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Prevention of Infectious Diseases and Injuries

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Measles in Europe. Where do we stand now?

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The choice of measles as the main theme of the workshop of the EUPHA section Infectious Diseases Control (IDC) requires, at least at first sight, further explanation. Isn't there other, perhaps more significant public health threats due to infectious diseases for Europe? We believe that the case of measles illustrates exactly what the public health approach, with respect to infectious diseases control, should be. Measles is a very old disease (fig 1), affecting mainly young children. Although the disease itself is usually mild, the course can be severe in case of malnutrition and vitamin A deficiency. Lethal outcome occurs in about 3-5 % of the cases in developing countries (1). Immunocompromised patients have a high risk for developing severe clinical manifestations. Subacute sclerosing panencephalitis (SSPE) can occur as a long term consequence of measles in about 1/100,000 cases. Safe, highly immunogenic and affordable live attenuated vaccines are available in order to prevent measles. After the isolation and the propagation of measles virus in tissue culture, by Enders and Peebles in 1954, vaccine development, testing, and licensure quickly followed. After the vaccine containing the Edmoston A and B strains, many further attenuated vaccines were developed and they are in active use worldwide (Schwarz, Moraten, Edmoston-Zagreb, etc) (2). Vaccination campaigns led to a decrease in mortality in developed countries of about 99%. Despite this fact, some areas in the world are still epidemic; the majority of cases are localised in Africa, where the mortality is also very high. In 2001 and 2002 respectively 615,000 and 880,000 people, mainly young children, died worldwide of this vaccine preventable disease (3).

Nowadays usage patterns and attitudes of the public towards vaccination can rapidly change. The seriousness of this disease has been underestimated by the

public since the incidence decreased. At the same time concerns with respect to the vaccine safety and side effects tend to increase. The public health component of the vaccination campaigns – vaccinating to induce herd immunity and thus protecting the non-vaccinated as well – can come under pressure, when individual health risks are weighed against public risks. In the strongly individualized western societies, non-compliance issues can play an increasing role.

The WHO Regional Office for Europe has released a strategic plan for the European region with the objective to interrupt the indigenous transmission of measles by the year 2010 (4). But as the “European space” consists of a large variety of countries with different programmes, attitudes and perceptions of vaccination, it is worthwhile to focus on the measles eradication efforts in a few regions.

Measles in the EU Member States, 2001–2003

In September 1998, a proposal from the Commission of the European Communities was adopted as a Decision of the European Parliament and Council (5) to set up a network for the epidemiological surveillance and control of communicable diseases in the European Community. Case definitions for reporting of 40 communicable diseases to the Community network were defined and decided upon in 2000 (6). On the basis of a proposal from the Statens Serum Institut (SSI), an agreement was reached with the European Commission Directorate General Health and Consumer Protection (DG SANCO) whereby the Department of Epidemiology at the SSI was to coordinate a collaborative project. This project, EUVAC.NET was created in 2000 with the aim of epidemiological surveillance and control of vaccine-preventable infectious diseases, beginning with measles (7,8). EUVAC.NET involves surveillance institutions in the 15 European Union (EU) countries that existed prior to the extension in 2004 and Malta, plus Iceland, Norway, and Switzerland, figure 2.

In order to meet the strategic plan of the WHO, EUVAC.NET has entered a Memo of Understanding with the WHO whereby measles data is received monthly by email from each of the central surveillance institutions in the participating countries. The case definition used follows the EU and the WHO recommendations and a data set of 23 variables was entered into a database for epidemiological investigation. Validated data was forwarded to the CISID database at the WHO Regional Office for Europe.

A total of 44,876 measles cases were reported: 7428 in 2001, 23,765 in 2002 and 13,683 in 2003. Data was received from all countries except France, where the existing sentinel surveillance system was not sensitive enough to produce valid data. Three countries reported aggregated data in 2001 whereas all countries reported case based data in 2003. Most cases were reported from Italy and Germany while no measles cases occurred in Iceland during the period. Three other countries, Denmark, Finland and Malta, also reported absence of measles in 2003. Countries with highest incidence of outbreak occurrence were Italy,

Germany, Ireland and Switzerland. The majority was diagnosed as clinical cases and only 17.8% were laboratory confirmed and/or epidemiologically linked to other measles cases. Measles were reported in both children and adults with most cases, however, in the 1-9 year age group. Vaccination status was reported on 70% of cases of which 91% were not vaccinated against measles. Most cases were reported to occur in the first half of the year, particularly during late winter and early spring (9).

From the data it can be concluded that measles is still endemic in parts of Western Europe and that the distribution of notified measles cases varies considerably among the participating countries. Some countries report incidence rates indicating a near-elimination situation. While the general quality of data collected has improved and many participating countries are regularly reporting data, other countries still need to put such reporting in place.

National plans should be developed emphasising contact tracing of cases, laboratory diagnostic procedures, and active and timely interventions to reach the WHO goal of measles elimination by 2010. Surveillance of measles, the immunisation and control programmes, and the close collaboration between Member States need to be strengthened. Networking should facilitate measles elimination in the EU, and the EUVAC.NET will support these activities through documentation and sharing of experience gained, and by creating political awareness.

Up-date on measles elimination in Italy

The epidemic curve of measles in Italy from the sixties to 2000 is characterised by periodical epidemic peaks, with a light trend toward reduction of cases which, however, were still as many as several thousands in 1996. Since 1983 the infants' vaccine coverage has been increased and in 2000 the national mean coverage was 72%. In 2002 an epidemic occurred, which hit some Southern Regions such as Campania and Calabria. During this outbreak 40,000 cases were notified, and it is likely that the real number of cases rose up to 100,000. Hundreds of hospitalisations and some deaths were registered.

Molecular epidemiology can help us to control the measles epidemics. Therefore, WHO currently recognizes 20 genotypes and one proposed genotype of measles virus based on phylogenetic analysis of the N gene. In spring 2003 in Liguria an outbreak of measles was registered with a total of 187 cases. Out of 16 pharyngeal swabs collected, 8 were viremic and they were categorised by nucleic acid sequence analysis of the Nucleoprotein gene (N) and the Haemagglutinin gene (H).

The phylogenetic analysis permitted genotyping of all 8, and relatedness between the viruses as well as the appropriate reference sequences was studied.

Sequences from Liguria formed a distinguished cluster from genotypes previously described as D7 genotype, even if with a difference of 5% from the reference strain.

Molecular epidemiology studies have made a significant contribution to the identification of the source and the transmission pathways of the measles virus, and they allowed the clarification of the epidemiological links during the measles outbreak through the separation of the indigenous strains from the newly imported ones.

The rational of measles elimination by vaccination is based on the concept of the reproductive rate of the infection (R_0), which is the number of cases which are supposed to be infected by a single case in a completely susceptible population.

Measles is a highly infectious disease, and R_0 has been estimated as 12.5 to 18. In order to achieve the goal of measles elimination it is necessary that the susceptible subjects are not more than 15% at the age of 0-5, not over 10% between 5 to 9 years, and no more than 5% in subjects over 9 years.

The goal of the Italian plan of measles elimination is to maintain, after 2007, the measles incidence below 1 case per 100,000 inhabitants.

The departments of the Italian Local Health Agency are the centres for the planning, organizing and carrying out of the measles elimination plan. To achieve the goal a close collaboration among public health experts, paediatricians, nurses, GPs, and also between universities and hospital is necessary. The measles elimination plan foresees the following:

- Within 2003: improving the surveillance system, by virus isolation and definition of the clades and the genotypes, for the identification of the imported or indigenous cases.
- Within 2004: increasing the coverage of infants to 85%, and improving the information of the vaccination database.
- Within 2005: increasing the infant measles coverage to 90%.
- Within 2006: increasing and sustaining a high routine coverage (95%), achieving a 95% coverage rate in children aged 3-15, and maintaining the measles incidence below 1 case per 100,000 inhabitants.
- Within 2007: maintaining the children rate coverage at 95% or over and increasing the two doses coverage of children aged 5-6 to 90%.

The assessment of the average coverage in August 2004 was, for the entire country, about 83.6% and the last assessment carried out in September allowed estimation that the coverage rate was equal to 84%. However, the coverage rates are dissimilar in the different Italian Regions. While Tuscany had 92.5% of children under 24 months covered with MMR vaccine, in Calabria less than 60% had been immunized.

Measles in Poland

Measles cases have been notifiable in Poland since 1919. The first dose of measles vaccine for children aged 13-15 months was introduced in 1975, and the second dose of the vaccine at the age of 7 years was introduced in 1991. In

1996 individual measles reports replaced the aggregated reports. In 1999, based on WHO recommendations, reports on both confirmed and suspected cases were introduced. In the last decade the measles elimination programme was implemented. It is co-ordinated at the National Institute of Hygiene. The largest outbreaks of measles, involving often more than 200,000 persons, occurred in the 1960s and 1970s. After the introduction of mandatory vaccination in 1975 the size of outbreaks systematically decreased. The last compensatory outbreak occurred in 1998 and involved 2,255 persons.

Summaries of vaccination coverage are collected by local Health Departments from health providers. Individual case reports are filled by physicians and sent to local Health Departments. Immunisation summaries and case reports are analysed at the National Institute of Hygiene, Warsaw. Case reports are analysed at the Department of Epidemiology. Blood samples are analysed at the WHO accredited Laboratory at the Department of Virology. The National Institute of Hygiene gives feedback information in bi-weekly publications sent to all local health departments. Aggregated summaries of cases are sent to the WHO Regional Office on a monthly basis. Measles incidence, vaccination coverage, and surveillance indicators for the period 1991–2003 were analysed at national and regional levels.

The number of registered measles cases decreased from 196,109 in 1973 to 48 in 2003. Since 1991 the vaccination coverage systematically improved. The percentage of 3-year old children vaccinated with the first dose at country level increased from 93.5% in 1991 to 97.5% in 2003. The percentage of 8-year old children vaccinated with the second dose at country level increased from 46.9% in 1991 to 96.8% in 2003. The immunisation coverage at regional level improved in the period 1991–2003 and since 1998 has been maintained at a constantly high level. A serologic survey was performed in 1998 to indirectly assess the vaccination effectiveness. 3,000 systematic blood samples were collected in 6 regions of Poland. The results of the survey showed that persons aged 15 to 19 were most susceptible to measles infection. The outbreak during the same year confirmed these findings (mostly people aged 16–20 were affected by the disease). The number of reported cases during the last decade was decreasing, indicating the progressive elimination of measles in Poland. The negative tendency was the insufficient detection of suspected febrile rash illnesses, required by WHO guidelines. The total number of suspected and confirmed cases reported decreased from 112 in 1999 (88.4% confirmed) to 55 in 2003 (87.3% confirmed). The timeline of reporting was analysed. The median number of days between rash onset and serum sample collection increased from 9.5 in 1999 to 11.0 in 2003. The median number of days between first visit and reporting to local Health Department decreased from 7.0 to 4.0 days.

Despite a remarkable decrease of measles incidence in Poland in the previous 30 years, the implementation of the measles eradication programme faced numerous difficulties. The excellent vaccination coverage led to the reduction of

measles cases and deaths; the surveillance of confirmed and suspected measles cases was therefore insufficient in reference to the WHO indicators. The main tasks for the Polish authorities in the near future are: the maintenance of high vaccination coverage, the establishment of high coverage of rubella vaccination (included in the National Immunisation Programme since 2003), improvement of the case-based surveillance including detection and virological examination of suspected febrile rash illnesses, and reporting the case-based data to WHO Regional Office for Europe.

Eliminating measles from the Netherlands: Where are we?

In the Netherlands (16 million inhabitants) national, non-compulsory vaccination against measles was introduced in 1976, and replaced by MMR vaccination in 1987. Currently, the first dose of MMR is given at 14 months, and the second dose at 9 years. The overall vaccination coverage in the Netherlands is high but this conceals clusters of unvaccinated individuals. In 2003, coverage for MMR-1 was 95%, but less than 80% in 2% of all municipalities (about 300,000 people). Areas of low vaccination coverage are geographically linked in the so-called 'bible belt', where vaccination is commonly refused on religious grounds. Surveillance of measles in the Netherlands aims to monitor the incidence, detect outbreaks, and provide data to predict which vaccination schedule would most effectively protect the vaccine-accepting population.

Surveillance of measles in the Netherlands is based on clinical notifications, with a pilot saliva confirmation study ongoing. In addition, data on vaccine coverage and seroprevalence are available. The latter, obtained from a population survey in 1995–6, was used to predict the impact of changes in the vaccination schedule on the number of cases during an epidemic year, in order to inform vaccination policy.

Between 1976 and 2002, three large and two smaller national outbreaks occurred (in 1976, 1988, 1999; and 1983, 1992 respectively). In 1999–2000, 3,292 cases were reported, 94% of whom had not been vaccinated. Cases' area of residence closely matched areas of low vaccination coverage (the bible belt). Only 1 patient had received 2 doses of vaccine. Three patients died and an estimated 157 patients (95% CI: 145–179) were hospitalized. In total, 16% of reported patients had complications (most frequently pneumonia and otitis media). Unvaccinated individuals were 224 times more likely (95% CI, 148–460) to acquire measles than were vaccinated individuals; the relative risk increased with decreasing vaccine coverage in the respective municipality. Herd immunity outside unvaccinated clusters was high enough to prevent further transmission.

Modelling suggests that advancing the age of the second MMR vaccination (at 4 years of age instead of the current policy at 9 years) will prevent considerably more cases in the long term than an extra early measles vaccination or by dropping the age of the first MMR vaccination. However, effects on immunity

against rubella by advancing the age of the second MMR are uncertain, and this schedule is not currently recommended.

Measles continue to be endemic in the Netherlands, and large outbreaks occur periodically. Clusters of persons refraining from vaccination, geographically linked in the bible-belt, interfere with measles elimination. The surveillance of rash illnesses in the Netherlands is being enhanced by offering laboratory confirmation on saliva samples to notified cases and clusters of suspected measles, rubella or parvo virus infection.

Measles and rubella – a vision for 2010

The World Health Organization European Region is a very diverse region with 52 Member States and a population of about 880 million persons (10); the newly expanded European Union (EU) comprises about 50% of the countries and 50% of the population in the European Region. Since the early 1990s, there has been a 92% reduction in incidence of measles reported to the European Region's office in Copenhagen; however over 27 000 cases were still reported in 2003. The decline in incidence (94%) in EU countries during this time period mirrors what has happened in the European Region as a whole, and 49% of measles cases reported in 2003 were from EU countries; 99% of these cases were reported from the 15 countries in the old EU. Recent measles outbreaks in some western European countries demonstrate that this disease remains an important cause of vaccine-preventable morbidity and mortality (11-12).

The recently published *Strategic plan for measles and congenital rubella infection in the WHO European Region* (13) identifies six key strategies for meeting the 2010 targets of interrupting indigenous transmission of measles and preventing congenital rubella infection, as measured by less than one case of congenital rubella syndrome per 100 000 live births. These strategies include: achieving and sustaining very high coverage with two doses of measles vaccine, through high-quality routine immunization services; providing a second opportunity for measles immunization through supplementary immunization activities (SIA); using the opportunity provided by SIA to target populations susceptible to rubella; ensuring protection to women of childbearing age against rubella; strengthening surveillance systems; and improving the availability of high-quality, valued information, for health professionals and the public, on the benefits and risks associated with immunization. While the European Region has previously had targets for measles and rubella, its diversity economically, socially and with regard to health systems and governance has posed significant challenges to the achievement of the targets.

The approach in the European Region has been to integrate measles and rubella control and surveillance activities. All 25 EU countries and 47 out of 52 countries (90%) in the European Region use measles and rubella vaccines in their childhood immunization programmes; 46 (88%) as combined vaccine,

mostly MMR. All 52 countries in the European Region now have national two-dose measles vaccine programmes.

A measles incidence of less than 1 per 1 000 000 has been proposed as one criterion for assessing whether a country has achieved measles elimination (14). Using this indicator, 19 countries in the European Region and 13 within the EU achieved this level of control in 2003; however, seven of these EU countries are among the 10 recent EU accession countries. Data on rubella infections are not as complete as five countries in the European Region do not have national surveillance for this disease; four of these countries are in the EU. Since all countries in the EU currently use combined measles-rubella vaccines, measles outbreaks likely indicate inadequate protection against rubella as well. The very limited surveillance for congenital rubella syndrome also does not provide an accurate estimate of the burden of this condition.

Considerable progress has been made over the last two years toward achieving the European Region targets for measles and congenital rubella infection; however, some of the larger EU countries are the ones now needing the most attention. Strong policy-level support for the European Region's strategic plan will be needed in all countries. In addition, strengthened surveillance is needed for monitoring the successful achievement of the targets, including movement to case-based reporting among all countries with good disease control programmes; clear identification of import and import-related cases; and the investigation of outbreaks with collection of clinical specimens for virus detection and isolation. Achieving the measles and congenital rubella infection targets are an opportunity for EU countries to seek resources for strengthening their own immunization programmes, and also an opportunity for them to support this activity among poorer countries in the European Region. The high coverage required for measles elimination means that all countries need to develop and implement strategies to reach the hard-to-reach, and improve accessibility to immunization services for all children and all women of childbearing age.

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Historians suppose that measles originated in Sumeria in 3,000 BC, and from there the disease spread out towards West and East following civilisations such as the Egyptian, the Greek, the Indus and the Chinese, and obviously the expansion of the Roman Empire. Unpopulated areas such as the Sahara and Gobi Deserts were natural barriers to the spread of measles.

Figure 1. The history of measles

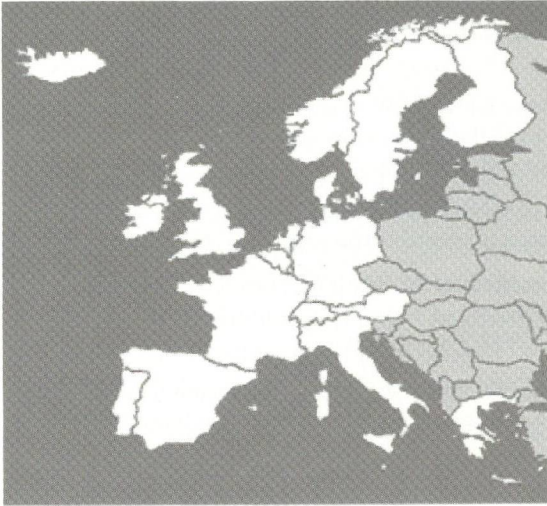


Figure 2. Participating countries in the EUVAC.NET measles surveillance until 2004.

- **European Union -**
15 member states prior to 2004
- **Accession countries prior to 2004 -**
Malta
- **Other countries -**
Iceland
Norway
Switzerland

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