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Immunosurveillance and the evaluation of national immunization programmes: a population-based approach

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SUMMARY

Mass vaccination can change the epidemiological dynamics of infectious diseases. It may result in a limited persistence of natural and vaccine-induced immunity and a higher mean age of infection, which may lead to a greater risk of complications. The epidemiological situation should be monitored and immunosurveillance based on the assessment of specific antibodies against vaccine-preventable diseases in human serum is one of the tools. In order to estimate the immunity of the Dutch population reliably, a large-scale, population-based, collection of serum samples was established (8359 sera in a nation-wide sampling and 1589 sera from municipalities with low vaccine coverage). In contrast to collecting residual sera from laboratories, this approach gains extensive information by means of a questionnaire regarding the determinants of the immune status and the risk factors for the transmission of infectious diseases in general. The population-based approach gives a better guarantee that the data are representative than collecting sera from laboratories does.

INTRODUCTION

In the Netherlands, we have established a bank of sera from the general population for public health research. This article describes the use of seroprevalence data for the evaluation of the National Immunization Programme (NIP), the design used for the data collection and the advantages of a population-based approach. Such an approach may be useful for future sero-epidemiological studies in other countries. Results drawn from seroprevalence data from this study on vaccine-preventable diseases will be published separately.

Long-term epidemiological effects of mass immunization

As in other countries, the incidence of most vaccine-preventable diseases (and their complications) in the Netherlands decreased considerably after the introduction of immunization with diphtheria, tetanus and pertussis (DTP) vaccine in 1952, inactivated polio vaccine (IPV) in 1957, rubella vaccine for girls in 1974, measles vaccine in 1976, measles, mumps and rubella (MMR) combination vaccine in 1987 and *Haemophilus influenzae* type b vaccine in 1993. The vaccine coverage is high and amounts to 97% of all 12-month-old children for three immunizations against DTP-IPV and 94% of all 14-month-old children for one immunization against MMR [1]. However, despite this high vaccine coverage, epidemics still occur (e.g. measles and pertussis), and the (re)emergence of diphtheria is possible [2–5]. Furthermore, mass vaccination may have some secondary effects in the longterm, as the epidemiological dynamics of infectious diseases can change. Once a pathogen has been pushed back to a large extent and its circulation is limited, the force of infection (the rate at which those who are susceptible acquire infection) decreases

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[6]. This means that the chance of infection will decrease, which will result in delaying the infection of susceptible (unvaccinated) individuals. The expected increase in mean age for some vaccine-preventable diseases is related to a greater chance of complications. For example, the frequency of orchitis due to mumps infection increases with age, the case fatality rate for measles was highest for unvaccinated individuals in older age groups and the shift in rubella infections to childbearing age could result in a greater risk of congenital rubella syndrome (CRS) [7–9].

The lower force of infection also results in lack of boosting opportunities of both natural and vaccine-induced immunity. In contrast to the past, natural immunity may not persist lifelong, and vaccine-induced immunity may be lost even faster [10, 11]. This may also result in a shorter duration of passive immunity due to maternal antibodies in infants [12]. Therefore, in order to assess the long-term effects of mass immunization, insight into the (possibly changing) duration of vaccine-induced immunity and natural immunity is necessary.

Herd immunity implies that non-immune individuals are protected from infection by the presence of immune individuals [13]. Thus, in order to prevent the further spread of an infection, a proportion of immune individuals in the population below 100% is sufficient. The threshold value is dependent on the contact rate between individuals and the probability of transmission. This was estimated (homogenous mixing assumed) at 82–87% for diphtheria, poliomyelitis and rubella, at 85–90% for mumps and at 90–95% for measles and whooping cough [6]. Nevertheless, even in countries with high vaccine coverage, infections are still a threat, since high coverage on the average does not warrant sufficient herd immunity. For example, in the Netherlands, groups who reject vaccination on religious ground, are sociodemographically and geographically clustered. In such situations where the condition of homogeneous mixing is not fulfilled, herd immunity can break down and epidemics can occur as a result. Such an event took place during the polio epidemic in 1992–3 [14]. This epidemic was restricted to religious groups in a closely knit social network. The high incidence of CRS after a rubella epidemic among the Amish people in the United States is another example of insufficient herd immunity. Due to the low vaccine coverage and social clustering in combination with the absence of regular contacts outside their own community, the number of susceptible individuals had increased [8]. Potential long-term secondary effects of mass immunization should be anticipated by surveillance and possible adaptations of vaccination policy should be considered.

Evaluation of immunization programmes for seroprevalence data

Epidemiological methods play an important role in the evaluation of an immunization programme. These methods include monitoring vaccine coverage, surveillance of the occurrence of vaccine-preventable diseases, case investigations, outbreak investigations, vaccine efficacy and effectiveness studies, surveillance of vaccine safety and serological surveillance [15, 16].

Important information on vaccine-preventable diseases can be derived from the latter method known as serosurveillance, which is the assessment of specific antibodies in serum as a sign of previous contact with the pathogen [17]. These antibodies could have been induced either by natural infection with the virulent pathogen or by immunization with the inactivated or live, attenuated pathogen. However, in general no serological methods are yet available to distinguish between natural and vaccine-induced immunity for vaccine-preventable diseases. Nevertheless, for some diseases the distinction can be made indirectly. Combining anti-Hbs and anti-Hbc tests the presence of the former in absence of the latter indicates vaccine-induced immunity against hepatitis B virus. Poliovirus specific IgA antibodies seem to discriminate between natural or OPV-induced and IPV-derived immunity [18, 19]. For most vaccine-preventable diseases, specific antibodies can be used as an indicator of protection against the disease (for instance the presence of neutralizing antibodies against poliomyelitis).

Antibodies induced by natural infection give information about both clinical and subclinical infections. Thus, this surveillance source is not limited to individuals with diseases that are otherwise considerably underreported [20–23]. For example, evidence was found of subclinical pertussis infections in which one-fifth of the youngest children had antibodies to pertussis toxin, even though they had no history of whooping cough [24].

Serosurveillance offers an opportunity to look for clustering of susceptible individuals within specific age, social or geographical groups based on serological profiles. Ideally, identifying these groups should result in preventive interventions (for example, efforts to increase vaccine coverage in such groups or

to adapt the vaccination strategy) before more cases (re)emerge. Low antibody levels for diphtheria and tetanus found in adults stress the need for re-vaccination of adults [25–28]. Seroprevalence studies support the two-dose immunization strategy for MMR to prevent the disease from shifting to older age groups [29–31].

Seroprevalence data can also benefit modelling studies [6]. On the one hand, seroprevalence data derived from serological surveys can be used to estimate input parameters in modelling studies. The dynamics of the disease occurrence can then be predicted. For example, the data can help estimate the force of infection, the average age of infection and the minimum proportion of immune individuals needed to prevent transmission (the herd-immunity threshold). On the other hand, serological data are important in modelling studies to test the accuracy of the model predictions and epidemiological assumptions. Differences in the predicted serological profile and observed serological profile may indicate the (in)correctness of the model assumptions [9, 32–34]. Results from serological surveillance in England reveal that the proportion of school children susceptible to measles was increasing after the introduction of the MMR vaccination programme in 1988. Mathematical models were used to interpret these data. As the models predicted an epidemic of measles in 1994, a national campaign for measles and rubella vaccination was held in the United Kingdom [9]. In the Netherlands in 1987, the selective vaccination strategy against rubella and CRS was changed to a mass vaccination strategy with MMR vaccine. Seroprevalence data were used as an input parameter in the mathematical models. These models played a major role in the decision-making process for changing the strategy [35].

In order to make reliable estimates of the immunity of the population, the sample of sera used for serosurveillance should be representative for the total population in age and sex structure. The sample should also be representative for other demographic and socio-economic factors. Therefore, ideally, a population-based survey should be repeated periodically to study any changes in the population immunity. Sera from blood banks, military recruits or specialist clinics are biased towards certain age groups and sections of the community. Many serosurveys use serum samples from the more readily accessible sources [26, 27, 30, 31, 36–43]. Although these studies are important in monitoring the effects of immunization programmes, they may lack or be representative to an unknown degree. Stark and colleagues suggest that immunity against diptheria in blood donors might lead to an overestimation of the immunity in the population, as blood donors might be more health conscious than the average individual [26]. Whether individuals attending special clinics are more or less likely to have antibodies for a specific pathogen than those in the general population is unknown. Apart from not being representative, another disadvantage is that the information about individuals from whom such sera were derived is often limited to age, sex and sometimes vaccination history.

Serosurveys based on random samples are described, but often limited to a small age range or specific region or city [24, 44–46]. The National Health and Nutrition Examination Study (NHANES) in the United States is a rare example with a population-based serum collection and with extensive information on study subjects [25].

In the Netherlands we have also had the opportunity to collect sera from the general population together with questionnaire data on determinants. This nationwide study includes individuals from the general population in all age groups 0–79 years. Furthermore, sera were also collected from the general population in municipalities with the lowest vaccine coverage. Differences in immune status of individuals from the nation-wide sample and the latter sample are of particular interest in the Netherlands with its specific unvaccinated groups. The data can give some insight into the effects of clustering of unvaccinated individuals on herd immunity.

A population-based collection of serum samples in the Netherlands

Sampling

A two-stage cluster sampling technique was used to draw a nationwide sample. In each of five geographic regions, with approximately equal numbers of inhabitants, eight municipalities were sampled proportionally to their size. Within each municipality, an age-stratified sample of 380 individuals was drawn from the population register. The population register contains all individuals with a home or postal address. Homeless without a postal address and illegal aliens are not included in the register. The age strata were 0, 1–4, 5–9, … 75–79 years. In each of the first two strata 40 individuals were sampled, while in each of the following strata 20 individuals were sampled. This

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oversampling was based on an expected lower response (25% instead of 50%) from very young children and the importance of sufficient data in these age groups. Otherwise, we could not obtain insight into the level of maternal antibodies and the mean age of infection.

Because of the particular situation in the Netherlands with its geographically clustered groups who refuse immunization, records from the population registers of eight municipalities with a consistently low(er) immunization coverage were also sampled. The vaccine coverage in these municipalities for three DTP-IPV immunizations of 12-month-old children was 65–87% in 1995 [1]. The objective was to gain access to more unvaccinated individuals and to obtain more accurate estimates of seroprevalence in this subgroup. The expected number of unvaccinated individuals in the national sample would be too small to estimate seroprevalence for the diseases in the NIP in this subgroup.

The number of clusters (municipalities) and units (individuals) per cluster were chosen that the expected accuracy of the seroprevalence estimates would be optimal within financial and logistical constraints. The accuracy is determined mainly by the total number of clusters and to a lesser extent by the number of units per cluster, as the expected variance between clusters is greater than within clusters [47]. In total, 18217 individuals were invited: 15189 in the national sample and 3028 in the sample of the municipalities with a low vaccine coverage.

Data collection

The data were collected from October 1995 to December 1996 in collaboration with the public health services, an organization well known to the local inhabitants. The prospective participants were approached by mail and were asked to fill in a questionnaire at home and to visit the special clinic to give a blood sample (20 ml). The questionnaire asked for data on gender, occupation, level of education, country of birth and nationality, participation in military service, vaccination (participation in the NIP, opinion on the necessity of vaccination against DTP-IPV, MMR and Hib, (re)vaccination against DTP, tetanus, Hib, hepatitis A, hepatitis B, influenza), religion, travel, long-term coughing, pertussis, otitis, diabetes, gardening, contact/keeping animals, recreation in fresh waters, sexually transmitted diseases, self-perception of health, chronic diseases, smoking and drinking habits. Participants were asked to bring their immunization certificates. In a pilot study in 1994, it turned out that self-reported vaccination history was not reliable [48]. Therefore the analysis of serological data to investigate waning immunity will be directed toward individuals with verified vaccination history.

An invited individual received a letter of invitation, along with a brochure giving information on the study, a questionnaire and a prescheduled appointment time (between 09.00 and 17.00 h). If the suggested time was not convenient, the participant could choose another time during the 2 days when the clinic was held in the municipality. The walk-in clinic was open from 17.00 to 19.30. An extra clinic appointment could be made 1 week later, or a house-visit could be arranged. Turkish and Moroccan residents received a letter of invitation in their own language. They were told that a Turkish and Moroccan speaking nurses would be present. Special attention was given to these nationalities because we expected a lower response rate, considering the results of the pilot study. These nationalities were important as the seroprevalence might be different. There might be a different force of infection and a different vaccination policy in their countries of birth. Access to the NIP and healthy baby clinics could be limited by language problems and frequent change of address for those who had not been in the Netherlands long. Before the consultation days, we telephoned invited individuals to remind them of the study, to answer any questions and to ask if they were willing to participate. In the pilot study, it was shown that the approach by telephone led to a 6% increase in the response rate [49]. When individuals declined to participate, they were asked to fill in the questionnaire or at least to answer some questions for the non-response survey (by telephone or mail). Individuals who could not be reached by phone were sent a written reminder. Participants were offered a gift voucher. Participants had to sign a written informed consent form that stated that the sera were to be tested for specific antibodies against infectious diseases (with the exception of HIV), that the data would be processed anonymously, that the serum would be coded and stored for a long time for the purpose of public health research and that they would not be informed of the test results. The study proposal was approved by the Medical Ethical Committee of Netherlands Organisation for Applied Scientific Research (TNO), Leiden, The Netherlands.

Table 1. (*Non*)*response rates in the nation-wide and low vaccine coverage sample*, *Pienter project 1995–6*, *The Netherlands*

	Nation-wide sample		Low vaccine coverage sample	
	n	(%)	*n*	(%)
Participants				
Questionnaire and blood sample	8539	(55·0)	1589	(52·5)
Nonparticipants				
Full questionnaire	1618	(10·7)	375	(12·4)
Nonresponse questionnaire	1053	(6·9)	187	(6·2)
Information from the population register	4159	(27·4)	877	(29·0)
Total invited	15189	(100)	3028	(100)

Non-response survey

Information about the participants regarding age, gender, marital status and nationality was available from the population registers. In addition, individuals who declined to participate were asked to fill in the original questionnaire or a short non-response questionnaire that contained questions about their level of education, religion, participation in the NIP, opinion on vaccination against diseases in the NIP and self-perception of health. The information about non-participants offers us the opportunity of correcting the seroprevalence data for possible selective non-participation.

Serum processing and storage

The blood samples were stored in a refrigerator during the day and at night. The sera were harvested the next day and divided into portions of 350 μl which were stored at minus 86 °C in different freezers.

The methods used are described in more detail in reference number 50.

The serum bank

A serum bank of 9948 samples has been established. All public health services and municipalities co-operated in the study. The (non)response rates for both samples are given in Table 1.

The adjustments (reminder before consultation hours, Moroccan and Turkish speaking nurses, translated letter of invitation to individuals with Moroccan or Turkish nationality) made on the basis of the findings of the pilot study seem to have been successful because the participation rate increased from 40% in the pilot study to 55% [49]. The participation rate was only slightly lower in the sample of municipalities with a low vaccine coverage (52·5%).

The serum bank can facilitate many sero-epidemiological studies. It will mainly be used for vaccine-preventable diseases, but the serum bank can also be used to obtain insight into the occurrence of infectious diseases with a course that is frequently subclinical and into the prevalence of other determinants. A procedure has been set up for release of the sera for further research. Research proposals will be judged on the relevance for public health and on scientific quality by a team of experts.

Seroprevalence studies for diphtheria, tetanus, poliomyelitis, mumps, measles, rubella, *Haemophilus influenzae* type b, hepatitis A, B and C are currently in progress.

CONCLUSIONS

It appeared feasible to establish a serum bank in the Netherlands for public health research through a large-scale nation-wide population-based cross-sectional study of the general population. The data will primarily be used for the evaluation of the effects of the NIP. Therefore, following an identical sampling scheme, a parallel study was done in municipalities with low-vaccine coverage. These municipalities are of particular interest in our country, with its specific religious groups who refuse vaccination. A response rate of 55% was achieved. The result was a collection of nearly 10000 sera. In contrast to the collection of residual sera from laboratories, this approach allowed for the collection of extensive information by means of a questionnaire regarding determinants of the immune status and risk factors for transmission of infectious diseases in general. An advantage of the population-based approach is that it gives a better

guarantee that the data are representative. Besides, the information on non-participants offers an opportunity to study the impact of non-participation on seroprevalence estimates. In order to monitor changes in the population's immunity the serosurvey should be repeated periodically, perhaps every 5–10 years, depending on the postulated rate of loss of immunity. It could also be considered to build up the serum bank in a more continuous way by collecting sera every year. This allows for the exploration of the effects of intercurrent epidemics (pertussis in 1996/7 or poliomyelitis in 1992/3 in our country) and either the introduction of new vaccines or changes in the (schedule of the) vaccines applied routinely [5, 14]. In the Netherlands we are now moving to such a continuous population-based serum collection. Although it would be even more interesting to include a longitudinal component in the survey it seems up to now not feasible since it would increase the already high costs of a population-based survey enormously. Despite the high costs of this population-based study compared to the use of residual sera, it might be worthwhile for other countries to consider a population-based collection of serum samples to study immunity against vaccine-preventable diseases. In 1996, the European Sero-Epidemiology Network (ESEN) was established to co-ordinate and harmonize the serosurveillance of immunity to vaccine-preventable diseases in six European countries (Denmark, UK, France, Germany, Italy and the Netherlands) [51]. Laboratory method should be standardized so that results from each centre are directly comparable. This is one of the major aims of the ESEN. However, comparability is also dependent on the representativeness of the study populations. In the ESEN, most of the countries had to rely on specimens submitted to laboratories for diagnostic purposes. Actually, not only should serological methods be standardized, the serum collection should be standardized as well, preferably by random sampling as advocated in this article.

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