Costing of Measles Elimination

Report on a WHO Meeting

Copenhagen, Denmark
23–24 October 2000
ABSTRACT

The meeting was organized as part of a WHO-funded project to estimate the potential savings for western Europe of measles elimination or eradication. The project being still in its initial phase, the meeting was convened to identify collaboration for the project and data availability in the participating countries. Progress towards measles elimination and rubella control in the WHO European Region was assessed, and in particular findings from the EUVAX and European Seroepidemiology Network (ESEN). Data on measles incidence and its associated costs, needed for the project, were summarized. It was concluded that the available data were predominantly from the United States, and much of them were not easily transferable to the European setting. While some European data would have to be collected from scratch, others could be obtained from the EUVAX and ESEN databases.

The meeting came to the following key conclusions.

• A review by questionnaire will be made of the available data on the incidence and costs of measles cases and measles-associated adverse events in industrialized countries. This will allow an estimate to be made of the current cost of measles and measles vaccination in those European countries that have already achieved, or are close to achieving, measles elimination. It would thus allow the likely future costs of measles and measles vaccination to be determined, and thereby the savings that could accrue from measles eradication.

• In the present project, focus will be placed on western European countries. It is hoped, however, that the NIS and other countries in the Region can be included in a different project at a later stage.

• It is crucial to assess the importance of rubella vaccination alongside any measles elimination strategy.

Keywords

MEASLES – prevention and control
COST-BENEFIT ANALYSIS
RUBELLA – prevention and control
IMMUNIZATION – economics
EUROPE
EUROPE, EASTERN
COMMONWEALTH OF INDEPENDENT STATES
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1. Executive summary and conclusions

Immediate action points arising from the meeting were:

- Questionnaires will be sent to all participating countries. Questions will focus on costs and incidence of adverse events, incidence and costs of measles cases as well as estimated costs of future vaccination schedules. Expanded Programme on Immunization (EPI) managers in the respective countries will be overall responsible for completing these questionnaires.
- Data collection will be coordinated with the EUVAX and ESEN networks.
- It will be investigated whether there is any hospitalization data from Denmark and Iceland available from the pre-vaccination era.
- Data on hospitalization rates will be collected from recent measles outbreaks in Ireland and Holland.
- Data on hospitalization costs will be coordinated with pneumococcal vaccine studies currently undertaken by Maastricht University.

2. Background and objectives of the meeting

The World Health Organization (WHO) is currently undertaking a project to estimate the economic benefits of measles eradication and elimination to developed countries. Investigators of the study are based at City University and the Imperial College of Science, Technology and Medicine in the United Kingdom. The study is scheduled to last 6–9 months. The aim of the study is to determine the present value of potential savings from measles eradication to countries that have achieved (near) measles elimination. The methodology will be based on that of Miller et al. (1998). Because most developed countries have not yet achieved elimination, the cost–benefit of improving current immunization coverage will be evaluated. Costs will be estimated and presented from the societal perspective and from that of the health care providers.

The meeting was organized to inform representatives from western European countries about the project and to determine the data availability in these countries.

Meeting objectives were identified as:

1. By reviewing the available data on the incidence and costs of measles cases and measles vaccine associated adverse events in industrialized countries, to:
   - estimate the current cost of measles and measles vaccination in European countries which have already achieved, or are close to achieving, measles elimination; and
   - determine, from the above, the likely future costs of measles and measles vaccination, and thereby the savings that could accrue from measles eradication.

2. Review of rubella control programmes with emphasis on western Europe.
3. Opening session

Dr Bernardus Ganter opened the meeting by explaining that this is the beginning of a process aiming at calculating the true costs of measles elimination and eradication. By gathering key people from some of the western European countries WHO hopes that data from this region can be more easily identified and collected. The findings of the meeting will be presented at the Eleventh Meeting of the Interagency Immunization Coordinating Committee (IICC), which is scheduled for 27 November 2000.

Dr Ganter noted that during the last part of the meeting, issues concerning rubella control will be summarized and benefits of combining rubella control with measles elimination will be evaluated.

Dr Ganter kindly requested Dr Philippe Beutels to chair the meeting and Ms Ulla Kou to act as rapporteur.

4. Economics of elimination

Dr Edmunds started off by stating that the topic of the next few days is to discuss ways of evaluating whether Europe will save money from measles eradication. This will be assessed by estimating the costs of measles vaccination, including adverse events, as well as treatment of remaining measles cases. Dr Edmunds stressed that elimination is a prerequisite from eradication. Therefore, even if elimination is not cost-effective, eradication might well be.

Dr Edmunds summarized basic theories of the epidemiology of elimination. He explained the definition of the basic reproduction number $R_0$ as:

\[ \text{the average number of secondary cases a typical infectious individual will cause in a completely susceptible population.} \]

$R_0$ measures the intrinsic potential for an infectious agent to spread. The effective reproduction number, $R$, is the average number of secondary cases generated by a single case. Hence, $R = R_0 \times \text{proportion susceptible}$. If $R < 1$, then each case will generate fewer than 1 additional case and if this is maintained (via vaccination), then elimination will occur.

Dr Edmunds explained that for measles elimination to occur, coverage must be relatively high. This is partly due to the fact that the efficacy of a single dose of the vaccine is estimated to be only around 90%.

To achieve elimination the susceptibility must be kept below the EURO targets. Elimination can be achieved if the proportion susceptible in each age group is maintained below these levels. However, the targets are not “fixed”. If susceptibility is slightly higher in one age group than the targets, then elimination can still be maintained by further reducing the proportion susceptible in other age groups. The targets are different than in the United States, where there are no age specific targets. The aim of the targets is to do better than natural infection through the immunization programme.

Dr Edmunds then went on to outline that from a theoretical viewpoint elimination may not be the most cost-effective level of coverage to achieve, since high levels of effort are required to be maintained in perpetuity. However, elimination is a necessary prerequisite of eradication, which
may well be attractive economically (indeed if elimination has been achieved then eradication will always be cost-saving).

If future benefits are not discounted to their present value then eradication programmes are potentially infinitely cost-effective, since after eradication the costs tend to zero and the benefits (in terms of absence of cases) continue in perpetuity. However, if future benefits and costs are discounted then whether eradication is cost-effective depends on the time (and effort) required to achieve eradication, the potential savings that accrue from eradication and the discount rate applied to future benefits and costs.

5. Estimating the benefits of measles elimination: areas of research

Dr Edmunds argued that when excluding the value of altruistic benefits from eradicating measles, there are three main areas of financial benefits: (1) measles cases averted; (2) savings to vaccination programme (may switch from two to one dose measles/mumps/rubella vaccine – MMR); and (3) adverse events from measles component of vaccine avoided.

Savings derived from measles cases averted depends on complication rates, consultation and hospitalization rates, average length of stay and the incidence of measles (depends on past immunization programmes and local epidemiology (birth rate)).

To determine the savings derived from vaccination programmes, it should be known whether MMR would still be used after eradication. And if not, what savings would be released by the use of MumpsR? Furthermore, would one or two doses be given? If only one dose, would a scheduled visit be avoided, i.e. is the second dose given at the same time as other vaccines?

- Savings derived from reduced adverse events depends critically on likely future immunization programmes. If MMR is to be used, the incidence of adverse events associated with MMR vaccine should be investigated, as well as the costs. If MumpsR is to be used it should be investigated what adverse events occur due to the measles component, the incidence of these events and the average cost of each event.

Other issues that will determine the total costs savings from measles eradication are discount rates, time to eradication and uncertainties.

Dr Edmunds summarized the need for the proposed research as follows.

- Significant extra funds are now becoming available for immunization programmes in the developing world.
- Polio eradication programme is entering its final phase.
- Measles eradication is being discussed on the international agenda.
- Would major donor countries benefit financially from sponsoring eradication efforts?
- Important to know cost savings even if costs would be higher than savings.

During the subsequent discussion the following issues were touched upon.

- The measles component is the cheapest part of the MMR vaccine. Therefore, countries might continue with MMR even after eradication. The question is whether two doses are
still needed after eradication. However, even if only one dose is given, there might still be a second vaccination visit scheduled and the savings will therefore not be great.

- For estimating likely cost savings from adverse events we need to distinguish the adverse events of MMR versus mumps/rubella (MR).
- It would be useful to measure how measles eradication can contribute to increased quality of the routine immunization programmes. In the Pan American Health Organization (PAHO) the elimination programme greatly contributed to this and it also made it easier for programmes to adopt new vaccines.
- For advocacy reasons it is important to include the elimination of mumps and rubella in the strategy.

6. Estimating the benefits of measles elimination: what is known

Dr Carabin summarized a concise literature search on the data needed for estimating the benefits of measles elimination to Europe. She also presented some preliminary results of the analysis which will be done when more data is collected.

With regard to measles associated adverse events, this is difficult to quantify due to the frequent use of the MMR vaccine in European countries. Therefore, it becomes difficult to disentangle the effects of the measles component in the MMR vaccines on the frequency and type of adverse events. The best source for the occurrence of adverse events from the MMR vaccine is a review paper by Duclos and Ward from 1998, which unfortunately did not include any costs data.

Evidence of costs associated with adverse events is scarce.

Associations have been found between measles-containing vaccines and the occurrence (rare) of encephalitis or encephalopathy, febrile seizures and thrombocytopenia purpura or thrombocytopenia. There is no current evidence to accept or reject an association between measles-containing vaccines and neurological sequelae, optic neuritis, sensineuronal deafness, subacute sclerosing panencephalitis and transverse myelitis. In addition, most recent data seems to reject any evidence of an association between measles-containing vaccines and the occurrence of acute encephalopathy, autism, Chrohn’s disease, death, Guillian-Barré syndrome, multiple sclerosis. The MMR vaccine has also been associated with the occurrence of anaphylaxis, fever, rash, allergies and febrile and afebrile seizures.

To estimate the costs of adverse events, data is needed on the frequency and the costs of hospitalization, divided into normal wards and intensive care units (ICU), the number of telephone consultations, the number of visits to the family physicians/paediatrician and the number of hours/days of work lost for parents. These data are likely to be country-specific and it will therefore be important to collect that information separately. Very little data is available on this and no data was found from European countries.

For estimation of the costs of measles cases, data is needed on the country-specific frequency and costs of hospitalization in normal and ICU wards, telephone and clinic consultations with general practitioners (GPs) and paediatricians, use of over the counter and prescribed drugs, parents’ and individual’s loss of work and earnings. Data found in the literature on hospitalizations, indicates the following.
The most common complication of measles are upper respiratory infections and otitis media. The average duration of a measles case has been estimated to 10.8 days with a range between 1 and 35 days. There would be an average of 8.33% of measles cases that are uncomplicated (range between 4% and 18%). This does correspond with the reported proportion of cases that are hospitalized varying between 1.15% to 32.5% with a median around 10%. The very high estimates come from a study conducted in California during a large outbreak at the end of the 1980s. The length of stay of an average measles hospitalized case would vary between 3.5 and 11.7 days. These data do include a lot of American studies and are likely not to represent the reality of European countries. The cost per hospitalized case has been reported to vary between € 1581.87 and € 2052.64. The reported costs per average case vary between € 81.20 (study from Finland) and € 781.09 (study from Canada). Directly applying these values to European countries is difficult because of the different types of health services.

In the subsequent discussion, the following issues were debated.

- It is difficult to compare costs in different European countries due to different delivery systems in terms of public, private or insurance based systems.
- It will be important to incorporate the newly independent states (NIS) in the analysis. Even though these countries are far away from elimination and even though it is likely to be difficult to collect data in these countries, it is important for advocacy to include them.
- It was noted that the Finnish cost data presented by Dr Carabin was significantly lower than what could have been expected.
- The reason for the big difference in total cost savings between the preliminary results presented by Carabin and the results presented by Dr Miller et al. were questioned. Dr Carabin responded that there are a number of different reasons for this difference. First of all, it should be emphasized that the results are very preliminary. Secondly, the cost data is based on the one study from Finland. Thirdly, contrary to the Miller study, it has been assumed that no vaccine costs savings will be generated as countries are likely to continue with the mumps and rubella vaccine and this is not much cheaper than the MMR. In contrast, Miller et al. assumed that the mumps and rubella vaccine would be two thirds of the price. Finally, the size of the birth cohorts was significantly different.

### 7. Progress towards measles elimination: western Europe

**Dr Pebody** reminded the participants about the goals that have been set for the European Region:

1. To further reduce the morbidity and mortality from measles in the European Region.
2. To eliminate indigenous measles from the European Region by the year 2007.

To reach these goals, the following objectives have been decided upon:

- to reduce the estimated proportion of measles susceptibles in the population to low levels by the year 2005:
  - 1–4 years: 15%
  - 5–9 years: 10%
  - 10–14 years: 5%
  - adults: 5%
- to maintain these low levels until 2007.
To monitor the progress towards the targets, the WHO Regional Office for Europe sent out a questionnaire to all 50 Member States in 1996 and information was also collected by the European Union (EU) funded European Seroepidemiology Network that operated from 1996–1998. This network was set up to coordinate and harmonize the serological surveillance of immunity to several vaccine preventable diseases including measles. Seven western European countries participated and large, standardized serological surveys were conducted in these countries.

The following coverage rates have been reported in the European Region:

- 7 countries have more than 95% coverage
- 14 countries have between 90% and 95% coverage
- 8 countries have between 80% and 90% coverage
- 9 countries have between 80% and 50% coverage
- 3 countries have less than 50% coverage.

The average incidence of reported measles was 43/100 000 in 1987 and 7/100 000 in 1995. Deaths from measles in Europe have also been greatly reduced during the last three decades. While 2000 deaths were reported in 1970, less than 150 were reported in 1993.

WHO has divided the Region into three groups according to level of disease control and elimination.

**Group 1: Close to elimination**

- national reporting of suspected cases
- laboratory confirmation of a high proportion of cases:  
  - and either  
  - 95% coverage of dose 1 (for five years) and  
  - 95% coverage of dose 2 (in 10 cohorts)  
  - or  
  - low susceptibility.

**Group 2: Good control but potential for outbreaks**

- national reporting of suspected cases
- laboratory resources for confirmation of cases:  
  - 90% coverage of dose 1 (for five years)  
  - either  
  - a stable incidence of reported measles for five years  
  - or  
  - inter-epidemic period for more than five years.

**Group 3: Poor control**

- Less than 90% or unknown coverage for the first dose  
  - or  
  - no national reporting of suspected cases  
  - or  
  - an inter-epidemic period of less than five years.
Dr Pebody concluded that while measles elimination is feasible, there is only variable progress in Europe. There is an urgent need for political commitment to elimination, development of elimination plans according to local epidemiology and maintenance of high coverage levels on all geopolitical regions.

In the discussion following the presentation it was stated that campaigns would be the only solution to reach the susceptible schoolchildren in the Region. However, there is no immediate plan in any of the countries to carry out campaigns.

8. Progress towards measles elimination: eastern/central Europe and NIS

Dr Kramarz explained that measles vaccination was introduced in the NIS in 1960–1970, and in the rest of the Region in 1970–1980, with the exception of France, Belgium and Germany where it was introduced in the 1980s. Some of the NIS countries use Leningrad 16 vaccine strain, whereas other countries of the region use Schwartz, Edmonston-Moraten, or Edmonston-Zagreb strains.

Central Asian republics and Kazakhstan (CARK) countries overview

In Tajikistan, Turkmenistan, and Uzbekistan the first dose of measles vaccine is recommended routinely at nine months of age, in Kazakhstan and Kyrgyzstan during the second year of life. In all CARK countries second dose of the vaccine is recommended between the third and seventh year of life with the exception of Uzbekistan where it is recommended at 16 months of age.

According to the data from the 2000 EPI questionnaire, in 1999 all CARK countries exceeded 95% coverage with first dose of measles vaccine, except for Tajikistan (90%). Kazakhstan, Uzbekistan and Kyrgyzstan have also exceeded the target 95% coverage with second dose of measles vaccine, whereas Turkmenistan reported 91.5% and Tajikistan reported 46%. Annual reported incidence of measles in CARK countries is decreasing, with peaks every 3–4 years. As seen on the example of Turkmenistan, there is a seasonal pattern in measles incidence, with most cases occurring in winter and early spring.

Caucasus countries overview

In all countries in the Caucasian region one dose of measles vaccine is recommended routinely at 12 months of age. According to the data from the 2000 EPI questionnaire in 1999, Azerbaijan and Georgia exceeded 95% coverage and Armenia reported 91% coverage. Annual reported incidence of measles in Caucasian countries is decreasing, with peaks every 2–3 years.

Overview of the situation in Belarus, the Russian Federation and Ukraine

In Belarus and Ukraine first dose of measles vaccine (MMR) is recommended routinely at 12 months of age, in the Russian Federation first dose of M+M vaccines (measles and mumps) between the ages of 12 and 15 months. In Belarus second dose of MMR is recommended during the sixth year of life and in Ukraine the second dose of measles vaccine (single agent) is recommended at six years of age. In the Russian Federation the second dose of M+M vaccines is given at seven years of age.

According to the data from the 2000 EPI questionnaire, in 1997–1999 all three countries exceeded 95% coverage with first dose of measles vaccine. In 1999 Belarus and Ukraine have also exceeded the target 95% coverage with second dose of measles vaccine, whereas the Russian Federation did not report the second dose coverage in their questionnaire.
Annual incidence of measles in all three countries is decreasing, with peaks every 2–6 years. There is a seasonal pattern in measles incidence, with most cases occurring in winter and spring.

**Overview of the situation in Turkey and Yugoslavia**

In Turkey the first dose of measles vaccine is recommended routinely at nine months of age, the second dose at six years of age. In Yugoslavia the first dose of measles vaccine (MMR) is recommended routinely at 15 months of age, the second dose at 12 years of age.

According to the data reported annually to WHO/EURO by Turkey and Yugoslavia, neither one of them reached 95% coverage with first dose of measles vaccine during the past ten years. For example, in 1997, Turkey reported 76% coverage and Yugoslavia 92.5% coverage. No decreasing trend in annual measles incidence could be seen in Turkey; peaks occur every 2–6 years. Annual data on measles incidence in Yugoslavia were incomplete. Neither country provided monthly measles incidence data for evaluation of seasonal trends.

**National plans of measles elimination**

Among the NIS countries, Turkey and Yugoslavia, five countries have national plan of measles elimination, in two the plans are in preparation. Seven countries performed some supplemental vaccination activities (of unspecified magnitude) against measles during the last five years. Two countries immunize routinely against rubella, and six against mumps. Four countries performed some type of measles sero-prevalence surveys in the past.

**Summary of measles elimination workshops in the Region**

Workshops on measles elimination were conducted in Andorra, Bled, Baku and Issyk-Kul. Epidemiological data/problems were identified, e.g. susceptibility profiles identified from surveillance/coverage estimates differed from those estimated in sero-prevalence studies. Recommendations were derived, and draft plan of action was prepared.

**Summary**

In summary, epidemiological data from the NIS countries, Turkey, and Yugoslavia are incomplete and discrepant, even for incidence of measles and coverage with measles vaccines. Surveillance data are limited, in many cases with no laboratory confirmation. Most countries do not have plans of action or the plans are at a draft stage. National plans should identify timeline, resources, and immunization strategies, in detail.

**Recommendations**

Quality of surveillance should be improved, including the use of case definitions and collecting epidemiological data by age, immunization status, and geographical area. Laboratory confirmation of at least some cases/outbreaks should be introduced. National reference laboratories should be established. Laboratory diagnostic standards and quality control procedures of laboratory network need to be worked out and applied. Quality of data on measles vaccination coverage should be improved; coverage needs to be expressed by age and geographical region to identify populations at high risk of susceptibility. High coverage with first and second dose of measles vaccine should be maintained. Mass vaccination campaigns should be considered, when, for whom and where, justified.

**9. Progress towards measles elimination: are the criteria for measles elimination adequate for all of Europe?**

Dr Mossong reminded the participants about the 1997 WHO meeting where a strategy to achieve elimination of measles in the WHO European Region was proposed. The central idea of
this strategy is to immunize more people by vaccine than would have been infected from natural transmission. The criteria is that at least 85% of 1–4-year-olds, 90% of 5–9-year-olds and 95% of children above 10 years should be immune.

These criteria were established using results from a mathematical model where parameters were based on demography and transmission rates of measles in England and Wales. The model results are thought to be applicable to other western European countries with similar demographic and transmission patterns. It is, however, not clear whether these criteria are also adequate for other countries, particularly in the central Asian republics (CAR). These countries have different demographics with higher birth rates, lower life expectancy and younger population. They might also have a different epidemiology with higher (or lower) transmission rates, different force of infection and average age at infection, but there is not yet any evidence of this.

Dr Mossong put forward two main questions:

1. Will the current WHO criteria lead to elimination in central Asian republics?
2. If no, why not? And how do the current WHO criteria have to be adjusted or refined?

Dr Mossong explained the mathematical model he has used to answer these questions. It is a standard age-structured mathematical model of measles transmission which has been used by many authors, e.g. McLean & Anderson, 1988; Nokes & Swinton, 1995 and Gay et al. 1998. The model has 5 compartments (maternally protected → susceptible → latent → infectious → immune), 5 age classes (0–4, 5–9, 10–14, 15–20, 20+) to take account of age-varying forces of infection, and the model assumes that the country immunize (effectively) 85% of 1-year-olds, 33% of 5-year-olds and 50% of 10-year-olds to achieve WHO immunity profile (3-dose strategy).

Dr Mossong has incorporated the epidemiological characteristics of the central Asian republics into the model as follows:

- average life expectancy in CAR is ten years lower;
- population is younger; in CAR 37% of population is less than 15 years old compared with 17% in the EU;
- growing populations due to high total fertility rate in some countries (e.g. 4.1 in Tajikistan and 3.8 in Turkmenistan in 1995);
- different survival patterns (mortality profiles estimated from WHO Health for All database).

As a starting point the epidemiological characteristics of measles in CAR has been incorporated with force of infection estimates of measles in the United Kingdom. The main outcome of the model is that if the effective reproduction number, R remains less than 1 after introduction of a vaccination programme, measles can be expected to be eliminated.

**Key results and conclusions are:**

- The proposed WHO immunity profile will lead to elimination in Uzbekistan, Kyrgyzstan and Kazakhstan but not in Turkmenistan and Tajikistan.
- Sensitivity analysis shows that the most important factor for persistence is the high birth rates in the these countries (rather than different mortality patterns).
• This suggests that immunity profiles of 5–9-year-olds need to be higher than 90%.
• Model simulations show indeed that immunizing effectively 95% of 5-year-olds would lead to elimination in all five CAR.
• Elimination with a strategy based on WHO criteria might be difficult to achieve in countries with very high birth rates
• In countries with a rapidly growing population, model suggests that 85% of 1-year-olds and 95% of those 5 years and older need to be immune to achieve elimination.

10. Towards measles elimination in other regions

Dr Henao-Restrepo reminded the participants that measles remains the leading cause of childhood vaccine-preventable deaths worldwide. Although national immunization programmes prevent over 80 million measles cases and 4.5 million deaths annually, it is estimated that over 30 million cases and 880 000 deaths still occur every year. This represents 40% of the estimated annual 2 million deaths due to childhood vaccine-preventable diseases. The disease accounts for 10% of all causes of mortality among children under five years of age.

In May 1989, the Forty-second World Health Assembly established a global measles control goal.1 In 1990, at the World Summit for Children (WSC), world leaders endorsed a goal of a “reduction by 95% in measles deaths and reduction by 90% of measles cases compared to pre-immunization levels by 1995, as a major step to global eradication of measles in the longer run”.2 Regional elimination goals have been set for the American Region (AMR) by 2000, the European Region (EUR) by 2007, and the Eastern Mediterranean Region (EMR) by 2010. Extraordinary progress towards measles control has been made since 1989. Measles transmission has been interrupted in most countries in the WHO Region of the Americas.3 Worldwide in 1998, the estimated number of cases and deaths had declined by 63% and 83%, respectively, when compared with the pre-vaccine era estimates.

Failure to deliver at least one dose of measles vaccine to all infants remains the primary reason for the high measles morbidity and mortality. Between 1990 and 1998, global routine vaccination coverage among children aged one year with one dose of measles vaccine remained at between 70–80%.4 In 1998, 15 countries reported measles coverage at below 50%. The priorities over the next five years are to ensure reduction in measles mortality and to make significant progress toward interruption of measles transmission in regions and countries with elimination goals.

Five strategies are recommended for measles mortality reduction or measles elimination. These are: (1) strengthening routine immunization; (2) ensuring that all children have a second opportunity for measles vaccination; (3) disease surveillance with integration of epidemiological

and laboratory information; (4) vitamin A supplementation through immunization services (where appropriate); and (5) adequate case management for every measles case.

GAVI’s aim to ensure that 80% of developing countries have routine coverage of at least 80% in all districts by 2005 is an essential first step in reducing the burden of measles. However, it is important to note that at 80% coverage the remaining measles disease burden is high. A second opportunity for measles vaccination is required to protect all children against measles.

Supplementary vaccination campaigns, if implemented well, are an effective method for rapidly increasing population immunity. Special efforts should be made to ensure immunization safety and to identify and immunize children who have never received measles vaccine (“0 dose children”).

Measles surveillance should be strengthened in developed and developing countries to monitor programme progress. In vitamin A deficient countries, vitamin A supplements should be provided at the time of vaccination with measles (routine and supplemental). Management of complicated cases includes Vitamin A supplementation and adequate treatment.

In the subsequent discussion it was mentioned that the countries in the PAHO region are still getting outbreaks. They all have their individual problems. One problem is that many paediatric societies believe that the routine programme is sufficient and argue against campaigns. However, it is often proven that this is not the case.

11. Overview of rubella control in Europe

Dr Ciotti reminded the participants that the European target for rubella control is that by the year 2010 or earlier, all countries of the Region should have an incidence level for congenital rubella of below 0.01 per 1000 live births.

Two vaccination strategies to control congenital rubella syndrome (CRS) are being used in the region:

1. Selective vaccination of girls
   • allows acquisition of natural immunity in childhood
   • direct protection of women of childbearing age.

2. Universal vaccination
   • aims to eliminate rubella infection
   • indirect protection of women of childbearing age.

Dr Ciotti summarized the experience in Rumania as follows:

- no rubella control policy in place
- anecdotal reports of high numbers of CRS cases
- measles epidemic in older children in 1997
- planned measles campaign in schoolchildren over 10 years
- rubella vaccination recommended to girls over 13 years (funding for girls over 15 years)

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• effect predicted on basis of pre-vaccine seroprevalence (United Kingdom) and age-specific fertility.

Dr Ciotti, explained that during a meeting in Warsaw (November 1998) the European Advisory Group on the Expanded Programme on Immunization (EAG) recommended that countries planning a measles campaign should consider using MR instead of measles vaccine in teenage females in order to prevent congenital rubella syndrome. However, only in countries where routine coverage is high and can be sustained, should MR or MMR be used instead of measles vaccine during campaigns for children of both sexes.

Dr Ciotti summarized the experience in England and Wales with selective vaccination. In this region, high coverage in teenage schoolgirls has been obtained and only a small proportion of pregnant women is susceptible (less than 3%). Cases of rubella infection in pregnancy has thus been reduced. However, CRS still occurs as susceptible women are exposed to cases of rubella in children. There was a decision to switch to universal MMR in 1988.

Important surveillance data for rubella is coverage (of routine pre-school MMR vaccination programs (for each dose) and rubella (or MMR) in teenage girls), age- and sex-specific incidence (laboratory confirmed cases) and age- and sex-specific prevalence of antibody (serological surveys).

Dr Ciotti summarized the status of CRS control in the Region as follows:
• most countries will fail to reach target
• surveillance is inadequate or non-existent
• rubella vaccine not used in national programmes of 14 Member States
• where vaccine is used coverage levels range from 25–100%.

12. Seroepidemiology of rubella in western Europe

Dr Pebody stated that the aim of rubella vaccination services is to reduce morbidity and mortality from congenital rubella infection.

Rubella infection in pregnancy was explained as:

\[
\text{Number of infections in pregnancy} = \text{number of pregnancies} \times \text{proportion of pregnant women} \times \text{risk of infection in susceptible pregnancy}
\]

The key concerns of a rubella vaccination programme is that universal infant immunization may lead to an increase in the average of infection, but modelling predicts that infant vaccination coverage of less than 80% can increase the incidence of CRS.

Dr Pebody summarized the three stages of rubella control as:
• Stage 1: planning for rubella vaccine
• Stage 2: CRS prevention phase
• Stage 3: rubella elimination phase.

Dr Pebody repeated the European rubella elimination target as:
By the year 2010 or earlier all countries of the Region should have an incidence level for congenital rubella of below 0.01 per 1000 live births.

The operational targets are that infant vaccination coverage should be of at least 90% and there should be effective CRS and rubella surveillance in place.

Dr Pebody stated that many countries have failed to reach the targets for CRS control due to:
- surveillance is inadequate or non-existent in many countries
- rubella vaccine is not used in the national programme of 14 Member States
- coverage ranges from 25–100%.

Dr Pebody went on to explain the work of the European seroepidemiology network (ESEN). The aim of this network is to coordinate and harmonize the serosurveillance of immunity to communicable diseases in Europe. The network makes use of comparable sampling and a comparable assay method. The infections concerned are measles, mumps, rubella, diphtheria and pertussis. In the assay standardization, a reference laboratory for each infection has been established.

The main conclusions from the ESEN work are:
- Some progress towards European target, but patterns of susceptibility variable and largely dependent on vaccination history.
- High coverage with infant MMR should be maintained in all geo units and there should be laboratory confirmation of suspected rubella and CRS cases. In moderate/high susceptibility countries, routine infant immunization coverage should be increased and the role of adolescent selective vaccination programme should be assessed.
- Possible perverse impact of infant immunization programme in low infant immunization coverage countries.
- Beneficial impact of selective vaccination in high susceptibility countries.
- Quantify impact with mathematical models (predict the effect of different immunization strategies on incidence of CRS).

13. Modelling of rubella immunization in western Europe

Dr Edmunds reiterated the potential dangers of rubella immunization, namely:
- Mass vaccination could potentially lead to an increase in the incidence of CRS.
- Even if vaccination leads to a decrease in CRS it might be much smaller than would be expected.
- Could influence the distribution of health (disease) in the population.

He then went on to describe a recent study to investigate the impact of rubella vaccination programmes in countries covered by the European Seroepidemiology Network (which covered eight countries in western Europe). As part of ESEN a large amount of data were collected and collated on past immunization programmes and past serological and routine surveillance data as well as a current large serological profile covering all ages (the results of which were all statistically standardized to those of a reference laboratory). This large data set provided a unique opportunity to test and validate the behaviour of the model in a wide variety of scenarios.
Furthermore, one of the outcomes of the collection of historical data was the observation that the epidemiology of rubella appears to have differed significantly among different parts of Europe.

The model was able to capture pre- and post-vaccination patterns of infection and prevalence of serological markers under a wide variety of scenarios, suggesting that the model structure and parameter estimates were appropriate. Analytical and numerical results suggest that endemic circulation of rubella is unlikely in Finland, the United Kingdom, the Netherlands, and perhaps Denmark, provided vaccine coverage is uniform across geographical and social groups. In Italy and Germany vaccine coverage in infancy has not been sufficient to interrupt rubella transmission, and continued epidemics of CRS seem probable. It seems unlikely that the immunization programmes in these countries are doing more harm than good, but this may be partly as a result of selective immunization of schoolgirls. Indeed, in both these countries, selective vaccination of schoolgirls with inadequate vaccination histories is likely to be an important mechanism by which CRS incidence is suppressed (unlike the other countries, which have had sufficiently high infant coverage rates to withdraw this option). Reducing inequalities in the uptake of rubella vaccine should be an important aspect of rubella control.

Dr Edmunds then went on to illustrate, using recently published data from Greece, that poorly designed infant-only rubella immunization programmes can result in more cases of CRS than would have occurred in the absence of immunization. That is, that the risk of causing more harm than good is not just a theoretical one.

In the subsequent discussion, the following issues were touched upon.

- It was confirmed that coverage rates were modelled by the results of the serological survey of measles, mumps and rubella.
- The French data shows a short- to medium-term risk of CRS epidemic. The same in Denmark. In Denmark abortions due to rubella infections are registered. They have tried to reach young women with vaccinations, but find it difficult to achieve a high coverage rate.
- WHO cautious to come up with standard recommendation on rubella due to the danger of shifting the age group. This might be a problem in PAHO as many of these countries only do one dose of MMR.
- Hard to come up with a standard recommendation. Unless 90% coverage of infant immunization, it is very dangerous to implement rubella immunization in the childhood vaccination programme.
- Case definition of rubella would be quite easy if linked to the measles surveillance. First you test for measles. If negative, you test for rubella. This is done in PAHO, Southern Africa and other places.
- Adding rubella to measles campaigns should be considered.

14. Summary of findings from group work

During the afternoon of the first day, participants were divided into three working groups and asked to look at specific issues relating to estimating the costs of measles vaccination and measles associated illnesses in western European countries. Members of the three working groups are given in Annex 3. Findings of the group work are summarized below.
**Group 1: Estimating the incidence and costs of measles vaccine associated adverse events**

Group 1 concluded that to their knowledge there is not any more published data on measles associated adverse events than the articles included in the meeting folder. In the article by Dr Mark Miller et al. cost per adverse events per first dose of the MMR vaccine is estimated at about US $2.20 (1997 value).

The group felt that serious adverse events are extremely rare and costs of these events are therefore relatively small compared to the overall gains of eradicating measles. Due to the rarity of the events, it is likely to be problematic for countries to contribute with readily available cost data. It is likely that cost for treatment of the specific events must be discussed with clinicians from a number of countries. Furthermore, it will be difficult to define what adverse events are caused by the measles part of the vaccine and what is related to the mumps and rubella part. An expert panel of paediatricians should be gathered to decide on this.

The group had prepared the below questionnaire for each country included in the study to fill out. It was recommended that data should be collected from the last three years. However, the group felt that many countries are not likely to have a structured system for monitoring adverse events, and it will therefore be difficult for them to fill out the questionnaire. It was therefore recommended that information on to what extent countries have systems in place should be collected in advance and only countries with a system should be asked to fill out a detailed questionnaire. However, at the same time it is important to be representative and get data from all economic strata and health systems. Four different groups of countries should be sufficient.

It was recommended that the questionnaire is sent to EPI managers and it would be their responsibility to distribute it to relevant people. When the questionnaire is filled out, sources must always be noted down so that it is known whether the figure is an estimate or based on real data.

It should be investigated whether any of this data has already been collected from EUVAX project. Furthermore, it is important to coordinate with a future three-year project for adverse events that Dr Patrick Olin is involved in together with Dr Philippe Duclos from WHO. The project will start in January 2001. Countries and partners included in this project are Finland, Netherlands, United Kingdom, Switzerland, Sweden, EUVAC, CDC and WHO. The aim of the project is to develop a standard case definition for adverse events, thereby getting better estimates of incidence rates of adverse events. A field study will be carried out to compare active and passive surveillance for adverse events. Questionnaires will be given to parents asking to report adverse events within a given timeframe. The project will compare adverse events of old versus new vaccines and from different manufactures.
Table A1. Questionnaire for costs of adverse events

All countries should be asked the following questions:

1. Is there a national system for adverse events in place?
2. Who reports to the system?
3. How long has the system been in place?
4. What year was a measles component holding vaccine introduced?
5. What year was a second dose introduced?
6. What is the age of your first and second dose measles vaccine usage?
7. Is it a common practice to use antipyretics when fever occurs after immunization?
8. Is it a common practice to use antibiotic when unknown febrile episodes occur after immunization?
9. It is a common practice to use acyclovir in hospitalized cases with neurological symptoms after vaccination?

<table>
<thead>
<tr>
<th></th>
<th>Ambulatory</th>
<th>Hospitalized</th>
<th>Average stay</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Febrile seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afebrile seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
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<tr>
<td>Acute encephalitis/pathy</td>
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<tr>
<td>Sequeleae encephalitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other neurologic reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trombocytopenic purpura</td>
<td></td>
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<td></td>
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<tr>
<td>Anaphylaxis</td>
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<tr>
<td>Syncope</td>
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<td></td>
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<tr>
<td>Orchitis</td>
<td></td>
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<td></td>
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<tr>
<td>Paratiditis</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Benign meningitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Group 2: Estimating measles associated complication rates in developed countries and costs of measles cases

Group 2 identified the following data needed to be collected for estimating the total costs of measles cases for western European countries:

- complication rates
- hospitalization rates
- outpatient consultation rates
- costs per inpatient stay
- costs per outpatient consultation
- costs of prescription drugs.

Not much data from Europe will be readily available and it is often problematic to use data from the United States. However, it should be justified to use US data on complication rates for European countries (i.e. the percentage of complications related to pneumonia, otitis, etc.).

It is likely that data on age-specific hospitalization and complication rates will be available from the 1999 outbreak in Holland. The Dutch data is currently being analysed. It should also be investigated whether there is data from the outbreak in Dublin, Ireland during the end of 1999 where 1200 cases were identified.

Finland has a considerable amount of data from the pre-vaccination era and this should be analysed. It should also be investigated whether there is data on hospitalization rates from the pre-vaccination era in Denmark and Iceland where the vaccine was introduced relatively late (1988 in Denmark). Other countries that might have data on hospitalization rates are Italy, the NIS countries and Germany.
It might be possible to collect data on average costs per inpatient stay and outpatient consultations from a study currently being completed by the Maastricht University on cost savings from introducing pneumococcal vaccine for the elderly. Data on costs of inpatient stay and outpatient visits from Belgium, France, Germany, Holland, Italy, Spain, Sweden and the United Kingdom are being collected for this study. However, it must be assessed whether this data can be used for paediatric services too.

The group recommended that a questionnaire should be send to all countries asking about the following data:

1. past immunization coverage proportion for 1st and 2nd dose in all years since vaccination;
2. length of inpatient stay in general ward (number of days) for pneumonia, otitis, encephalitis and diarrhoea;
3. length of inpatient stay in ICU (number of days) for pneumonia, encephalitis and diarrhoea;
4. number of outpatient consultations for the same diseases;
5. prescription drugs for these disease;
6. average costs per inpatient stay on general paediatric ward;
7. average costs per inpatient stay in paediatric ICU;
8. average costs per outpatient visit?
9. (standard treatment procedures for pneumonia, otitis, encephalitis, diarrhoea);
10. costs per first and second line antibiotic treatment;
11. average salary of women aged 20–40 years old;
12. find the health specific price index to adjust for the combination of data from different periods of time.

For countries that have achieved elimination:

1. Do you do laboratory confirmation of measles cases? If so, what is the laboratory confirmed incidence? (if no, inflated data).

**Group 3: Estimating future vaccination schedules – strategies to reach elimination**

The group used the WHO grouping of countries to describe the current vaccination strategies. Group 1, which is mainly western Europe, have 2 dose MMR programmes. Group 2 and 3, the NIS countries and southern Europe, have 1 dose measles, 1 dose MMR or 2 dose MMR programmes.

To estimate the costs before and after elimination, the group mentioned the following factors to be considered:

- vaccine coverage level
- vaccine strategy
- surveillance/monitoring
- confidence in vaccine programme.
The following table describes how the three WHO country groups could reach elimination.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expand coverage</td>
<td>X</td>
<td>• 1st dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Health education</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Incentives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surveillance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Change schedule</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2nd dose: M/MR or MMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Change age of 1st dose</td>
</tr>
<tr>
<td>Sustain coverage with 2 doses</td>
<td></td>
<td>• Advocacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Health education</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surveillance</td>
</tr>
<tr>
<td>Campaign</td>
<td>X</td>
<td>• Catch-up:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M/MR/MMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-school/school</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Follow-up:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Every 3 to 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M/MR/MMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second dose MMR (5-12)</td>
</tr>
<tr>
<td>After sustainability</td>
<td>2 dose MMR or 1 dose M/MR/MMR (18m)</td>
<td></td>
</tr>
</tbody>
</table>

The group identified the following knowledge sources and gaps:

1. Expanding routine coverage: limited information in some countries (Germany)
2. Sustaining coverage:
   - health education (mass media)
   - campaigns (England and Wales 1994, France, use of other diseases as surrogate)
   - established systems (Germany).
3. Parents’ attitudes (United Kingdom HEA).
4. Incentive schemes (GP incentive scheme United Kingdom, Swedish system (tracking system for defaulters)).
5. Monitoring/surveillance
   - coverage:
     - cluster (Finland) versus administrative methods
     - local/central systems
   - disease surveillance programme:
     - United Kingdom (established), Germany (sentinel)
     - national reporting, lab confirmation, genotyping
   - supranational surveillance (WHO/EU)
     - EUVAC, EUVAX, serosurveillance
     - provide contact persons for questionnaire.
6. Campaign costs:
   - type of strategy
   - age group
   - type of vaccine
   - frequency of follow-up
– United Kingdom (established infrastructure)
– Romania/Albania (lack of infrastructure)
– use of other campaigns (e.g. men C).

7. Vaccine price – does it vary?
   – purchase mechanism (central/OTC)
   – type, number of doses
   – cost per dose
   – United Kingdom/Sweden central purchase
   – Germany individual
   – approach vaccine manufacturers.

8. Consultation costs:
   – United Kingdom/Germany/Sweden.

9. Material costs (syringes, etc):
   – type of equipment
   – purchase mechanism
   – disposal – system/cost
   – Sweden (central bulk distribution)
   – Germany (private insurance, individual purchase).

10. Indirect costs:
    – lost time for parents.
Annex 1

AGENDA

Monday, 23 October 2000

Session 1  
08.30–09.00  Registration
09.00–09.45  Opening – Dr Bernardus Ganter
Adoption of agenda and programme
Briefing on background, purpose and expected outcome
09.45–10.00  Economics of elimination – Dr John Edmunds
10.00–10.30  Coffee break

Session 2  
10.30–10.45  Discussion
10.45–10.55  Estimating the benefits of measles elimination to Europe – areas of research
Dr John Edmunds
10.55–11.25  Estimating the benefits of measles elimination to Europe – what is known
Dr Hélène Carabin
11.25–11.40  Discussion
11.40–12.00  Working group explanation
12.00–13.30  Lunch break
13.30–17.30  Workshops (coffee break 15.30–16.00)

Tuesday, 24 October 2000

Session 3  
09.20–09.40  Towards measles elimination in western Europe
Dr Richard Pebody
09.40–10.00  Are the criteria for measles elimination adequate for all of Europe
Dr Joël Mossong
10.00–10.20  Towards measles elimination in Eastern/Central Europe/NIS
Dr Piotr Kramarz
10.20–10.50  Coffee break
Session 4  Summary of findings from workshops
10.50–11.20  Group 1: Incidence of adverse events and discussion
11.20–11.50  Group 2: Incidence of complications and discussion
11.50–12.20  Group 3: Future vaccination schedules and discussion
12.20–12.30  Discussion
12.30–13.30  Lunch break
13.30–13.50  Towards measles elimination in other regions
Dr A. Henao-Restrepo
13.50–14.00  Discussion

Session 5  Rubella control
14.00–14.10  Overview of rubella control in Europe
Dr Massimo Ciotti
14.10–14.30  Seroepidemiology of rubella in western Europe
Dr Richard Pebody
14.30–14.50  Modelling of rubella immunization in western Europe
Dr John Edmunds
14.50–15.00  Discussion
15.00–15.30  Comments from the participants
Closing
Annex 2

PARTICIPANTS

Temporary Advisers

Dr Andre Ament
Associate Professor, Maastricht University
Health Organisation, Policy and Economics
P.O. Box 616
6200MD Maastricht
Netherlands

Dr Philippe Beutels (Chairperson)
Research Assistant
University of Antwerp (UIA)
Epidemiology and Community Medicine
WHO Collaborating Centre for the
Prevention and Control of Viral Hepatitis
Universiteitsplein 1
2610 Antwerp
Belgium

Dr Hélène Carabin
Wellcome Trust Centre for the
Epidemiology of Infectious Disease
University of Oxford
South Parks Road, Oxford
OX1 3 FY
United Kingdom

Dr Jitka Castkova
National Institute of Public Health
Srobarova 48
100 42 Prague
Czech Republic

Dr John Edmunds
Immunisation Division
PHLS Communicable Disease Surveillance Centre
61 Colindale Avenue
London, NW9 5EQ
United Kingdom

Dr Tuija Leino
Department of Vaccines
National Public Health Institute
Mannerheimintie 166
FIN-00300 Helsinki
Finland

Dr Joël Mossong
CRESIS, CRP-Santé
18 rue Dicks
L-1147 Luxembourg

Tel.: +31 43 38 81 723
Fax: +31 43 36 70 960
E-mail: a.ament@beoz.unimaas.nl

Tel.: +32 3 820 25 23
Fax: +32 3 820 26 40
E-mail: pbeutels@uia.ua.ac.be

Tel.: +44 1865 281880
Mobile: +44 07930 417231
Fax: +44 1865 281245
E-mail: helene.carabin@ceid.ox.ac.uk

Tel.: +420 2 67 08 24 86
Fax: +420 2 72 74 14 33
E-mail: jkyncl@szu.cz

Tel.: +44 (0) 20 8200 6868, ext. 4410
Fax: +44 (0) 20 8200 7868
E-mail: jedmunds@phls.nhs.uk

Tel.: +358 9 4744 8787
Fax: +358 9 4744 8675
E-mail: tuija.leino@ktl.fi

Tel.: +352 45 3213
Fax: +352 45 3219
E-mail: joel.mossong@crp-sante.lu
Dr Patrick Olin
EPI Programme Manager
Department of Vaccine Research
Swedish Institute for Infectious Disease Control
Nobelvagen 18
SE-171 82 Solna
Sweden
Tel.: +46 8 457 2533
Fax: +46 8 303 960
E-mail: patrick.olin@smi.ki.se

Dr Richard Pebody
Immunisation Division
Communicable Disease Surveillance Centre
61 Colindale Avenue
London NW9 5EQ
United Kingdom
Tel.: +44 208 200 6868 ext. 4563
Mobile: +44 40 348 2165
Fax: +44 208 200 7868
E-mail: rpebody@phls.org.uk

Dr Anne Marie Plesner
Senior Medical Officer
National Board of Health
Postboks 2020
Amaliegade 13
DK-1012 Copenhagen K
Denmark
Tel.: +45 3391 16 10, ext. 6003
Fax: +45 33 93 42 98
E-mail: apl@sst.dk

Dr Anette Siedler
Department of Epidemiology and Health Reporting
Robert Koch Institute
General Pape Str. 62 - 66
D-12101 Berlin
Dr Susan van den Hof
Department for Infectious Diseases
Epidemiology, PB 75
National Institute for Public Health and the Environment
NL-3720 BA Bilthoven
Netherlands
Tel.: +49 30 4547 3452
Fax: +49 30 4547 3514
E-mail: siedlera@rki.de
Tel.: +31 30 274 3685
Fax: +31 30 274 4409
E-mail: susan.van.den.hof@rivm.nl

World Health Organization

Regional Office for Europe

Dr Massimo Ciotti
Medical Officer
Communicable Diseases Surveillance and Response
Tel.: +45 39 17 14 49
Fax: +45 39 17 18 51
E-mail: mci@who.dk

Dr Sergei Deshevoi (Observer)
Medical Officer
WHO Project Office in Almaty
M. Makataev St. 13
Almaty
Kazakhstan
Tel/fax: +7 3272 301451
E-mail sed@online.ru

Dr Bernardus Ganter
Regional Adviser
Communicable Diseases
Tel.: +45 39 17 13 98
Fax: +45 39 17 18 51
E-mail: bga@who.dk
Dr Piotr Kramarz *(Observer)*  
Short-term Professional  
Communicable Diseases Control, Prevention and Eradication  
Tel.: +48 39 17 16 06  
Fax: +48 39 17 18 51  
E-mail: pkramar@priv4.onet.pl

**Headquarters**

Dr Ana Maria Henao-Restrepo  
Expanded Programme on Immunization  
Department of Vaccines & Other Biologicals  
Tel.: +41 22 791 3402  
Fax: +41 22 791 4192  
E-mail: henaorestrepo@who.ch

World Health Organization  
20, Avenue Appia  
1211 Geneva  
Switzerland

Ms Ulla Kou *(Rappoteur)*  
Associate Professional Officer  
Department of Vaccines & Other Biologicals  
Tel.: +41 22 791 42 89  
Fax: +41 22 791 42 10  
E-mail: kouu@who.int

World Health Organization  
20, Avenue Appia  
1211 Geneva  
Switzerland
Annex 3

WORKING GROUPS

Group 1
Dr Andre Ament
Dr Philippe Beutels
Dr Hélène Carabin
Dr Jitka Castkova
Dr Bernardus Ganter

Group 2
Dr Sergei Deshevoi
Dr John Edmunds
Ms Ulla Kou
Dr Piotr Kramarz
Dr Tuija Leino
Dr Joël Mossong
Dr Susan van den Hof

Group 3
Dr Massimo Ciotti
Dr Ana Maria Henao-Restrepo
Dr Patrick Olin
Dr Richard Pebody
Dr Anne Marie Plesner
Dr Anette Siedler