of age;26 and the decision not to implement a universal hepatitis B vaccination programme. As vaccination programmes succeed in eliminating infections, monitoring immunity of the population through serological surveys will assume even greater importance to ensure a scientific basis for decisions about national vaccination policy.

Acknowledgements

We are indebted to the staff of all the Public Health Laboratories and NHS hospitals that have provided sera, without whom none of this work would have been possible. We also thank Paddy Farrington, Kathy Harbert, Kevin Houghton, Sanga Leon, Doreen Moffat, Joe Rowlatt, Marie Rush, Janet Thomas, Joan Vurdien, Jean Wright and many others for their contributions to the success of the programme.

References


