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APPROACHING MEASLES AND RUBELLA ELIMINATION IN THE EUROPEAN REGION – NEED TO SUSTAIN THE GAINS

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While there is considerable focus in the World Health Organization (WHO) European Region on the introduction of new vaccines and promotion of underutilized vaccines, there are increasing challenges in sustaining the gains made with existing vaccines, where the estimated vaccine coverage rate for measles is 94% in the Region [1]. Analyses reveal that most children are not immunised on time according to national immunisation schedules and that there are pockets of low immunisation coverage at regional or local levels in the countries. These two factors set the stage for outbreaks of vaccine-preventable diseases, such as were seen with measles in the western part of the European Region [2].

In 2002, the WHO Regional Committee for Europe adopted a resolution to eliminate indigenous measles and rubella in the 53 Member States in the Region by 2010. Elimination is defined as a situation in which sustained virus transmission cannot occur and secondary spread from importation of disease will end naturally without intervention. Key strategies to achieve this goal are: achieving and sustaining high coverage ($\geq 95\%$) with two doses of measles and at least one dose of rubella vaccine through high-quality routine immunisation services; providing a second opportunity for measles immunisation through supplemental immunisation activities (SIA) in susceptible populations; using the opportunity provided by measles SIA to target populations susceptible to rubella with combined measles and rubella-containing vaccine; and strengthening measles, rubella, and congenital rubella syndrome (CRS) surveillance through rigorous case investigation and laboratory confirmation of all suspected cases [3]. The regional strategy encourages rubella vaccination opportunities, including supplementary immunisation activities, for all rubella-susceptible children, adolescents and women of child-bearing age. All national SIA conducted in the eastern part of the WHO European Region have included rubella vaccine. In addition, rubella vaccination is part of the routine immunisation schedule all member states.

Since 1998, measles incidence in the WHO European Region has declined from 110 cases per 1,000,000 population to historically low levels of ≤ 10 cases per 1,000,000 in 2007 and 2008. In 2008, 29 member states reported a measles incidence of less than one per 1,000,000 population, selected as one of the indicators for monitoring progress towards elimination. This progress is based on high immunisation coverage achieved through a routine two-dose schedule for measles-containing vaccine and SIA to reach susceptible populations. The estimated regional coverage for the first dose of measles vaccine increased from 88% in 1998

to 94% in 2008. Moreover, reported coverage for the second dose ranged from 62% to 99% in 2008. From 2000 to 2008, at least 17 countries conducted nationwide SIA, reaching approximately 54 million people. Surveillance has been strengthened by improving case investigation procedures, expanding case-based reporting and increasing laboratory testing.

In this issue of *Eurosurveillance*, articles by Richard *et al.* and Marinova *et al.* show that outbreaks in the Region are occurring primarily among children aged five to 14 years who have not been immunised or who have received only one dose of measles vaccine [4,5].

While measles incidence in the Region has declined to low levels, there has been a resurgence of measles cases in western European countries owing to suboptimal coverage of measles vaccine leading to pockets of susceptible people (Figure 1). In 2008, 92% of reported measles cases ($n = 8,264$) occurred in western European countries, primarily Austria, France, Germany, Italy, Spain, Switzerland and the United Kingdom. The majority of cases were not immunised (82.2%) [6]. This contrasts with the situation from 2004 to 2006, when more measles epidemics occurred in the eastern part of the Region, with six of the newly independent states of the former Soviet Union accounting for 75% of reported cases [6] (Figure 2).

With the decline in the number of measles cases, many national immunisation programmes in the Region are challenged by a combination of beliefs that lead to questioning the value of immunisation and the health threat posed by measles, and result in parents' hesitancy to vaccinate children.

The two articles in this edition of *Eurosurveillance* clearly show that measles can be a serious health threat and lead to complications (40.5% in Bulgaria) and hospitalisation (15% in Switzerland and 69.7% in Bulgaria; important to note that percentage hospitalised can be affected by national policies on treatment). Furthermore, Richards *et al.* report one measles-related death in a previously healthy child. In addition, deaths have been reported from France and the Netherlands in 2009 [10]. Genotyping data from both countries revealed that measles are exported to other countries in the European Region. Immunisation should be seen as a social responsibility in the European Region [11]. As demonstrated in this issue for Switzerland, the ongoing transmission in western Europe has in several cases led to exportation of measles to other WHO regions, including the Region of the Americas, where the disease

was eliminated in 2002 [4,7,9]. The cost to society and health care systems of investigating and controlling measles outbreaks needs to be further analysed. The results should be used for high-level advocacy and to ensure political commitment from governments.

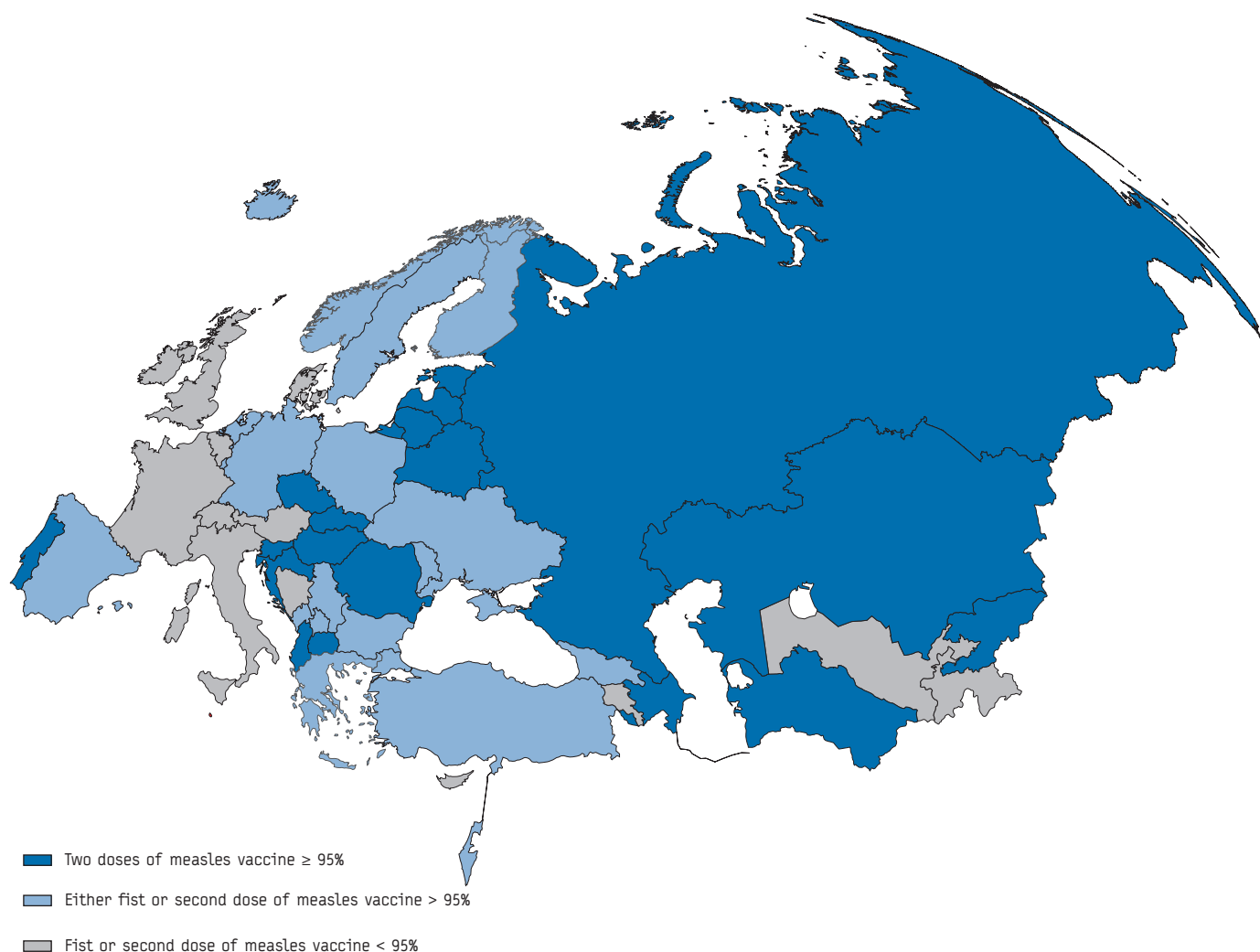
In addition to measles outbreaks, large, sustained mumps outbreaks have been reported in the Region. Stein-Zamir *et al.* report in this issue on a mumps outbreak in religious academies in Jerusalem with a high number of cases in fully vaccinated people [12]. While it is unclear how vaccination coverage was ascertained, the finding that outbreaks occur in individuals who have received two doses of mumps vaccine has been also reported in other countries, especially in universities, the military and other closed settings, such as in Ireland, Luxembourg, the Republic of Moldova, the former Yugoslav Republic of Macedonia and the United Kingdom [13,14,15,16,17,18]. Vaccine failure, waning immunity and programmatic documentation of vaccine histories

have been given as explanations for these outbreaks and further studies are needed to understand and document the causes.

As the WHO European Region approaches measles and rubella elimination, there is a need to better monitor progress. The three agreed criteria for this purpose are disease incidence, quality surveillance and immunity profile. Surveillance needs to be strengthened through advocacy with member states and adoption of the recently revised WHO regional surveillance guidelines, which have been adapted to address lower measles incidence levels and to emphasize the importance of laboratory confirmation, case-based reporting and the use of standardised performance indicators [19]. In October 2009, a group of international experts from all continents met in Geneva to assess the current standardised surveillance performance indicators and the indicators for monitoring progress towards measles elimination. Interruption of indigenous measles transmission for 36 months is considered one of the criteria for

FIGURE 1

Coverage of measles containing vaccine (first and second dose), WHO European Region, 2008



Note: The designations employed and the presentation of this material do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers and boundaries.

Source: World Health Organization Regional Office Europe, 2009

elimination. Follow-up is needed at the global level to finalise the modifications based on the findings from WHO regions.

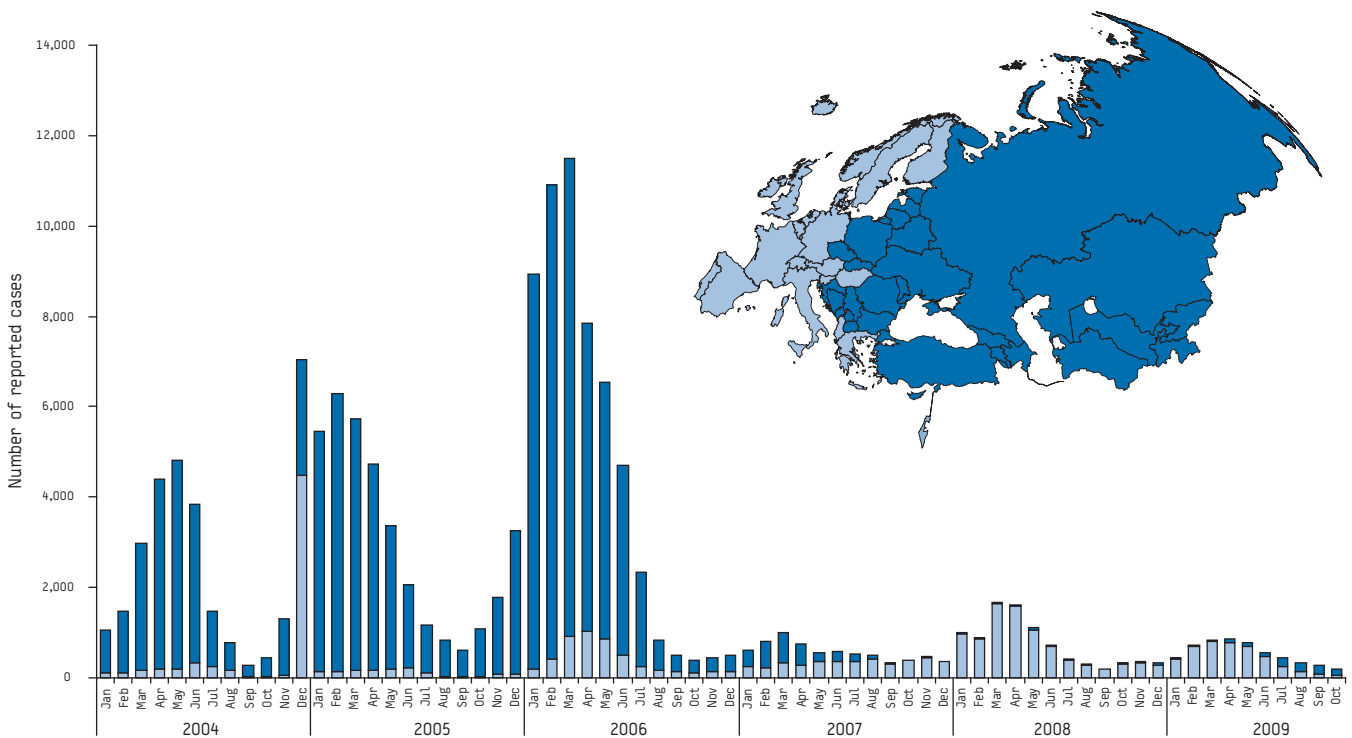
Kelly *et al.* from Australia report that many industrialised countries will not be able to meet the targets for the indicators, especially for the surveillance indicators. The annual process of certification of the European Region's polio-free status shows that many countries do not meet the targets for the surveillance performance indicators and not all countries conduct acute flaccid paralysis (AFP) surveillance. The national and regional certification commissions have therefore validated countries' documentation of polio-free status using other indicators related to their health systems, including the ability of the country to detect a wild poliovirus. For verifying measles and rubella elimination in member states, it is expected that once national and regional commissions for verifying elimination are formed, they will evaluate the available evidence with regard to the quality of the surveillance system of a country, with the indicators of incidence and immunity in order to verify if a country has eliminated measles and rubella. Similar criteria will also be used to document and verify elimination of rubella. As described by Aytac *et al.* [20], serosurveys are useful in determining rates of seropositivity but interpretation and generalisability of results should be carefully evaluated prior to developing immunisation policy in a country.

With 2010, the deadline for measles and rubella elimination, approaching, the WHO European Region faces serious threats to sustain the gains made and to reach the goal. The ongoing monitoring of performance measure indicators, disease incidence

and coverage should be continued to guide the programme and verify that elimination has been achieved. To achieve elimination, enabling factors, including resources and societal support, will need to be strengthened while barriers to immunisation need to be removed. To this effect, high-level political and societal commitments are required to increase and sustain high level coverage (> 95%) with two doses of measles vaccine in children. Improving immunisation coverage to $\geq 95\%$ must be of primary importance to prevent transmission especially among hard-to-reach populations, which include cultural or ethnic minority groups, nomadic groups, and populations that are experiencing civil unrest and/or political instability, are geographically isolated or refusing vaccination owing to religious or philosophical beliefs.

The WHO Regional Office for Europe is working with member states to identify and target populations at risk and health care professionals to communicate the need for immunisation, as well as to trace children who have not received two doses of vaccine. The annual European Immunization Week held each April provides an opportunity for member states to tailor their messages actively to communicate the benefits and risks of immunisation and strongly advocate the protection of children with political leaders, health care professionals and the general population [7].

FIGURE 2
Reported measles cases, WHO European Region, 2004–2009



Source: World Health Organization Regional Office Europe, 2009

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QUANTIFYING THE RISK OF PANDEMIC INFLUENZA IN PREGNANCY AND INDIGENOUS PEOPLE IN AUSTRALIA IN 2009

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An increased relative risk of infection with the 2009 pandemic H1N1 influenza virus associated with pregnancy and Indigenous status has been a common finding in many countries. Using publicly available data from May to October 2009 in Australia, we estimated the relative risk of hospitalisation, admission to intensive care unit and death as 5.2, 6.5 and 1.4 respectively for pregnant women, and as 6.6, 6.2 and 5.2, respectively for Indigenous Australians. Pregnancy and Indigenous status were associated with severe influenza. More complete analyses of risks in these groups are required to understand and prevent influenza morbidity and mortality.

Introduction

The 2009 H1N1 influenza pandemic in Australia corresponded with the expected influenza season, although pandemic virus circulation began relatively early. In the populous states of New South Wales and Victoria, pandemic influenza virus circulated for about 10-13 weeks [1,2]. The death rate due to pandemic H1N1 influenza was reported as approximately 9 per million for Australia, in the middle of the range of 5-15 per million that was reported for other populous countries in the southern hemisphere [3]. Groups most at risk in the pandemic were recognised to be Indigenous people, pregnant women, the morbidly obese and people with recognised comorbidities [4]. Before the end of the 2009 pandemic in Australia, we used publicly available data to estimate the increased risk of hospitalisation for pregnant women as 3.2 (95% confidence interval (CI): 2.6 to 4.1) [5]. We now use the same data sources to provide estimates of the relative risk of hospitalisation, intensive care unit (ICU) admission and death for pregnant and Indigenous Australians throughout the entire pandemic period.

Methods

We obtained population data from the Australian Bureau of Statistics [6]. Data extracted included estimated total population in 2009, population by sex and age group, estimated number of live births and proportion of the Australian population identifying themselves as Aboriginal or Torres Strait Islanders (Indigenous Australians). We obtained data on the hospitalisations, ICU admissions and deaths in pregnant women and Indigenous

Australians due to pandemic H1N1 influenza from reports published by the Australian Department of Health and Ageing [7].

We estimated the cumulative incidence of all outcomes for the entire pandemic period, from May to October 2009. To estimate the relative risk (RR) for the two nominated risk groups, we compared the cumulative incidence of each outcome in the risk group with the same outcome in the entire population minus the estimated population in the risk group. Confidence intervals for RR were calculated using the method outlined in Bland and Altman [8]. We estimated the number of at-risk pregnant women as previously described by using the fertility and abortion rates in women aged 15-44 years [5] and compared this number with the estimated number of live births in 2009. We used the estimate of the proportion of Indigenous Australians in 2009 from the projected Australian census data.

Results

Our previous estimate of at-risk pregnant women in Australia was 237,215 and equivalent to about 1.1% of the Australian population [5]. The minimum prevalence of pregnancy should be 40 weeks divided by 52 weeks multiplied by 296,600, which is the estimated number of live births for 2008 [9] and the estimate we used for the number of live births in 2009. The fraction of live births represents the expected duration of pregnancy and leads to a minimum estimate of the number of pregnant women in Australia which was 228,154. The proportion of the Australian population who identify themselves as Aboriginal or Torres Strait Islanders is estimated as 2.5%, i.e. 534,350 Indigenous Australians [10]. This estimate attempts to correct for under counting in census data and we could find no more exact estimate of the number of Indigenous Australians.

More than 4,800 hospitalisations, 650 admissions to ICU and almost 200 deaths due to pandemic H1N1 influenza were reported in Australia between May and October 2009. Estimations of the RR of hospitalisation, ICU admission and death for pregnant and Indigenous Australians ranged between 5.2 and 6.6, with the exception of the RR for death in pregnant women, which was only 1.4 (95% CI: 0.3 to 4.3). This imprecise estimate was based on only three deaths (see Table). We also calculated the RR of

hospitalisation in pregnant women compared with not pregnant women of reproductive age (15-44 years). Of an estimated 4,492,701 women of reproductive age, 1,030 were hospitalised. This gave an RR of 5.1 (95% CI: 4.5 to 5.8), similar to the comparison with the general population.

Our estimate of pregnant women at risk was 3.8% higher than the minimum number of pregnant women estimated from the number of live births. Using the minimum estimate of pregnancy did not change RR estimates for pregnancy to any appreciable degree (data not shown).

Discussion

Before the end of the 2009 pandemic in Australia, we had estimated the RR for hospitalisation of pregnant women due to pandemic H1N1 influenza as approximately 3.2 [5], comparable to an early estimate from the United States of 4.3 [11]. At the end of the 2009 pandemic in Australia, this risk appeared to be higher, of the order of 5.2. We had not previously estimated the increased risks associated with Indigenous status. These risks appear to be at least as high as the risk associated with pregnancy, with a much higher risk for death in Indigenous Australians (RR=5.2) compared with pregnant women (RR=1.4).

Limitations of these results include the potential underascertainment of cases, but this is more likely for those perceived not at increased risk (the denominator) than those at increased risk, pregnant and Indigenous Australians (the numerator). For the entire pandemic period, efforts were concentrated in identifying pandemic H1N1 influenza in vulnerable population groups, and testing was also prioritised for hospitalised patients. Increased ascertainment of the group perceived not to be at risk would result in lower estimates of RR than we have reported. We therefore think it is unlikely that our estimates of RR for any of the outcomes are spuriously low. A further limitation of the reported RR estimates results from necessarily imprecise estimates of the at-risk populations. Moreover, with access only to data in the public domain, we could

not report age-stratified or age-adjusted rates or adjust for the presence of co-morbidities. A more thorough analysis of risk is warranted, with risk during pregnancy stratified by gestational age.

In a 2008 review of influenza vaccination in pregnancy, Mak and colleagues concluded that during severe influenza seasons and the pandemics of 1918-19 and 1957-58, pregnant women were at increased risk of influenza-related hospital admission compared with not pregnant women or women post-partum [12]. They also noted that the risk rose with increasing gestation and the presence of co-morbidities. A study from Tennessee between 1974 and 1993 found the excess rates of hospitalisation of pregnant women for an acute cardio-respiratory illness in the second trimester to be 6.3 and in the third trimester 10.8 per 10,000 healthy woman-months. Much lower estimates of excess hospitalisation rates, in the range of 0.4-2.0 per 10,000 healthy woman-months, were reported for influenza-attributable hospital admissions 1990-2002 in Nova Scotia [12]. Reflecting the non-systematic approach to risk quantification in the influenza literature, none of the reported risks were due to laboratory-confirmed disease. In a more recent systematic review of influenza immunisation in pregnancy, Skowronski and De Serres confirmed that studies using laboratory-confirmed outcomes are scarce [13]. This lack of quality data continues to frustrate our understanding of the burden of influenza and prevents direct comparison with the data presented here [5].

Point estimates for RR, defined as the incidence rate ratio, of up to 3.8 for hospital admission coded as influenza in Aboriginal children in Western Australia between 1996-2005 have recently been made (personal communication, Hannah Moore, Telethon Institute for Child Health Research, Perth, Western Australia). This outcome is more specific than the outcomes studied in pregnant women but again is not strictly comparable to the data presented here.

While it is generally accepted that both pregnancy and Indigenous status increase the risk of adverse outcomes due to

TABLE

Estimated relative risk of the cumulative incidence of hospitalisation, admission to an intensive care unit or death from pandemic H1N1 influenza in pregnant and Indigenous Australians, May-October 2009

Outcome	Number	Population at risk	Rate/100,000	Relative risk	95% confidence interval	Comparator
Hospitalisation, all	4,833	21,373,998	22.6	n.a.	n.a.	Comparison of at-risk population derived from total population
ICU admission, all	650	21,373,998	3.0			
Death, all	186	21,373,998	0.9			
Hospitalisation, pregnant women	278	237,215	117.2	5.2	4.6 to 5.8	Pregnant women versus all non-pregnant
ICU admission, pregnant women	47	237,215	19.8	6.5	4.8 to 8.8	
Death, pregnant women	3	237,215	1.3	1.4	0.4 to 4.5	
Hospitalisation, Indigenous status	803	534,350	150.3	6.6	6.2 to 7.2	Indigenous versus non-Indigenous
ICU admission, Indigenous status	100	534,350	18.7	6.2	5.0 to 7.6	
Death, Indigenous status	24	534,350	4.5	5.2	3.4 to 7.9	

ICU: intensive care unit; n.a.: not applicable

laboratory-confirmed influenza, quantification of these risks is surprisingly scarce. We have provided estimates of RR from data available in the public domain from the Australian pandemic of 2009, but acknowledge the need for more complete analyses.

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AN UPDATE ON AN ONGOING MEASLES OUTBREAK IN BULGARIA, APRIL-NOVEMBER 2009

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Earlier this year, an outbreak of measles was detected in Bulgaria, following an eight-year period without indigenous measles transmission, and continues to spread in the country. By the end of 48 week of 2009 (first week of November), 957 measles cases had been recorded. Most cases are identified among the Roma community living in the north-eastern part of the country. Measles has affected infants, children and young adults. The vaccination campaign that started earlier in the year in the affected administrative regions continues, targeting all individuals from 13 months to 30 years of age who have not received the complete two-dose regimen of the combined measles-mumps-rubella (MMR) vaccination.

Introduction

This is an update of an article published in July 2009 that reported an outbreak of measles in Bulgaria. The outbreak was first clearly noticeable in April 2009 and had involved 79 cases by mid-June [1]. Since then, the outbreak has intensified and continues to spread throughout the country. It occurred eight years after the last indigenous cases of measles in Bulgaria were reported in 2001 [2].

Measles has been a statutorily notifiable disease in Bulgaria since 1921, obliging medical practitioners and microbiologists to immediately report suspected measles cases to the Regional Inspectorate for Protection and Control of Public Health (RIPCPh). Notifications of measles cases are collected and analysed centrally at the National Centre of Infectious and Parasitic Diseases in Sofia. In 2005, the Council of Ministries of the Republic of Bulgaria approved the Bulgarian national programme for the elimination of measles and congenital rubella infection (2005-2010) [3]. National case-based notification was initiated in 2004 and the European Union (EU) case definition and case classification have been adopted since 2005 [4,5].

In Bulgaria, the measles vaccine is given as the combined measles-mumps-rubella (MMR) vaccine. Since 1993 the first dose has been recommended at the age of 13 months and the second dose at the age of 12 years, but at least one month after the first dose. For 2005-08, the national vaccine coverage was estimated at 95.9-96.2% for the first MMR dose in two year-old children and at 92.4-94.3% [6,7] for the second dose in 12 year-old children.

We aim to report an update on the ongoing measles outbreak in Bulgaria by analysing measles data provided for the first 48 weeks of 2009.

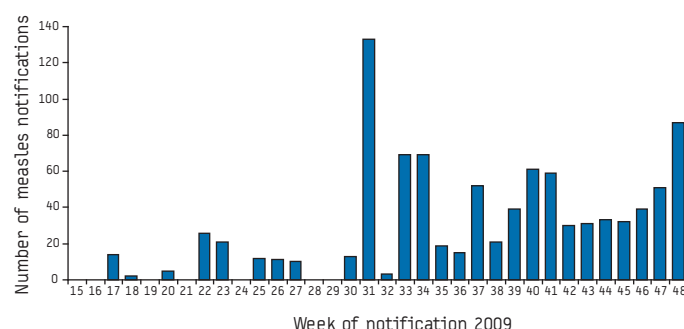
Outbreak description

The outbreak has spread to five more administrative regions since the last report [1], now affecting nine regions (Figure 1). By week 48 of 2009 (week beginning 23 November), there have been 957 notifications of measles, giving a crude incidence of 12.5 per 100,000 inhabitants, with large regional variations. Most cases (97%) were reported from the north-eastern part of the country, i.e. the regions of Dobrich, Silistra, Burgas, Varna, Shumen and Razgrad (Figure 2). Although no data by ethnicity are available, it was clear to the outbreak investigators that at least 90% of cases occurred in the Roma ethnic community. Members of this community usually belong to large families and frequently travel within and across borders. So far, during the current outbreak, several family clusters have been recorded among this group.

Of the total, 429 cases (45%) were laboratory-confirmed by detection of measles IgM antibodies in serum. An epidemiological link to laboratory-confirmed cases was identified in 337 (35%) cases. The remaining 191 cases (20%) were classified as clinical cases only. The World Health Organization (WHO) Regional Reference Laboratory (RRL) for Measles and Rubella in Berlin identified the virus as measles genotype D4. The nucleotide sequence was identical to that detected between January and June 2009 in northern Germany, confirming the epidemiologically link with the index case who had stayed in Hamburg during that period. Apart from the index case all cases acquired measles in the country and are therefore indigenous cases.

FIGURE 1

Notified measles cases by week of notification, Bulgaria, April-November 2009 (n=957)



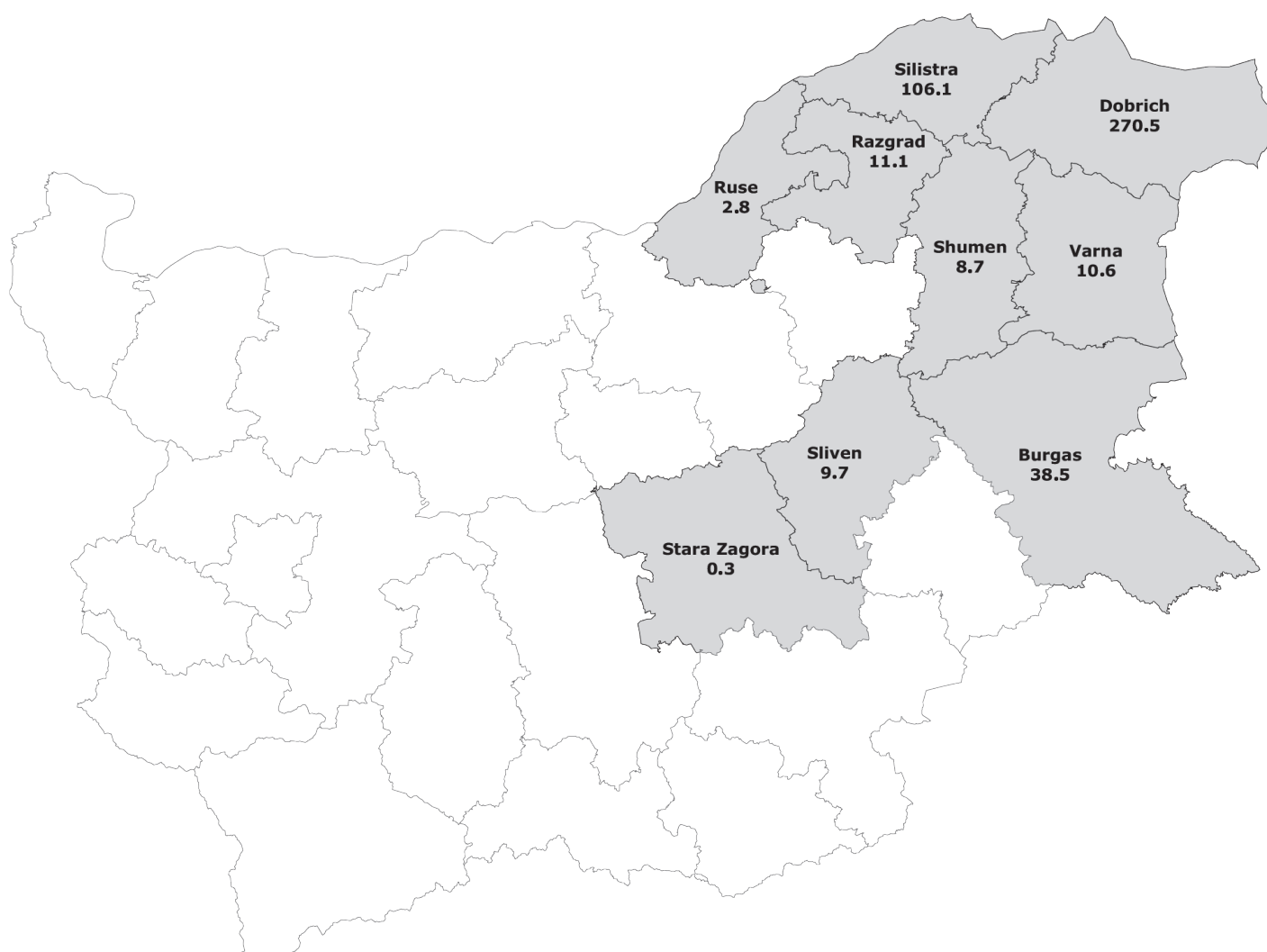
Our analysis on age, vaccination, hospitalisation and complications variables was based on the 748 case-based reports received by week 44 as data on the remaining 209 cases reported in weeks 45-49 are still being processed. The age was known for 730 cases (98%). The median age was 10 years (range: four days to 38 years). The cases were distributed between age-groups with 96 (13%) aged under one year, 149 (20%) aged 1-4 years, 123 (17%) aged 5-9 years, 131 (18%) aged 10-14 years, 137 (19%) aged 15-19 years, 73 (10%) aged 20-29 and 21 (3%) older than 30 years. The status of measles vaccination was known in 482 cases (64%). Overall, 142 were unvaccinated (29%), 248 (52%) had received one dose of measles-containing vaccine and 91 (19%) had received two doses (Figure 3). A total of 522 cases (69.7%) were hospitalised, and 303 cases (40.5%) were reported with measles-related complications including pneumonia (n=95; 31.3%) and abdominal symptoms and diarrhoea (n=35; 11.5%). No cases of acute encephalitis or measles-related deaths were reported.

Control measures

Several control measures continue to be implemented by local health authorities, according to the Bulgarian national programme for the elimination of measles and congenital rubella infection. Activities have been undertaken to increase awareness of the ongoing outbreak among the public in general and healthcare professionals in particular. General practitioners and other medical staff were requested to pay special attention to rash/fever symptoms and to strengthen routine immunisation of children aged 13 months (first dose) and 12 years (second dose) by directly reaching out to the parents and explaining the benefits of vaccination. In addition, a supplementary MMR vaccination campaign that had started earlier in the year in the affected administrative regions continues targeting all individuals from 13 months to 30 years of age who had not received the complete two-dose vaccination regimen. The MMR vaccine is supplied by the Ministry of Health and is offered free of charge through the routine immunisation services (family doctors). Special outreach teams consisting of regional epidemiologists, health inspectors and local Roma community leaders have been deployed in the campaign to immunise the Roma community.

FIGURE 2

Measles incidence per 100,000 population by region, Bulgaria, April-November 2009 (n=957)



Discussion

Despite the high national immunisation coverage with MMR vaccine, this outbreak highlights the presence of pockets of vulnerable individuals, particularly those members of the Roma community that are still susceptible to measles infection. They are only brought to light when the measles virus is imported from abroad. A similar experience was made in Croatia in 2008 [8]. It is generally believed that the vaccination coverage among members of the Roma community in Bulgaria does not differ from that of the rest of the population, since all citizens are well integrated into the primary healthcare system that provides easily accessible and free immunisation services. However, travelling members of the Roma community may be overlooked, if they delay or even fail to use the immunisation services. There is therefore a need for innovative ways to improve vaccination coverage in such groups that are hard to reach by standard immunisation programmes. In doing so, the herd immunity would be maintained at a high level conducive to measles elimination in Bulgaria.

The age distribution changed towards increasing numbers of older children, adolescents and young adults compared with what we noticed during first 10 weeks of the outbreak [1]. This provides more accurate insight into the susceptible age groups. Obtaining an accurate vaccination history presents challenges, but the large proportion (50%) of cases who reported having received one measles vaccine dose is indicative of vaccine failure and raises concerns about the maintenance of the cold-chain. However, a proportion of these cases may have received a vaccine dose offered as part of the outbreak control measures, when they were already infected with the measles virus and in the incubation period. Further data including the date of vaccination of such cases would need to be collected for more in-depth analysis of this hypothesis. The high hospitalisation rate noted is explained by the large number of patients from crowded households and poor living conditions of affected Roma families.

The current measles situation in Bulgaria underlines the need for more urgent preventive and control measures to be taken. To achieve the goal of measles elimination, awareness of the disease as well as a commitment by the public health authorities in Bulgaria

are essential to strengthen vaccination programmes. The WHO's strategic plan for the elimination of measles from the European region stipulates that vaccination programmes should achieve and sustain a minimum of 95% coverage with two doses of vaccine and better target susceptible individuals in the general population and high-risk groups [9].

Acknowledgements

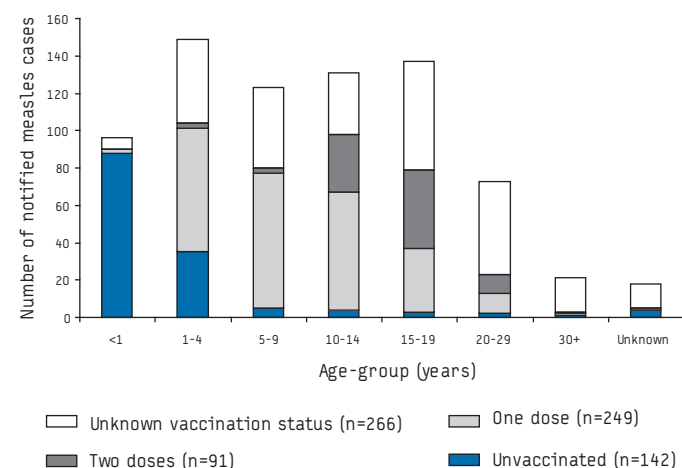
We thank A Mankertz and S Santibanez (Robert Koch Institute, Berlin, Germany) for the prompt investigation and identification of the origin of Bulgarian measles strains. We also thank all colleagues from the Bulgarian regional inspectorates for public health prevention and control in Razgrad, Shumen, Silistra, Dobrich, Burgas, Varna, Sliven, Ruse and Stara Zagora for providing essential epidemiological data. We extend our gratitude to H Bang (Statens Serum Institut, Denmark) for the graphic.

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FIGURE 3

Notified measles cases by vaccination status, Bulgaria, April-October 2009 (n=748)



MUMPS OUTBREAK IN JERUSALEM AFFECTING MAINLY MALE ADOLESCENTS

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From mid-September 2009 to 7 December 2009, 173 cases of mumps have been reported in the Jerusalem District. Most cases (82.1%) were male adolescents (median age 14.5 years) who are students in religious boarding schools. The majority of them (74%) are appropriately vaccinated for their age; 67% had received two doses of mumps-containing vaccine. An epidemiologic connection has been reported with visitors from New York, some of whom had recently had mumps.

Mumps is a notifiable disease in Israel by law. From mid-September 2009 to 7 December 2009, 173 cases of mumps have been reported to the Jerusalem District Health Office. The patients were mainly (147/173; 85%) students in yeshivas (religious academies operated as boarding schools) in several Jerusalem neighbourhoods and two neighbouring cities, and 142 of 173 (82%) were males. The epidemic curve is presented in Figure 1 and shows a pattern compatible with person-to-person transmission. The median age of the patients was 14.5 years and the mean was 14.8±7.3 years. Their age and sex distribution are presented in Figure 2. Altogether, 60 schools have been affected (see Table). The outbreak spread to other regions of the country, and up to 7 December over 250 cases have been reported with similar demographic and epidemiologic characteristics.

The clinical picture included unilateral and bilateral parotitis. One patient (a 19 year-old) was hospitalised in a urology department with orchitis and another three were admitted to ear, nose and throat departments. A further six patients were observed for varying periods in hospital emergency departments and discharged.

Case ascertainment included: positive mumps IgM antibody (in 20 patients) and positive real-time RT-PCR in urine (in four patients). The virus was classified by the central virology laboratory of the Israel ministry of health as genotype G5. The remaining 149 cases were diagnosed on the basis of clinical features together with an epidemiologic association.

Of the 173 patients, 116 (67%) had received two doses of measles-mumps-rubella (MMR) vaccine (Priorix GlaxoSmithKline Biologicals – Jeryl Lynn strain), 29 (16.8%) had received one dose (age-appropriate in 12 of them), 20 (11.6%) were not immunised, and in another eight patients (4.6%) the immunisation status was unknown (see Figure.3).

A number of patients reported contact with yeshiva students from the United States (New York-) who visited Israel during the

High Holidays in mid-September 2009 and some of whom were reported to have recently had mumps.

Outbreak control measures included investigations in the relevant schools to determine the students' vaccination status and referral for completion of MMR vaccination where necessary. Information on the outbreak was circulated to all health maintenance organisations in the District and to the public via the mass media.

Discussion

Mumps is an acute viral infection; a third of infections are subclinical, another 30-40% are expressed clinically as unilateral or bilateral parotitis. Complications occur more frequently in adults than in children; 10-15% of mumps patients develop meningo-encephalitis. Orchitis occurs in 20-50% of post-pubertal men, but sterility is rare. Other complications include pancreatitis, oophoritis, deafness, arthritis, thyroiditis, and myocarditis. Transmission is through droplet infection. Confirmation of mumps infection includes serological testing (for IgM antibodies by various methods), identification of mumps RNA by RT-PCR and viral isolation in cell culture [1].

Mumps vaccination was included in the routine childhood immunisation schedule in Israel in 1984, and since 1994 has been administered in a two-dose schedule at ages 12 months and six years (first grade in school) in the form of the MMR vaccine, and since 2008 as measles-mumps-rubella-varicella (MMRV) vaccine. The average overall immunisation coverage for the first dose of mumps vaccine (MMR/MMRV) in the Jerusalem District has been maintained between 93 and 96.7% over the past decade [Jerusalem District Health Office, unpublished data]. It is to be noted that in 1992, the coverage for the first dose of MMR among the Jewish population of Jerusalem was a mere 82.3%.

Mumps control in Israel improved significantly during the 1990's [2], although periodic outbreaks still occurred due to under-vaccination, primary vaccine failure and waning immunity. In 1998 and 2005, two outbreaks (each of the order of 100 cases) occurred in Israel. In 2006, 12 cases were reported; six were reported in 2007 and 13 in 2008. Serological studies performed in the late 1990s revealed relatively low mumps antibody levels among adolescents and army recruits in Israel, ranging from 59 to 83.3% positivity; such levels do not guarantee adequate herd immunity [3,4].

Mumps outbreaks, mainly involving adolescents and young adults, have emerged recently in several countries. A nationwide

mumps outbreak occurred in the United Kingdom in 2004-2005, with 56,390 reported cases. The majority (79%) were aged 15-24 years; two thirds were unvaccinated. Non-availability of MMR vaccine probably contributed to susceptibility of the birth cohorts 1983-1986 [5].

FIGURE 1

Mumps outbreak in Jerusalem September-December 2009, epidemic curve (n=173)

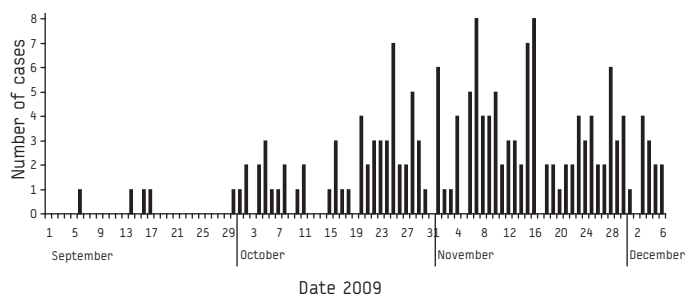
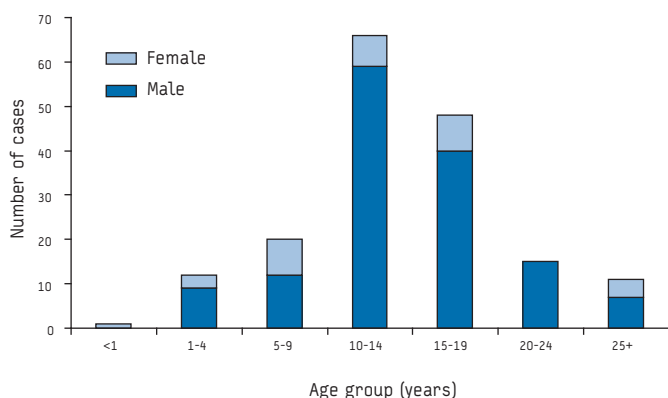


FIGURE 2

Mumps outbreak in Jerusalem September-December 2009, cases by age and sex (n=173)



TABLE

Mumps outbreak in Jerusalem, September-December 2009, distribution of cases in the affected schools (n=147)

Number of Mumps cases per school	Total number of cases	Number of schools
1	37	37
2	18	9
3	9	3
4	12	3
5	10	2
6	6	1
9	9	1
10	10	1
11	22	2
14	14	1
Total	147	60

In the United States, the largest outbreak in 20 years occurred in 2006-2007, encompassing more than 6,000 cases centred in college campuses. Of the students aged 18-24 years, 84% had been vaccinated with two doses of mumps vaccine [6]. The epidemic occurred despite high vaccination rates and low mumps activity in the community [7].

England and Wales are currently in the throes of an outbreak of mumps centred in college campuses, with 998 cases reported in January-February 2009, and further cases still being reported, mainly among college students. The circulating genotype is G5 [8].

Other European outbreaks have been reported in recent years. In an Austrian outbreak involving over 200 cases [9], 49% of the patients were unvaccinated – a very different situation from the outbreak we report. In the Republic of Moldova, an extremely large outbreak of nearly 20,000 cases was reported in 2007-2008 [10]. Most of the patients (96%) had received only one dose of MMR. A two-dose schedule was introduced in that country in 2002, for birth cohorts from 1995 onwards.

In an ongoing mumps outbreak in the United States (New York, New Jersey), and Canada (Quebec), 179 and 15 cases, respectively, were reported in August-October 2009. The affected individuals are mainly members of a Jewish religious community (83% males; median age 14 years). Of those for whom vaccination status is known 72% were vaccinated with two doses. The virus was of genotype G [11].

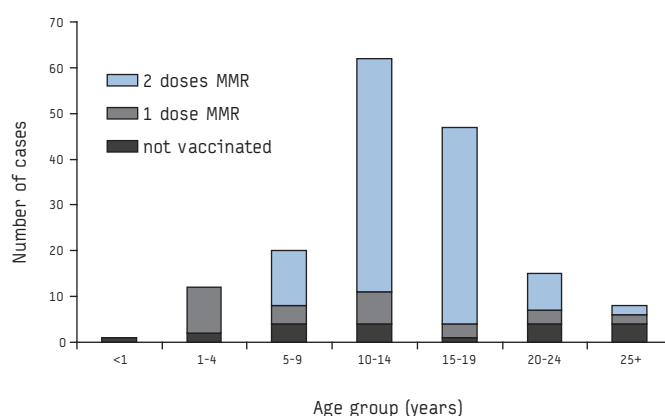
Conclusions

The two main characteristics of the current outbreak in Jerusalem are the predominance of male adolescents in religious boarding schools and the fact that most cases (74%) are appropriately vaccinated for their age. The male predominance is striking, and requires further study.

It had been observed that the mumps component of the MMR vaccine provides inferior protection compared to the measles and rubella components. Unlike the levels of 95% and 98% provided by the latter two, the mumps protection levels are approximately 62.85% and 85.88% for the first and second doses, respectively. Recently, the effectiveness in the United Kingdom was determined as 88% and 95%, respectively. However, the effectiveness of one

FIGURE 3

Mumps outbreak in Jerusalem September-December 2009, cases by age and vaccination status (n=165)



dose waned from 96% in two year-olds to 66% in 11-12 year-olds, and the effectiveness of two doses from 99% in 5-6 year-olds to 86% in 11-12 year-olds [12].

The reasons for the particular characteristics of these mumps outbreaks are unclear. Possible explanations include a combination of primary and secondary vaccine failure, waning immunity, inadequate vaccine effectiveness and previous low immunisation coverage. Contributory factors include living conditions in specific population groups such as college freshmen, army recruits and adolescent students in boarding schools.

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FIRST HUMAN CASE OF USUTU VIRUS NEUROINVASIVE INFECTION, ITALY, AUGUST-SEPTEMBER 2009

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We report the first worldwide case of Usutu virus (USUV) neuroinvasive infection in a patient with diffuse large B cell lymphoma who presented with fever and neurological symptoms and was diagnosed with meningoencephalitis. The cerebrospinal fluid was positive for USUV, and USUV was also demonstrated in serum and plasma samples by RT-PCR and sequencing. Partial sequences of the premembrane and NS5 regions of the viral genome were similar to the USUV Vienna and Budapest isolates.

Introduction

Usutu virus (USUV) is an arthropod-borne virus of the family *Flaviviridae*, genus *Flavivirus*. It is included in the Japanese encephalitis virus (JEV) group [1] being closely related to human pathogens such as JEV and West Nile virus (WNV). In the last decade, USUV was detected in a variety of central European birds with encephalitis, myocardial degeneration, and necrosis in liver and spleen [2-5]. As far as we know, the virus had never been associated with severe or fatal disease in humans [6]; it was isolated once in the Central African Republic in a man with fever and rash [7]. Here we report evidence of a neuroinvasive infection clinically related to USUV in Italy.

Case report

In May 2009, a woman in her 60s from Emilia Romagna region, Italy, underwent hemicolectomy because of a diffuse large B cell lymphoma. Six courses of chemotherapy were administered (including rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), with last administration on 21 August 2009. Some days later, there was a reactivation of genital herpes treated with valacyclovir. On 1 September, a fever of 39.5°C with resting tremor appeared and antibiotic (moxifloxacin and amoxicillin clavulanate) therapy started however the temperature persisted. On 5 September, the patient was admitted to hospital for hyperpyrexia resistant to antipyretic and intravenous antibiotic treatment (meropenem and teicoplanin). Once admitted, the patient received blood transfusion because of a critical anaemia.

Examination of blood, urine and stool cultures and virological assessment for herpes virus simplex (HSV1/2) and cytomegalovirus

(CMV) antigen were negative. A total body computerised tomography was performed without evidence of lymphoma. Suspicion of meningoencephalitis was addressed by neurological examination which showed distal resting tremor, positivity to the Romberg test, dysmetria and weakness at four limbs without cranial nerve affection. Magnetic resonance imaging (MRI) of the brain showed a signal alteration of the substantia nigra of the parietal and frontal subcortical areas that did not change after injection of contrast medium. On 11 September, the cerebrospinal fluid (CSF) was therefore collected and examined. The CSF was limpid without any alteration detected in the clinical-chemical analysis, activated lymphocytes were evident in the sediment. As further analysis of the same CSF specimen revealed the presence of flaviviruses (see below), steroid treatment was started. This therapy resolved the fever but did not lead to any improvement of the neurological symptoms. The electroencephalogram still registered diffuse slow theta waves and slow spike prevalent in left frontal parietal areas. The neurological functions, mainly the resting tremor, improved following the administration of levodopa and carbidopa.

Virological analysis

When tested for the presence of viral agents, the CSF collected on 11 September was negative in molecular tests for CMV, HSV1/2, Epstein-Barr virus, adenoviruses, parvovirus B19, polyomavirus JC and BK, enteroviruses, mumps virus and WNV and positive to a heminested RT-PCR specific for the NS5 region of the *Flavivirus* genus [8]. The amplicon was directly sequenced and analysed by BLAST (<http://www.ncbi.nlm.nih.gov/blast>), revealing a 98% identity with both the USUV Budapest (gbIEF206350.1) and Vienna (gbAY453411.1) isolate.

To confirm the identification of the species Usutu virus, we performed two USUV-specific RT-PCRs targeting the NS5 [2] and premembrane (preM) regions (primer sequences available on request) of the USUV genome on two plasma specimens collected on 8 and 11 September 2009 and one serum specimen collected on 14 September. The amplified products were sequenced (583 bp of NS5 and 602 bp of preM) and aligned with the corresponding sequences deposited in Genbank (gbAY453411.1;

gbIEF206350.1) using ClustalW. The alignment of the preM gene shared 99% nucleotide identity with the USUV Budapest and Vienna sequences, whereas the NS5 gene sequences shared 100% nucleotide identity with USUV Vienna and 99% with USUV Budapest.

Further specimens of serum (26 May and 13 October) and plasma (19 October) before and after the acute phase of meningoencephalitis were analysed to demonstrate the absence of the virus. The two USUV-specific RT-PCRs performed on these three samples did not detect any USUV RNA. These samples were also analysed for WNV because a WNV outbreak was ongoing in the area at the time [9], and were negative.

Discussion

To our best knowledge this is the first human disease with neurological involvement caused by USUV. The detection of USUV only in those samples collected during the acute phase of clinical manifestation is clear evidence that the virus caused the meningoencephalitis in the patient. Its capability of causing neurological lesions and death has already been reported in birds of central Europe [10]. The presence of USUV in Emilia Romagna has also been reported [4] and, in the past few months, the virus was isolated from black birds found dead in Northern Italy [G. Savini, personal communication 22 October 2009]. A surveillance programme in sentinel chicken flocks to monitor the possible appearance and/or circulation of WNV and other flaviviruses has been in place for several years. In the clinical case reported here, the immunosuppressed status of the patient due to both the underlying disease and the treatment, particularly with rituximab, may have played an important role in USUV infection and in its pathogenicity. It is known that rituximab can reactivate hepatitis B virus in patients with lethal fulminant hepatitis.

However, a possible unusual neuroinvasiveness and neurovirulence of this particular USUV strain cannot be excluded. The fact that neurological symptoms occurred prior to hospital admission excludes the transfusion as a possible source of infection. Conversely, since USUV as well as competent viral vectors are circulating in the patient's area of residence [4], it is likely that the infection was transmitted to the patient through mosquito bites.

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USUTU VIRUS INFECTION IN A PATIENT WHO UNDERWENT ORTHOTROPIC LIVER TRANSPLANTATION, ITALY, AUGUST-SEPTEMBER 2009

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We report a case of Usutu virus (USUV)-related illness in a patient that underwent an orthotropic liver transplant (OLT). Post transplant, the patient developed clinical signs of a possible neuroinvasive disease with a significant loss of cerebral functions. USUV was isolated in Vero E6 cells from a plasma sample obtained immediately before the surgery, and USUV RNA was demonstrated by RT-PCR and sequencing. This report enlarges the panel of emerging mosquito-borne flavivirus-related disease in humans.

Introduction

In recent years, several mosquito-borne flaviviruses were identified as new emerging pathogens in animals and humans worldwide. The widespread occurrence of flaviviruses, such as West Nile virus (WNV), Dengue virus (DENV), Japanese encephalitis virus (JEV), yellow fever virus (YFV) and tick-borne encephalitis virus (TBEV) represents an important global health problem [1]. In the past ten years, infections with Usutu virus (USUV), a mosquito-borne flavivirus of the JEV serogroup and related to WNV, has been detected in a variety of birds in central European areas such as Austria, Hungary and Italy [2,3,4]. To date, USUV did not show considerable pathogenicity for humans [5]. In particular, no clinically evident USUV-related infections have so far been documented in humans.

Here we report a case of USUV-related disease in a female patient who, during a viraemic episode caused by USUV, received an orthotropic liver transplant (OLT) as a final consequence of a thrombotic thrombocytopenic purpura (TTP). This patient developed a neurological disease with severe impairment of the cerebral functions within the first days after OLT.

Case report

On 10 August 2009, a few days after returning to Italy from a holiday in Egypt, a woman in her 40s developed a TTP and received 18 plasma exchanges until 4 September 2009. Two weeks later, on 14 September, the patient presented with fever of 39.5°C,

headache, skin rash, mild increment of cytolytic liver enzyme, without signs of TTP relapse, and was treated with antibiotics (moxifloxacin and amoxicillin clavulanate) without any response. On 18 September, the patient was admitted to hospital for persisting fever and headache. Any sign of TTP was excluded by total body computed tomography (CT) scan, and a peripheral blood smear did not show schistocytes or other fragmented red blood cells. Within a few days, a fulminant hepatitis and impairment of neurological functions were observed and rapidly developed into a coma. The molecular and serological laboratory diagnosis for the most common viruses associated with hepatitis (hepatitis A, B and C virus, cytomegalovirus and Epstein-Barr virus) gave negative results.

Two weeks after the OLT the patient slowly regained a low level of consciousness as well as some motor function of cranial nerves and limbs, and an intensive rehabilitative programme was started.

Virological analysis

Since 3 September 2009, systematic screening has been performed on blood, tissue, stem cell and organ donations from individuals living in the Emilia Romagna region in Italy, where WNV transmission was observed in summer 2009 [6]. This screening activity was undertaken following the data about WNV circulation in wildlife, horses and mosquitoes obtained from the regional integrated surveillance system that was in place from 15 June to 31 October. Screening for WNV was done using a nucleic acid amplification test (NAAT-Transcription-Mediated Amplification (TMA): PROCLEIX WNV, Novartis Diagnostics).

On 24 September, a plasma specimen obtained from the above patient immediately before surgery, was positive in the WNV NAAT assay. The test was repeated twice and the results were confirmed. A second sample was obtained from the patient one day after the OLT and the WNV NAAT was again positive. The level of positivity obtained with the two specimens was quite low, suggesting either an extremely low concentration of WNV RNA in the blood or a false

positive reaction. Additional blood samples obtained during the following 15 days gave negative results.

The liver's donor was also investigated. The donor had been living in the area of Parma and her plasma, obtained before liver donation, was NAAT-negative for WNV.

The NAAT result was further investigated by real-time RT-PCR targeting the WNV envelope (env) gene [7]. Surprisingly, the result was negative. Consequently we extended the investigation to additional members of the Flaviviridae family, including at first TBEV, because this agent was already reported in Italy and because the illness caused by this virus can involve the central nervous system with a possible association with liver injury [8]. The plasma specimens were analysed by real-time RT-PCR specific for the 3' non-coding region of the TBEV genome [9], and resulted negative.

A further step in the aetiological investigation was the use of a heminested RT-PCR with primer pairs which amplify the NS5 region of the Flavivirus genus. This method was developed for the detection by PCR of the principal pathogenic flaviviruses (including DENV, JEV, USUV, WNV YFV, and Zika virus) and subsequent identification by sequencing [3]. We performed the heminested RT-PCR as reported by Scaramozzino *et al.* [10] with minor modifications (details available on request) and obtained a single amplicon of the expected size (220 bp). Both strands of the amplicon were sequenced using the PCR primers and analysed by BLAST (<http://www.ncbi.nlm.nih.gov/blast>). This analysis revealed 98% sequence identity (over 203 nt) to the USUV genome sequences available in GenBank (please give the accession numbers), and no higher homology with any other published DNA sequence. Low homologies were observed to the WNV genome sequence (80% identity) and to the JEV genome sequence (79% identity); this partial homology is very likely due to the fact that these flaviviruses are closely related.

In conclusion, the sequencing results demonstrated the presence of USUV in the clinical samples of our patient. Additional confirmation of USUV viraemia was obtained by a PCR assay specific for USUV, performed as reported by Weissenböck *et al.* [11]. USUV was subsequently isolated in Vero E6 cells, and the identity of this isolate was confirmed by the heminested RT-PCR test reported above. As expected, the sequence obtained from the cultured virus isolate was identical to the one obtained from the amplified plasma sample. Complete sequencing of this human pathogenic USUV isolate is in progress.

Discussion

The results presented in this report, demonstrate USUV viraemia in an immunocompromised OLT recipient suffering from severe neurological impairment caused by an encephalitis. It is noteworthy that the NAAT test PROCLEIX WNV was capable of detecting a WNV-related virus, which indicates a potential problem with the specificity of this method.

The clinical findings observed closely resemble those reported in an animal model of USUV-related neurological disease [10]. To our knowledge, this report is the second description of the involvement of USUV in a human disease. Before, USUV-related infections had been reported as a cause of disease in animals, mainly birds, with no demonstrated pathogenicity for humans. Recently, it has been observed that USUV is circulating in owls and blackbirds in the North Eastern part of Italy, suggesting the possibility of USUV transmissions to humans in that area [12].

We are currently involved in an extensive serological investigation for USUV antibodies in the blood donors that were used for the plasma exchanges for our patient in order to define whether this therapy could have been the source of the infection or whether it was acquired naturally through a mosquito bite. In addition, a study is in progress to identify the presence of USUV in additional plasma and tissue specimens obtained from the same patient in order to quantify the viral load and the persistence of the USUV viraemic stage and to assess the possible involvement of USUV in the original liver disease. This case of USUV-related illness in humans has added this virus to the list of those that can be transmitted to humans by local mosquitoes and can cause severe diseases in immunocompromised individuals.

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Surveillance and outbreak reports

LARGE MEASLES EPIDEMIC IN SWITZERLAND FROM 2006 TO 2009: CONSEQUENCES FOR THE ELIMINATION OF MEASLES IN EUROPE

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Switzerland adheres to the objective of eliminating measles within the European region of the World Health Organization (WHO) by 2010. After several years with a relatively low annual incidence rate (0.3 to 1 case per 100,000 inhabitants), there has been a large epidemic of measles from November 2006 to August 2009. By mid September 2009, 4,415 cases were notified by physicians and laboratories, corresponding to an incidence rate of 15 per 100,000 in 2007 and 29 per 100,000 in 2008; by far the highest rates in Europe. This exceptionally long nationwide epidemic comprised three successive waves, with peaks in August 2007 (171 cases), March 2008 (569 cases) and March 2009 (417 cases). It mainly affected children aged from five to 14 years (48% of cases). Most cases were not vaccinated (93%) or were incompletely vaccinated (5%). In total 656 patients (15%) suffered complications or were hospitalised. Insufficient, spatially heterogeneous immunisation coverage (87% for at least one dose at the age of two years at the national level) has allowed a sequence of numerous outbreaks to occur, despite the gradual strengthening of measures to control the disease. Several exportations to Europe (81 in 2007 and 2008) and to the rest of the world (10 for the whole of the epidemic) have in some instances caused large outbreaks. The epidemic was a threat to the goal of eliminating measles in Switzerland and in Europe. The Federal Office of Public Health (FOPH) and its partners are currently working on a national strategy to eliminate measles.

Introduction

Interruption of the endemic transmission of measles by 2010 is one of the objectives of the World Health Organization (WHO) for its European region [1]. The strategy proposed consists in particular of achieving and maintaining $\geq 95\%$ vaccination coverage among young children (preferably before the age of two years), with two doses of MMR (measles, mumps and rubella) vaccine. Finland for example has achieved this objective, and many others are close to it [2,3]. Nevertheless, large-scale outbreaks have still been observed in Europe over the last ten years, for instance in the Netherlands, Italy, France, Germany and the United Kingdom, or in Israel [4-12].

In Switzerland, vaccination against measles has been recommended since 1976 (one dose at 12 months), with MMR vaccine being used since 1985. A catch-up vaccination has been recommended since 1985 for teenagers aged 12 to 15 years. A second dose of MMR was introduced in 1996 for children aged four to seven years, and this age was lowered to 15 to 24 months in 2001 to increase immunity before entering kindergarten or school. In addition, catch-up vaccination, to reach a total of two doses is recommended since 1996 for anyone born after 1963, who has not

been completely vaccinated, and has not had measles. Vaccination of young children and catch-up vaccination of children and adults are performed by pediatricians and general practitioners in private practice and reimbursed by mandatory health insurance. In some cantons, school medical services also ensure catch-up vaccination, usually during the first and the last year of compulsory school. For at least one dose at two years of age, vaccination coverage was stable at about 82% in Switzerland from the early 1990ies to the early 2000s, before increasing to 87% during the period from 2005 to 2007 [13,14]. At that stage it was 90% for children aged eight and 94% for adolescents aged 16 years. Coverage for a second dose only reached 71 to 76%, depending on age. Disparities in vaccination coverage are significant between the 26 Swiss cantons (range: 73–94% for at least one dose at two years). The coverage in the canton which recorded the highest amount of cases (Lucerne) was 78% in 2006 (86% at eight years and 94% at 16 years).

Despite over 30 years of vaccination against measles, this disease is still endemic in Switzerland with epidemic transmission occurring. From 1999 to 2006, an average of about 50 cases were notified per year (incidence rate 0.3 to 1 case/ 100,000) except in 2003, when there was an epidemic that affected the whole country (612 cases; 8.4/100,000) [15]. Whilst the circulation of the measles virus seemed very limited (three cases notified from July to October 2006), a new outbreak gradually spread across the country starting in November 2006 [16]. Since then, this epidemic has continued in three waves comprising numerous outbreaks [17,18]. The third wave began in the canton of Lucerne at the end of 2008 before spreading throughout the country. This report describes the measles epidemic that has been occurring in Switzerland over the past 34 months and the measures taken to control it. It also discusses causes and consequences of this particularly long nationwide outbreak.

Methods

Notification

The data analysed come from the mandatory notification system for measles (cases registered by the Federal Office of Public Health - FOPH, from 15 November 2006 to 17 September 2009). Since 1999, physicians have to notify the cantonal officers of health within 24 hours of any patient with a fever and a rash accompanied by at least one of the following three symptoms: cough, rhinitis or conjunctivitis. Laboratories must notify the cantonal officers of health and the FOPH within 24 hours of any confirmed measles case, whatever the test used. These initial rapid alerts allow the

cantonal physician to launch investigation and control measures. The physician later fills in a more detailed notification. The cantonal officers of health send the FOPH a copy of all notifications made by physicians.

Laboratory tests

The FOPH recommends laboratory confirmation of any suspect case of measles that has no epidemiological link to a confirmed case [19]. The analyses are carried out by numerous private laboratories or by public hospitals. Usually, Ig M and IgG are tested for in serum, using commercial tests. Two laboratories are able to test for the presence of measles virus RNA in clinical samples (throat smear or saliva) by RT-PCR. To trace the pathways of viral transmission, the WHO measles and rubella reference laboratory for Central Europe at the Robert-Koch Institute in Berlin, Germany, has genetically characterised 137 viruses and determined their genotype by sequence analysis of the variable part of the N-gene (456 nt) [20]. Since autumn 2008, genotyping of the measles virus has also been carried out at the Central Virology Laboratory of Geneva University Hospital.

Classification of cases

The definition of a clinical case corresponds to the notification criteria listed above. A case is considered confirmed if it i) is confirmed by a positive laboratory test and presents at least one of the typical signs of measles or ii) meets the clinical case definition and is epidemiologically linked to another laboratory confirmed case. A probable case is a clinical case that is not epidemiologically linked to a laboratory confirmed case. Possible cases include all reported cases without a positive laboratory result, which do not

meet the clinical case criteria (clinical manifestations incomplete or unknown). In the current outbreak many possible cases had an epidemiological link with another probable or confirmed case, or belonged to space-time clusters of measles. Cases with a double negative laboratory result (two negative IgM tests or one negative IgM test with absence of RNA by RT-PCR) are discarded, as are those with a single positive IgM test without any clinical symptoms of measles, due to a high probability of false positive tests.

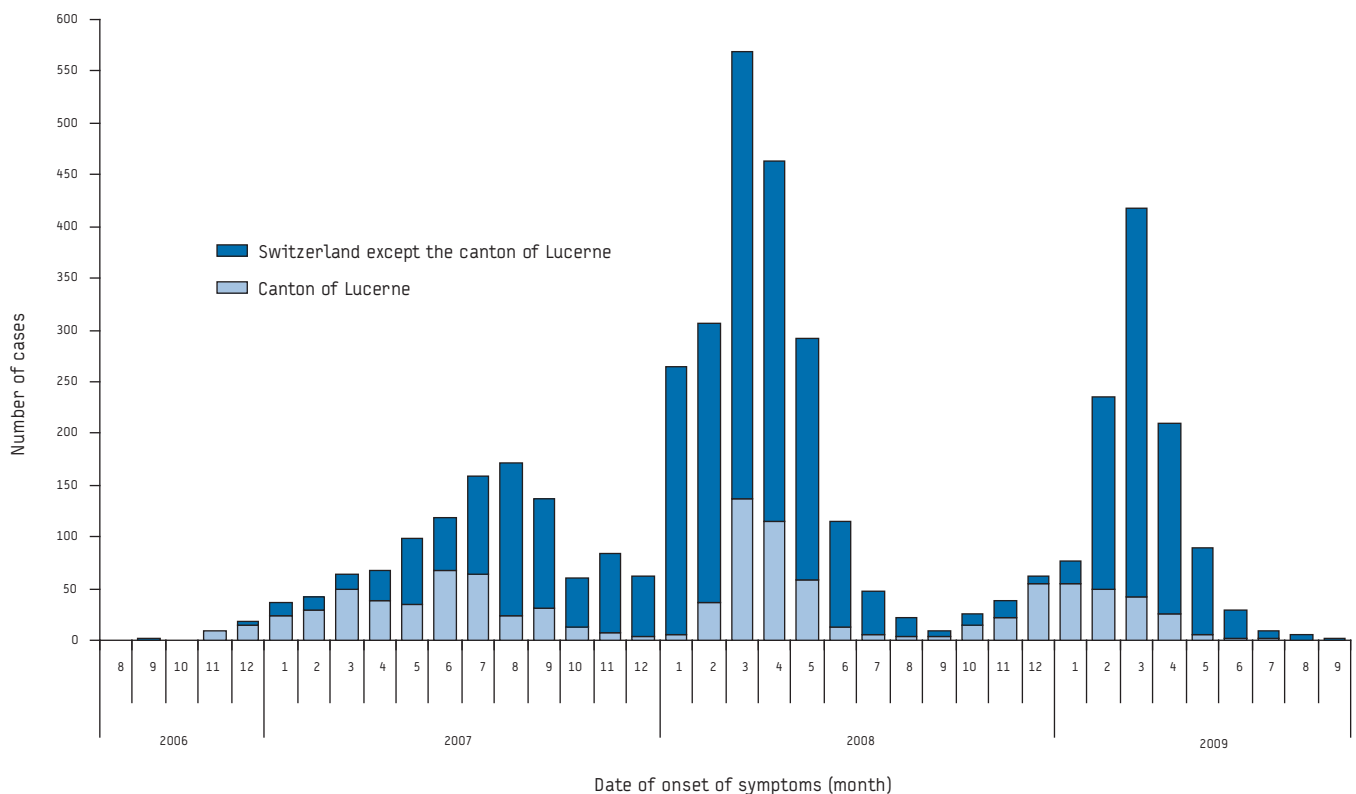
Description of the epidemic

The measles epidemic started in the canton of Lucerne in November 2006, probably following importation [16]. A first wave reached its peak in August 2007 (171 cases) (Figure 1). A second wave appeared in the Basel region around the end of 2007, with a surge from January 2008 and reinforced from February onwards by a strong return of measles in the canton of Lucerne (second peak in March 2008, with 569 cases). The number of cases then fell to a minimum of 10 in September, before constantly rising again, first in the canton of Lucerne, until March 2009 (417 cases). With only 29 cases in June, 10 in July, six in August and one case up to 17 September 2009, we consider that this epidemic has now come to an end. In total, 4,415 cases have been notified, 29 (1%) by the end of 2006, 1,098 (25%) in 2007, 2,214 (50%) in 2008 and already 1,074 (24%) by mid September 2009.

Of the total number of notified cases (4,565), 150 (3%) were discarded. Of the remaining 4,415 cases, 1,886 (43%) were confirmed, either by a positive laboratory result (35%), or by an epidemiological link with a laboratory confirmed case (7%). Of all cases, 48% were probable and 9% were possible.

FIGURE 1

Notified cases of measles by month, Switzerland, 1 August 2006 to 17 September 2009 (n=4,416)



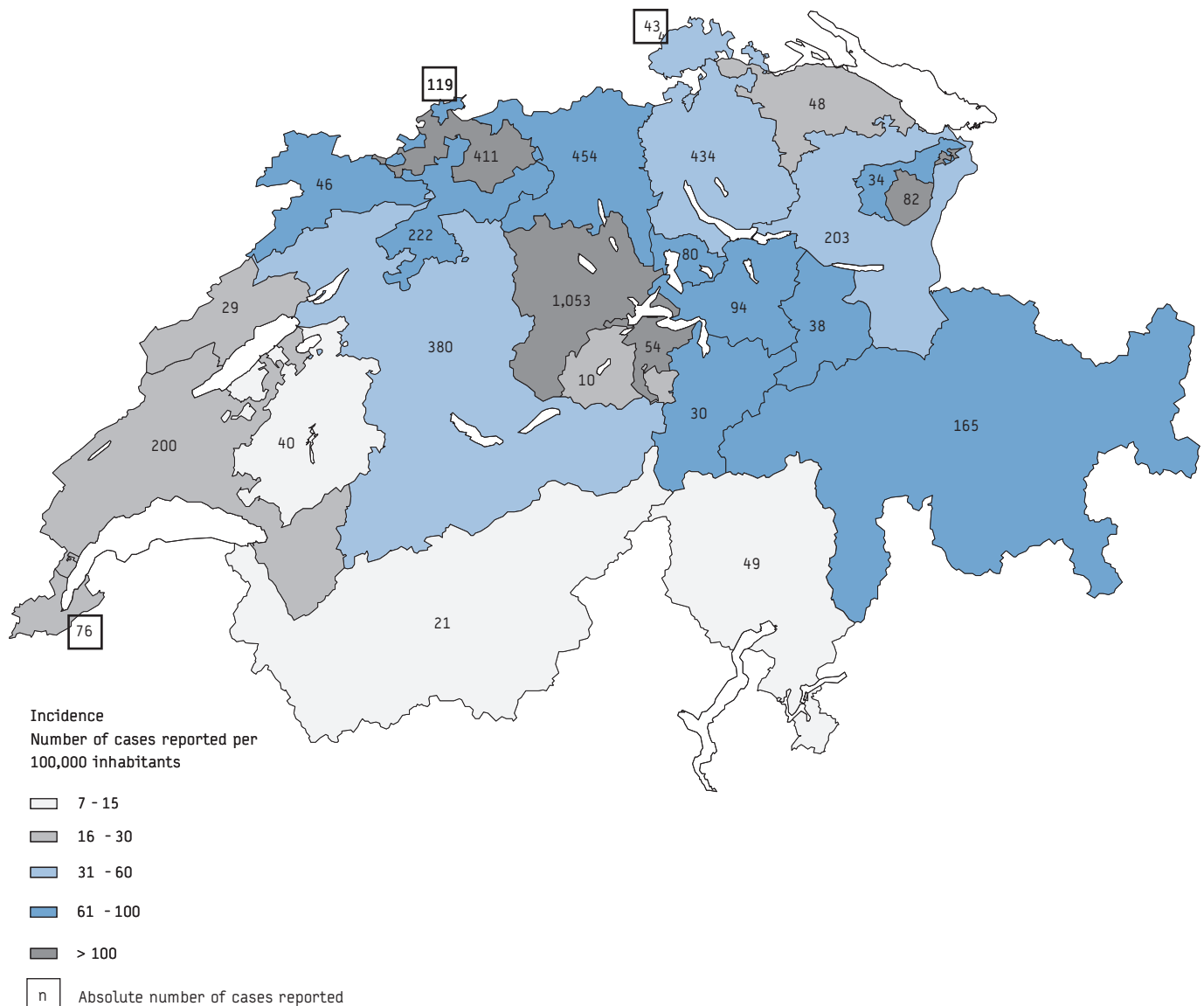
The epidemic has affected all 26 Swiss cantons. However, the total incidence rate for the whole of the epidemic has varied considerably from one canton to another, with a maximum of 530 per 100,000 in Appenzell Innerrhoden and a minimum of 7 per 100,000 in the canton of Valais, giving a national average of 58 per 100,000 (Figure 2). The cumulative incidence rate per canton has tended to be lower with increasing vaccination coverage (Figure 3). It reached 74 per 100,000 in the German-speaking part of Switzerland, compared with 21 per 100,000 in the French and Italian-speaking parts, with vaccination coverage of 84.7% and 92.3% respectively for at least one dose at two years of age. The first and third wave of the epidemic started in the canton of Lucerne and Lucerne contributed significantly to the second wave (Figure 1). Overall, that canton recorded 1,053 cases, 24% of the total (cumulative incidence rate 290/100,000).

The sex of 99.8% of the patients is known. The cumulative incidence rates were virtually identical for men and for women (59 and 57/100,000 respectively). Among the 99.5% of patients whose age is known, children aged five to nine years were most affected (25% of cases, cumulative incidence rate 285/100 000) (Table). They were followed by children aged 10 to 14 years and then adolescents from 15 to 19. Adults aged 20 or over made up 19% of cases, whereas cases in infants under one year were rare (< 3%). The median age of patients was 11 years.

The genotype of the measles virus is available for 105 of the 137 samples, with positive RT-PCR sent to the regional reference laboratory in Berlin, since the beginning of 2006. The genotype of further 20 virus samples was provided by a Swiss laboratory. In Switzerland in 2006, before the beginning of the epidemic

FIGURE 2

Incidence and number of notified cases of measles by canton, Switzerland, 15 November 2006 to 17 September 2009 (n=4,415)

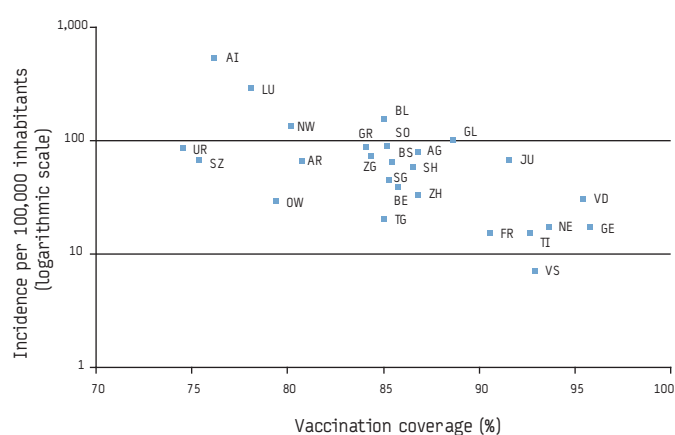


Source: Swiss Federal Office of Public Health

in November, only the B3 genotype was identified (Figure 4). It was found in a sporadic measles case returning from London in late January and an outbreak lasting from March to May in the neighboring canton of Lucerne. Genotype D5, which was the source of the recent epidemic, was identified in a total of 91 samples from 14 cantons, between November 2006 and March 2009. Also, 13 measles cases caused by D4 virus were identified between October 2008 and March 2009, in four cantons of the German-speaking part of Switzerland. In addition, two D4 viruses were found in June

in Geneva. In March 2009, there was an outbreak of genotype B3, mainly affecting the students from the Ecole polytechnique fédérale and from the University of Lausanne, following an importation of measles from Mali. B3 virus was identified in 13 patients, including the index case. In addition, two cases of B3 virus were detected in 2007 in isolated patients returning from abroad, as was a case of genotype A-related vaccine virus in a woman non-immune for rubella who developed a typical measles 12 days after a postpartum vaccination with MMR [16].

FIGURE 3
Cumulative incidence of measles by canton, Switzerland, 15 November 2006 to 17 September 2009



AG: Aargau GE: Geneva OW: Obwalden UR: Uri
 AI: Appenzell Innerrhoden GL: Glarus SG: St. Gallen VD: Vaud
 AR: Appenzell Ausserrhoden GR: Graubünden SH: Schaffhausen VS: Valais
 BE: Bern JU: Jura SO: Solothurn ZG: Zug
 BL: Basel Land LU: Lucerne SZ: Schwyz ZH: Zürich
 BS: Basel-Stadt NE: Neuchâtel TG: Thurgau
 FR: Fribourg NW: Nidwalden TI: Ticino

Note: Incidence displayed on logarithmic scale as function of vaccination coverage, ≥ 1 dose at two years of age according to the latest information available.

TABLE
Notified cases of measles and cumulative incidence per 100,000 inhabitants by age group, Switzerland, 15 November 2006 to 17 September 2009 (n=4,391)

Age (years)*	Number of cases	Proportion of all cases (%)	Incidence
< 1	114	2.6	153
1-4	531	12.1	180
5-9	1,095	24.9	285
10-14	1,033	23.5	244
15-19	775	17.6	170
20-29	399	9.1	43
≥ 30	444	10.1	9
Total	4,391	100.0	58

*information missing for 24 cases

Among the 3,916 (88.7%) patients for whom the vaccination status is known through a written document or by history, 92.9% had not been vaccinated, 4.5% had been incompletely vaccinated (one dose), 2.1% had been completely vaccinated (two doses) and 0.5% had been vaccinated with an unknown number of doses. There was a high preponderance of people who had not been vaccinated in each age group, although the proportion tended to decrease from adolescence, with more people who had been vaccinated and, in particular patients whose vaccination status was unknown (Figure 5).

A detailed notification is available for 4,278 cases (96.9%), of whom 339 (7.9%) were hospitalised. No complications were reported for 207 (61%) of hospitalised cases. The frequency of hospitalisation was significantly dependent on age (chi-squared test, $p < 0.0001$). It was 13% for infants, between 4 and 5% for each of the three five-year age categories covering children from one to 14 years old, 8% for adolescents from 15 to 19 years of age, 20% for adults from 20 to 29 years and 29% for adults aged 30 years or more. Among cases with detailed information available, 452 (10.6%) suffered from complications, of which 175 were pneumonia, 219 otitis and nine encephalitis. No follow-up information is available for the latter cases, however some were probably not severe because three of them were not hospitalised and a fourth was only a suspected case of encephalitis. Among cases with a complication only 135 (29%) were hospitalised. A 12-year-old girl living in the Haute-Savoie region of France, who had previously been in good health, died of measles encephalitis in late January 2009 at Geneva University Hospital.

In 2007 and 2008, thirteen and 68 importations respectively from Switzerland were reported by European countries participating to the European surveillance network for vaccine-preventable diseases (EU-VAC.NET), corresponding to 15% and 31% of the total of imported cases with a known origin [21,22]. Moreover, through the Swiss notification system and publications we are aware of at least 10 additional exportations outside of Europe during the epidemic: seven in North America; one in Asia, one in Africa and one in Australia. A number of these led to outbreaks, some of which were large, for instance in Germany, Austria, France and the United States [9,23-29]. Conversely, 54 possible or certain importations into Switzerland were reported during the epidemic, of which 33 were from Europe (in particular Italy, Germany and France), nine from Asia, seven from America (four from Latin America and three from the United States), four from Africa and one from an unknown Mediterranean country.

Public health measures Control of outbreaks

In Switzerland, public health measures to control outbreaks of infectious diseases are the responsibility of the cantons. The FOPH has no detailed overview on the measures taken by the cantonal health authorities and physicians, and their results. The FOPH has developed national guidelines to standardise the cantonal measures

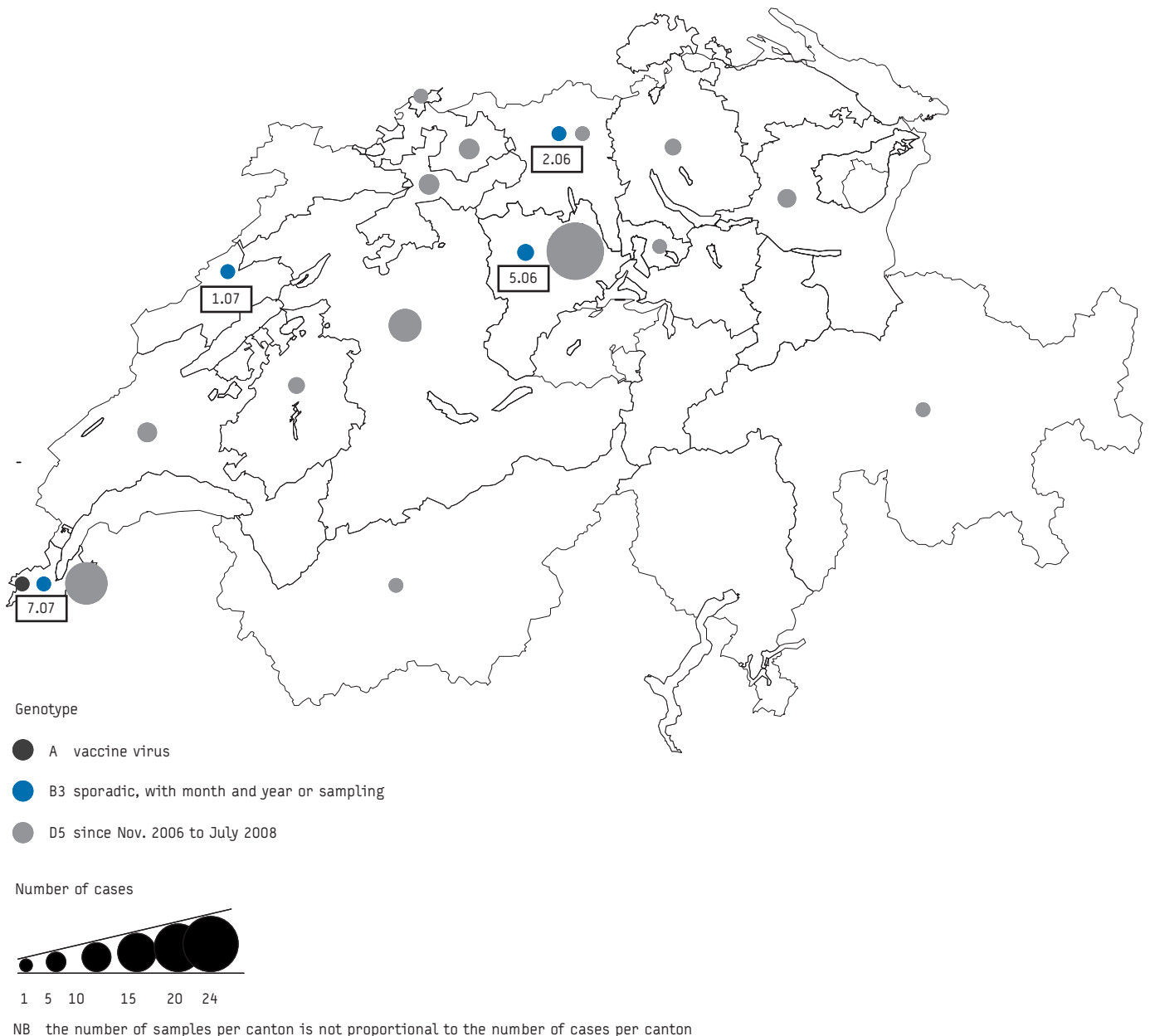
intended to limit or stop transmission. Although they have not yet been finalised, they have already been widely applied in some cantons. These measures include, in particular, information for contacts of the case in settings such as schools, kindergartens, and universities, with recommendations on vaccination, active case finding and identification of susceptible contacts, post-exposure vaccination of contacts within 72 hours after exposure, exclusion of the sick from kindergartens and schools for four days after the appearance of the rash, exclusion of susceptible contacts (except if they had post-exposure vaccination) for 18 days after their last exposure and actions to vaccinate the extended circle of

contacts. Post-exposure immunoglobulin is recommended for high risk groups. However, certain cantons, including some with a high incidence of measles, are not yet taking any measures or merely provide general information to the population or potential contacts.

In some instances, large-scale actions were carried out, in particular in the canton of Vaud. Following the notification of a case at the beginning of February 2009, an investigation of the contacts showed that there were already about ten non-notified cases in an anthroposophic school near Lausanne. As it was not possible to distinguish between people who had and had not been

FIGURE 4A

Circulating genotype of measles virus by canton, Switzerland, January 2006 to July 2008 (just before and during the first two waves of the epidemic, n=85)



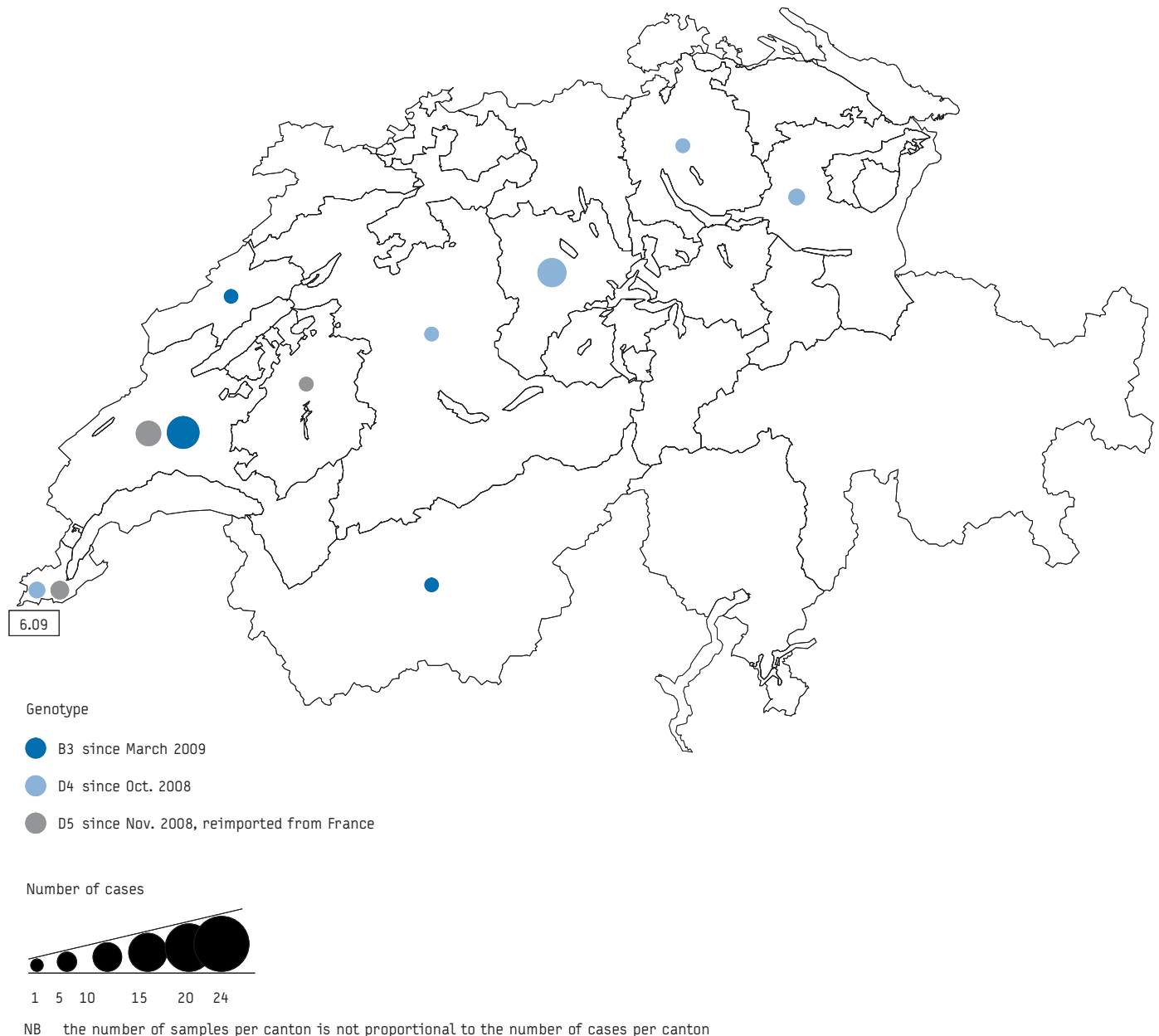
Source: Swiss Federal Office of Public Health

exposed, the cantonal officer of health immediately ordered that any pupil or teacher who had not been vaccinated at all and had not already had measles be excluded from the school and remain at home for 21 days which affected around 200 people. In March 2009, the campus of Lausanne was the centre of an outbreak of measles comprising about fifty cases. A large catch-up vaccination campaign was organised, to stop the transmission of the virus. All students and teachers were informed by email. More than 3,800 doses of MMR were administered within two and a half weeks, bringing vaccination coverage up to 97% for at least one dose of MMR vaccine from an estimated 90%.

For the first time following a risk linked to measles, in February 2009 the FOPH launched an international warning for passengers on two flights (Tel Aviv – Geneva via Zurich), with a direct search for some of the passengers. A girl, who had been infected in Switzerland before leaving for Israel, developed a rash soon after returning to Switzerland. She was thus infectious during the flights. At least one of the potentially exposed passengers sitting three rows in front and behind the girl obtained vaccination.

FIGURE 4 B

Circulating genotype of measles virus by canton, Switzerland, October 2008 to June 2009 (third wave of the epidemic, n=40)



Source: Swiss Federal Office of Public Health

Intensification of primary prevention

Primary prevention of measles has been intensified through information and vaccination in kindergartens, schools, universities etc. In 2008, a MMR catch-up action enabled 4,500 pupils in compulsory education in the canton of Vaud to be vaccinated. Following an outbreak in an army barracks at the beginning of 2009, which led to post-exposure vaccination of about forty soldiers, the army health directorate introduced free, voluntary catch-up MMR vaccination for all conscripts. In order to improve coverage for vaccines recommended by the FOPH, in particular the MMR vaccine, Switzerland took part in the European vaccination week for the first time in 2009. On that occasion, the FOPH revised its Internet site dedicated to the promotion of vaccination [30] and distributed two new brochures to the population via physicians and pharmacists, one brochure being specifically about measles.

Media coverage of the third wave of measles reached an unprecedented level for measles. The messages of the federal and cantonal health authorities, in particular calls for vaccination, were transmitted on a large scale.

Political dimension of the elimination of measles

This epidemic has also become a political topic. The conference of cantonal health ministers has publicly committed to fight against measles in February 2009, with a view to its elimination, and to make further efforts to achieve $\geq 95\%$ vaccination coverage [31]. It will consider introducing compulsory vaccination against measles before children go to kindergarten or to school, if this objective cannot be achieved by other means. Parliamentary interventions originating in both federal chambers have also successfully

requested that the federal government launch a national plan to eliminate measles. This political impetus speeds up the preparation of such a plan, which was already underway at the FOPH. The main strategic focuses are to obtain the commitment of political and public health stakeholders, to reinforce the promotion of MMR vaccination through communication campaigns, to facilitate access and encourage vaccination through organisational measures, to control outbreaks of measles and to strengthen the surveillance of measles.

Discussion

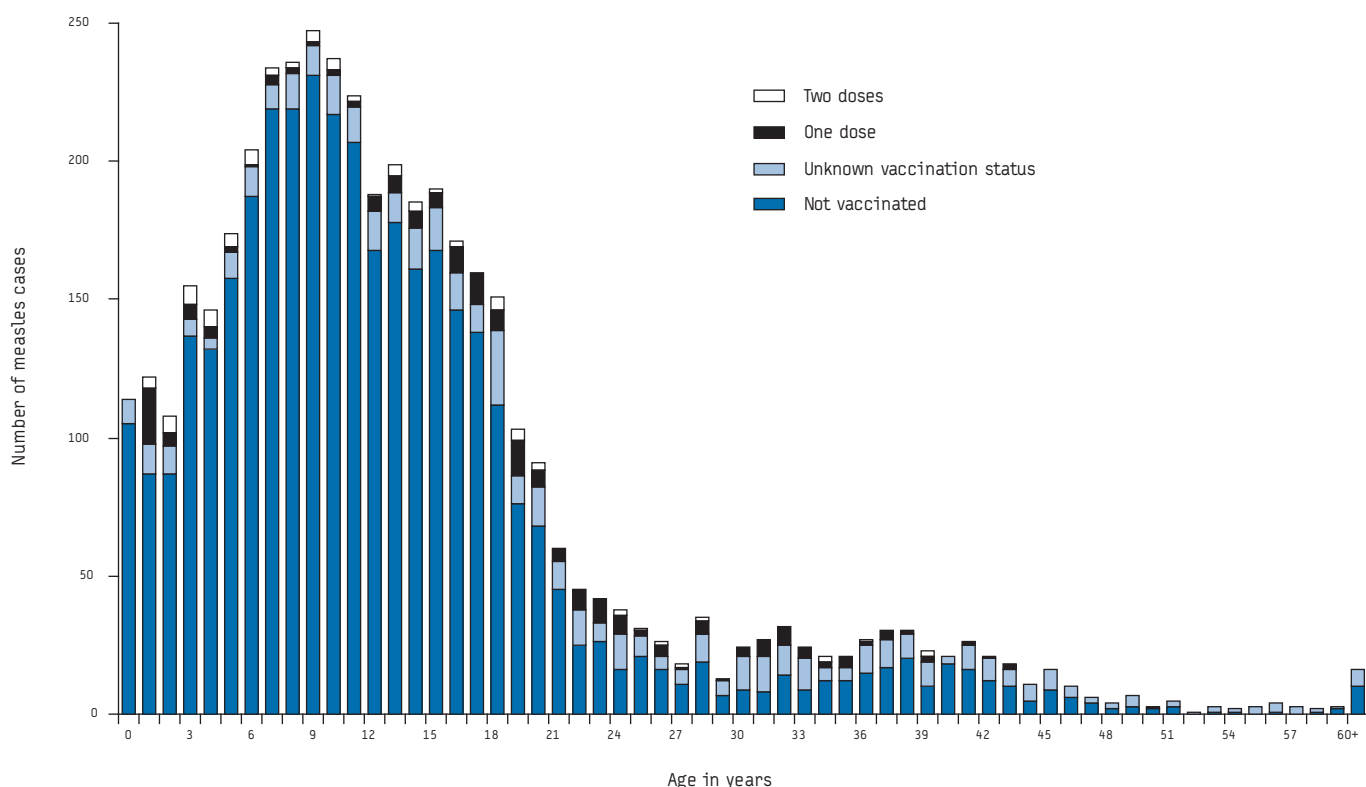
With 4,387 reported cases, since the end of 2006, Switzerland has recorded the largest and longest lasting measles epidemic since compulsory notification of this disease was introduced ten years ago (82% of all cases notified). However, the actual number of cases is certainly higher: an intensive survey of contacts suggests that only about one out of two cases were diagnosed by a physician and notified [personal communication Dr. E. Masserey]. The epidemic mainly affected younger school children and to a lesser extent adolescents and adults who had not been vaccinated. Ninety eight percent of patients had not been vaccinated or had been incompletely vaccinated.

In 2007 and 2008, Switzerland reported more cases, over a quarter of the total, with a 20-times greater incidence rate than the average, than any of the other 31 countries taking part in EUVAC. NET network [21,22].

The current epidemic is unusually long for Switzerland: 34 months with three distinct waves. In comparison, the 2003

FIGURE 5

Vaccination status by age for notified cases of measles, Switzerland, 15 November 2006 to 17 September 2009 (n=4,391)



epidemic only lasted six months, with six times less cases. Epidemics with several thousand or tens of thousands of cases, lasting for two to three years have been recorded recently in Europe, in particular in Romania, Georgia and Ukraine [32]. The proportion of people susceptible to measles in the Swiss population, their spatial distribution and the intensity of their contacts with parts of the world where measles are endemic are factors that allowed this prolonged though fluctuating circulation of the measles virus at the national level. During the last three years it led to numerous local and regional outbreaks, occurring successively or simultaneously, sometimes re-affecting regions that had already been affected.

Despite many importations of measles, only the D5 virus was circulating widely throughout Switzerland from the start of the epidemic until summer 2008. The beginning of the third wave, in autumn 2008, seems to coincide with the appearance of a new virus, D4, MVs/Enfield.GBR/14.07, that is endemic in the United Kingdom since April 2007 [33]. It was found in Eastern and Central Switzerland, from where the previous D5 virus was no longer reported. However, the same variant of the D5 virus reappeared in the French-speaking part of Switzerland at the beginning of 2009, following reintroduction from France, where it had been imported from the German-speaking part of Switzerland in spring 2008 [27]. Before this epidemic in Switzerland and the secondary outbreaks in neighbouring countries, the D5 virus had recently only been reported in Europe as rare, with sporadic cases or limited outbreaks, generally related to importations [34].

Inadequate vaccination coverage for many years and relatively low incidence of measles since 2004 has allowed the number of non-immune individuals to build up, feeding the current outbreaks. As expected, the incidence of measles per canton tends to increase with lower vaccination coverage. In addition, the high proportion of unvaccinated patients among cases confirms that this large epidemic was mainly due to inadequate vaccination coverage. The number of people in Switzerland who are under 20 years of age and are not immune to measles is currently estimated to be 214,000 (13% of this age group) from data on vaccination coverage and on notified cases. No seroepidemiological survey has been performed recently. The proportion varies from 9% to 18% depending on the canton, but is always above 5%, the threshold below which herd immunity establishes itself [35]. In addition, an unknown but likely small proportion of adults, in particular those under 45 years of age, is not immune.

This unsatisfactory situation can be explained by the deliberate choice not to vaccinate, made by certain parents, rather than by limited access to vaccination. Indeed, vaccination is widely available through paediatricians and family doctors. Up to 90% of the cost is covered by the compulsory health insurance scheme and several cantons offer free catch-up MMR vaccination in schools. The low amount payable by parents is probably just a minor barrier to access to vaccination. Indeed, vaccination coverage with at least three doses of a vaccine against diphtheria, tetanus, pertussis and poliomyelitis reaches approximately 95% compared with 87% for measles, while the recipient must also pay at least 10% of the invoice. In addition, vaccination coverage for measles decreases with the increasing level of education of the mother, and children of foreign nationality have a higher rate of vaccination than Swiss children [36]. As a result, vaccination coverage for measles is most probably higher in families with a lower income than in affluent families. Children of families using alternative medicine are in particular less often vaccinated than others. The canton of Lucerne where there are relatively high numbers of homeopathic medical

practitioners, has recorded about a quarter of all cases, often notified by such physicians. Some of these families who chose not to vaccinate their children also favour alternative education, in particular in private anthroposophic schools, which are often major foci as soon as measles are introduced. This was recently observed in Switzerland in the area of Basel, in Lausanne and in Berne, and elsewhere in Europe [25,26,37,38]. In addition to reluctance to vaccinate, missed opportunities certainly contribute to the accumulation of non-immune people. However, they seem to relate in particular to the second dose in children and catch-up vaccination for adults born after 1963.

Although they are still insufficient, interventions to control outbreaks of measles have continuously increased throughout this epidemic. In general they are well accepted by the population, but still have to be extended to the country as a whole. The prior aim of the measures is to stop the transmission of the virus rapidly, if not to prevent it. To this end, rapid notification of cases is crucial. This is why the delay for notification was reduced from one week to 24 hours in 2006. However, sometimes physicians are slow in notifying or do not notify cases at all. In these instances intervention is more difficult and its effectiveness reduced. Where implemented, measures such as exclusion of susceptible contacts from school have encouraged vaccination: parents have preferred to vaccinate their children rather than risking their eviction.

Consequences for the elimination of measles

Despite its magnitude, the current epidemic has only slightly (-1.4%) decreased the proportion of non-immune people in Switzerland aged less than 20 years. Although the epidemic is now over, a new one could start at any time. Therefore, it is essential to achieve very high vaccination coverage ($\geq 95\%$) of each new birth cohort with two doses of MMR vaccine; but this will not be enough to eliminate measles in Switzerland: in parallel, catch-up vaccination has to be intensified for susceptible people born after 1963 ensuring that they are vaccinated with two doses of MMR.

The situation in Switzerland is a national challenge and a threat for the elimination of measles from the WHO European Region, as shown by the numerous exportations of measles. Further efforts are necessary and are planned by the national and cantonal health authorities so that with the help of partners and of the population, vaccination coverage can be increased to $\geq 95\%$ and measles can be eliminated in Switzerland.

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RUBELLA SEROPREVALENCE IN CHILDREN IN DOGANKENT, A RURAL AREA OF ADANA PROVINCE IN TURKEY, JANUARY-FEBRUARY 2005

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A cross-sectional study was performed to determine the rubella seroprevalence in 331 children aged between 0 and 59 months in Turkey who were not vaccinated for rubella and lived in the area covered by Dogankent Health Center, a rural area with a large proportion of residents of low socioeconomic status. Rubella seropositivity was found to be low, with 17.5%, increased with age and low socioeconomic level, and was particularly high in children who live in a household with one member going to school, and in children of uneducated parents ($p < 0.05$). The asymptomatic infection rate was 98.3%. There was no significant difference in seropositivity with regards to the gender, history of rubella infection, size of the household, or number of children at home ($p > 0.05$). Rubella vaccine has only been included into the national vaccination programme in the form of the measles-mumps-rubella (MMR) vaccine since 2006 and is performed at the age of 12 months, in the first year of primary school and at the age of about 15 years. In order to eliminate rubella and congenital rubella syndrome, it is necessary that use of MMR vaccine is expanded to include the children born before 2006.

Introduction

Although rubella is a self-limiting disease in childhood, it can cause congenital rubella syndrome (CRS) when the mother is infected during the first trimester of pregnancy. In CRS, fetus and placenta are infected following maternal viraemia, which can result in abortion, premature birth or cataract, retinopathy, deafness, cardiac defects, hepatitis, haemolytic anaemia, thrombocytopenia, endocrinopathies, microcephaly, psychomotor retardation and progressive rubella encephalitis. The risk of clinical manifestations in the fetus or newborn decreases with the gestational age at the time of vertical transmission [1-3]. The most effective way to eliminate CRS is vaccination against rubella. A rubella elimination strategy should be based on universal childhood vaccination as well as immunisation of susceptible women at childbearing age. Unfortunately, there is no information about the CRS rate in Turkey.

In Turkey, rubella vaccine has been on the market since 1989 and has been administered in the form of the combined measles-mumps-rubella (MMR) vaccine, mainly in private practices and paid by the parents. A study conducted in Istanbul in 2002 reported that 13.3% of children were vaccinated by MMR [4]. Rubella vaccine has been incorporated into the Turkish national

immunisation programme only in 2006. In the beginning of vaccination programme, it was applied as MMR vaccine at the ages of 12 months and ca. seven years (in the first year of primary school), and as rubella vaccine at the age of about 15 years.

In studies on rubella seropositivity carried out in children in Turkey, Aksit *et al.* reported a seropositivity of 38.3% in 1-4 year-olds in Izmir in 1999 [5] and Cavusoglu *et al.* one of 12.5% in 2-5 year-olds in Istanbul in 2001 [6]. Ay *et al.* reported 66.7% rubella seropositivity in primary school students in a rural district in Istanbul in 2003 [7]. In 2006, Gurgoze *et al.* reported a seropositivity of 47.3% in 1-4 year-olds and of 89.2% in 13-16 year-olds in Elazig, a city in eastern Turkey [8]. In Adana, Karakoc *et al.* found the seropositivity to be 92.5% in adolescent girls in 1999 [9] and in 2006, Oner *et al.* found it to be 93.7% in the same age group in Edirne, a city in northwest Turkey [10]. In pregnant women and women of childbearing age, reports from Turkey indicate that rubella seropositivity varies widely, ranging from 55.0% in Mersin province to 100% in Istanbul city [11,12]. Therefore, many women may be susceptible to rubella infection especially in rural areas. In the beginning of the rubella vaccination policy, children aged 1-6 years may not be vaccinated until they go to primary school, and as most of them are seronegative for rubella, they may be a risk for pregnant women. Hence, the objective of this study was to determine rubella seroprevalence in 0-59 months-old unvaccinated children in Dogankent, a district in Adana, Turkey.

Materials and Methods

Adana is an industrialised city in the southern part of Turkey with a population of approximately two million. Between 11 January and 17 February 2005, a cross-sectional study was conducted in Dogankent, a rural district, 20 km from of Adana, with a low socio-economic level and a population of 12,000. Dogankent has three elementary schools and one health centre. Main employment is in agriculture and stockbreeding. Although the mean size of a household in Turkey is four members, the mean household in Dogankent had seven members. Most of the adults were unemployed [13].

A systematic sampling method stratified by age and sex was applied, on the basis of data from the Dogankent primary health centre. This primary health centre was established in 1982 and

is under the supervision of the Department of Public Health of Cukurova University for which it serves as research and training area. The lowest seropositivity in 0-59 month-old children reported in all areas in Turkey was 12.5% [6]. At the time of study, 1,233 children between 0 and 59 months of age were living in Dogankent. The sample size of the study was calculated as 330 based on the 12.0% estimate of rubella immunity, with a 95% confidence level and worst acceptable result as 9%. The list of the subjects was obtained from the directorate of the Dogankent health centre. An additional 33 reserve subjects were also defined from the same age group, to be called if any of the 330 children could not be reached.

This sample size of 331 subjects comprised 26.8% of the 0-59 month-old children in the district. A maximum of one child from every house was included to the study. If we could not reach a child, a subject was chosen from 33 children on a reserve list. Subjects who had a telephone number were called to the primary health centre; those who did not were visited at home by one of the investigators. Twenty-nine subjects could not be included in the study for the following reasons: three did not want to participate, 26 moved away. Instead, 29 children from the reserve list were included in the study.

A questionnaire was completed about socio-demographic features, rubella vaccination and history of rubella infection of each child and family. Parents were asked if their child had ever been diagnosed for rubella by a physician or vaccinated with rubella vaccine, about the number people living in the household and the

number of siblings aged 0-14 years living at home, the number of siblings going to school, and about the parents' employment and education level. Educational level of the parents was classified either as no education (not even primary school) or as having attended primary school (not necessarily graduating). Employment was defined according to the International Labour Organization [14]. There were four types of health insurance schemes in Turkey at the time of study: one for civil servants, one for self-employed people, one for workers, and a green card which covers the very poor people. People not included in any of these four insurance systems had to pay for healthcare. Since 2008 children under the age of 18 years have been entitled to free healthcare.

With permission of the parents, 3-5 ml venous blood was obtained from each child. Serum samples were stored at -20o C and tested for rubella antibodies. Anti-rubella IgG was analysed by ELISA (DSL-05-10-RBG; Diagnostic System Laboratories). Values over 0.283 were defined as positive for the presence of antibody. The statistical analysis was done using SPSS- 10.0, and chi-square test. A p value of <0.05 was accepted as statistically significant.

The study was approved by the local ethics committee of the faculty of medicine and informed consent was obtained from all parents.

Results

The study was carried out in 331 children (162 boys, 169 girls). The mean age of the children was 30.3±16.0 months (range: 1-59 months, median age: 29 months). There was no statistically significant difference in the number of children in terms of sex and age group (p>0.05). The age distribution of the children is shown in Table 1.

Of the 331 children, 135 (40.8%) had no social health insurance, 141 (42.6%) had the green card, and 55 (16.6%) belonged to a social insurance system. Half of the fathers (48.9%) and almost all (99.1%) of the mothers were unemployed; 23.9% of fathers were workers, and 25.1% were self-employed.

None of the children participating in the study had received the rubella vaccine. Fifty-eight children (17.5%) were positive for rubella antibodies. The Figure shows the rubella seropositivity in different age groups. Rubella seropositivity increased with age (p<0.05). There was no significant difference between boys and girls in terms of rubella seropositivity (p>0.05).

Only five children were reported by the parents to have a history of rubella infection and one of those five had rubella antibodies. However, 57 (17.5%) of the 326 children without reported rubella history were positive for rubella antibody. Thus 57 of 58 children had negative rubella history, although they had had the infection in the past. Rubella seropositivity was not different between children who had a family member with (20.0%) or without (17.5%) rubella history (p>0.05). Neither was there any statistically significant relation between household size and the number of children in the house (p>0.05). The rubella seropositivity was higher in children living in a household with members who were going to school (Table 2, p<0.05). The parent's educational level was inversely associated with the prevalence of anti-rubella antibodies in the sense that as the educational level increased rubella seropositivity decreased (Table 2, p<0.05).

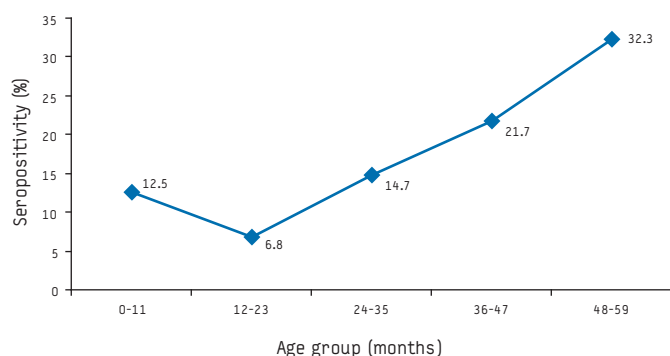
TABLE 1

Children, by age and sex, participating in the rubella seroprevalence study in Dogankent Turkey, January-February 2005 (n=331)

Age group (months)	Boys		Girls	
	n	%	n	%
0-11	24	50.0	24	50.0
12-23	38	51.4	36	48.6
24-35	33	44.0	42	56.0
36-47	37	53.6	32	46.4
48-59	30	46.2	35	53.8
Total	162	48.9	169	51.1

FIGURE

Age-specific rubella seropositivity in children of low socioeconomic status in Dogankent Turkey, January-February 2005 (n=331)



Discussion

In our study, rubella seropositivity was 17.5% among children aged 0-59 months. The major limitation of our study is that the results are from a single centre. Therefore our results may not necessarily be representative for other parts of Turkey. However, they could provide a benchmark for future assessments. In other studies carried out in Turkey, rubella seropositivity ranged from 22.5% [15] to 38.3% [5] in 0-1 year-olds, 47.3% [8] to 51.3% [16] in 1-4 year-olds, 12.5% in 2-5 year-olds [6] and 73.1% in 2-6 year-olds [15]. In adolescents, seropositivities of 92.5% [9] and 93.7% [10] have been reported. In developing countries, rubella seropositivity was found to be 97.0% in 2-7 year-olds in Iran [17], 69.2% in 1-5 year-olds in India [18] and 58.0% in 2-4 year-olds in Zaire [19]. The rubella seropositivity we found in our study was higher than the 12.5% observed by Çavusoglu *et al.* [6], but lower than those found in the other studies in similar age groups. This low level of rubella seropositivity we observed in Dogankent may be due to the geographic region or the fact that the study was performed in a rural area.

In the present study, rubella seropositivity was highest in the age group of 48-59 month-olds. Although rubella can be encountered at all ages, it is generally seen in the age group of 5-9 year-olds in countries that do not have routine rubella vaccination and rarely in those under one year of age due to maternal antibodies [1]. Several studies report that maternal antibodies are eliminated rapidly in the first 5-8 months of life [20-22]. The drop in seropositivity from 12.5% in the age group 0-11 months to 6.6% in the age group 12-23 months that we observed is probably due to the elimination of maternal antibodies.

Serologic studies conducted in Jordan [23], Nigeria [24], Yemen [25], Saudi Arabia [26], Lebanon [27], Taiwan [28], Italy [29], Ethiopia [30] in the past 20 years show that seropositivity increases with age. Seroprevalence data from the European Sero-Epidemiology Network (ESEN) study performed between 1996 and 2003 showed that women in several countries were not sufficiently protected against rubella infection. According to the European

Centre for Disease Prevention and Control (ECDC), 1,498 rubella cases were reported from 22 European countries in 2005, with the highest incidences in Lithuania (3.44 per 100,000) and the Netherlands (2.23 per 100,000) [31]. Rubella susceptibility studies in our country also showed that seropositivity increases by age [6-11, 32]. Similarly, our study revealed that seropositivity increased from the 12th month of age, and this is in line with the findings in the literature.

Of 331 children in our study, only five had a history of rubella (as reported by the parents) and only in one of them, rubella seropositivity was determined. However, rubella seropositivity was found in 57 (17.5%) of the 326 children for whom no rubella history was reported. Thus, 98.3% of the children with rubella antibodies must have experienced an asymptomatic infection. However, the parents may have been unaware of infection symptoms or there may be recall problems. In a study by Kanbur *et al.* in adolescents [33], 66.0% of the seropositive cases had a positive history; however, the children in that study had been asked if they had had an eruptive disease, not specifically rubella. Two possible explanations for the lower rate of rubella history in seropositive children in our study, in comparison to Kanbur *et al.* [33] could be that the children in our study were younger and that we asked whether they had a history of rubella rather than any eruptive disease. The fact that the majority of cases were asymptomatic emphasises the importance of serological studies in determining the definite prevalence of rubella in a community.

In our study, the rubella seroprevalence in children with parents who had education of any level was statistically lower than that in children with parents who never had any education. We have no explanation why this would be the case for an air-borne infection such as rubella. A higher number of infectious diseases in children of parents (especially mothers) with low education and low socioeconomic status is to be expected, as also observed by other authors [8,34]. However, Karakoc *et al.* [9] did not find a relation between rubella seropositivity and socioeconomic status.

TABLE 2

Rubella seropositivity in children according to parents' education, siblings going to school, sex and number of people living at home in children of low socioeconomic status in Dogankent Turkey, January-February 2005 (n=331)

		Seropositivity		Seronegativity		ALL		p value
		n	% ^a	n	% ^a	n	% ^b	
Gender	Boys	26	16.0	136	84.0	162	48.9	0.49
	Girls	32	18.9	137	81.1	169	51.1	
Mother's educational status	Not educated	39	22.4	135	77.6	174	52.6	0.02
	Primary school or high school	19	12.1	138	87.9	157	47.4	
Father's educational status	Not educated	18	26.5	50	73.5	68	20.5	0.045
	Primary school or high school	40	15.2	223	84.8	263	79.5	
Siblings going to school	No	20	12.3	142	87.7	162	48.9	0.02
	Yes	38	22.5	131	77.5	169	51.1	
Number of people living at home	3-4	10	12.5	70	87.5	80	24.2	0.11
	5-6	22	17.2	106	82.8	128	38.7	
	7+	26	21.1	97	78.9	123	37.1	
Total		58	17.5	273	82.5	331	100	

^a Percentage refers to the total in the same row.

^b Percentage refers to the sum of totals in the column.

Whether or not the children had a family member with a history of rubella infection did not make a statistical difference in terms of rubella seropositivity. One reason for this may be the fact that rubella infection is not as contagious as measles and chickenpox. While one measles case can infect 10-14 other people, a rubella case can spread to five or six people [2], and rubella inter-household infection is 50-60% [3]. Also, as 25-60% of rubella infections are asymptomatic [2,3], it is not possible to know whether people reporting no history of rubella are actually seronegative or not, which would result in an underestimation of cases in households with a history of rubella. Another reason may be the fact that poor people from low socioeconomic background might not have a chance to see a doctor. This finding of our study can therefore not be considered to be reliable.

Although crowding is known to play a role in the dissemination of rubella, we did not observe a statistically significant difference between rubella seropositivity and the number of household members. However, the risk of rubella was 1.6 times higher in children living in a household of seven or more members than in children living in a household of three or four people (21.1% versus 12.5% seropositivity).

In our study, the number of siblings did not increase the seropositivity, but seropositivity was higher if the child had a sibling going to school (22.5% versus 12.3%). It is well known that rubella is less frequent in children before they have started school. Cengiz *et al.* [16] reported that rubella seropositivity was 12.5% before school and increased to 65.3% in primary school. Moreover, our study did not detect a statistically significant difference between rubella seropositivity and the presence in the household of children aged between 0-6 years. Rubella is seen mostly in five to nine year-old children and the rubella incidence reaches its peak in this age group [3]. The infection rate of the disease is about 100% in susceptible people in closed quarters such as schools and military barracks and 50-60% in the home environment [3]. Higher rubella seropositivity in children with brothers or sisters in school is therefore an expected finding,

Conclusion

Rubella vaccination was integrated into the national immunisation programme in Turkey in the form of MMR vaccination only in 2006. In our study, rubella seropositivity was low in children aged between 0-59 months. For this reason, it is necessary to ensure that MMR vaccination is expanded nationwide to cover the children born before 2006. Epidemiological studies should continue as the epidemiological characteristics of the disease may change depending on the uptake of MMR vaccination, while seroprevalence studies should continue in order to determine the seroconversion rate and period of preventive effectiveness of MMR vaccination. In order to eradicate rubella and CRS, it is necessary to vaccinate women at child-bearing age who are found to be susceptible as a result of serological tests and children born before 2006 with rubella vaccination.

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WHO CRITERIA FOR MEASLES ELIMINATION: A CRITIQUE WITH REFERENCE TO CRITERIA FOR POLIO ELIMINATION

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Smallpox was formally declared as eradicated in 1979. Smallpox is the only infectious disease of humans that has ever been eradicated. Poliomyelitis has been eliminated from three of the six World Health Organization (WHO) regions although not all countries within those regions always meet the elimination criteria. Elimination criteria for measles are being discussed. We use poliomyelitis and measles as examples to illustrate our assertion that the current approach to documenting measles elimination relies too heavily on criteria for surveillance quality, disadvantaging countries with long established and relatively inflexible surveillance systems. We propose an alternative approach to documenting measles elimination, with the two key criteria being molecular evidence to confirm the lack of a circulating endemic genotype for at least one year and maintenance of 95% coverage of one dose of measles-containing vaccine, with an opportunity for a second dose. Elimination status should be reviewed annually. We suggest four principles that should guide development of final criteria to document measles elimination: countries that have eliminated measles should be able to meet the elimination criteria; quality surveillance criteria are necessary but not sufficient to define elimination; quality surveillance criteria should be guided by elimination criteria, not the other way around; and elimination criteria should not differ between the WHO regions without good reason.

Introduction

Smallpox is the only infectious disease of humans that has been successfully eradicated, with a formal declaration made in December 1979 [1]. At this time, eradication was defined by the World Health Organization (WHO) as the absence of circulating wild virus, manifested as no cases in a defined geographic area for a period of at least three years after cessation of vaccination.

In 1988, the World Health Assembly resolved to eradicate polio globally by the year 2000. The eradication of poliovirus requires zero cases of poliomyelitis due to wild poliovirus for three years, high quality disease surveillance which meets international standards, and demonstrated capacity of the countries to detect, report and respond to imported polio cases, including those caused by vaccine-derived polioviruses. In addition, laboratory stocks need to be contained and safe management of polio vaccine manufacturing sites assured before the world can be certified as polio-free [2]. Eradication by 2000 was not achieved, but in 2009,

polio remained endemic in only four countries. The eradication of polio is now seen as an achievable goal within the next four or five years [3], although some commentators question even this timeline.

More recently, goals for progress towards measles elimination, rather than eradication, have been proposed by a number of WHO regions, including the European and Western Pacific Regions. Member states of the Western Pacific Region, which include Australia, have resolved to eliminate measles by 2012 [4]. The European region aims to eliminate measles by 2010 [5]. Elimination is defined as the sustained interruption of transmission of endemic virus within a defined geographic region. Sustained endemic transmission is defined as an outbreak of more than 100 cases or ongoing transmission with a measles genotype of identical sequence for more than three months [6]. Elimination does not imply that there is no virus within the defined region (this is eradication), but that the *transmission of endemic virus has been eliminated* [6].

We aim to review the criteria used to define polio eradication and measles elimination in the Australian, European and other international context and discuss alternatives to the criteria for the documentation of the elimination of measles.

Australia and polio

As a member state of the Western Pacific Region, Australia was declared free of circulating endemic poliovirus only in October 2000 [7], although the last case of endemic poliovirus infection probably occurred around 30 years earlier [8]. The cornerstone of the documentation of polio-free status is surveillance of patients presenting with acute flaccid paralysis (AFP), the most common clinical presentation of acute poliovirus infection, although such cases represent only between one in 100 and one in 1,000 cases of infection [9].

The WHO criteria for adequate AFP surveillance are

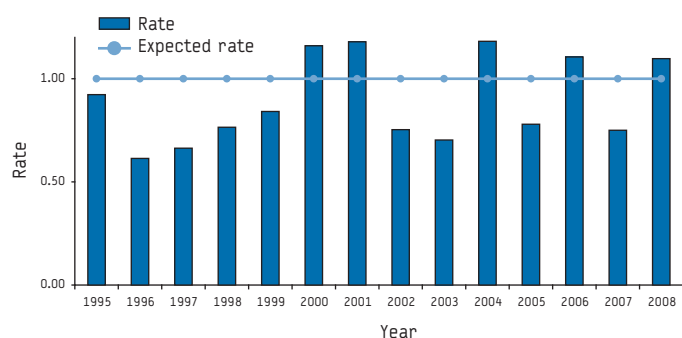
- An annual notification rate of one case presenting with acute flaccid paralysis per 100,000 population aged under 15 years,
- Collection of two stool samples 24 hours apart within 14 days of symptom onset from 80% of notified cases,

- Testing of stool samples in a WHO-accredited laboratory to exclude wild poliovirus as the cause of the patient's symptoms [9].

Although countries where polio had been endemic in the recent past have met these criteria, Australia has consistently failed to do

FIGURE

Acute flaccid paralysis notification rate per 100,000 population under 15 years of age, Australia 1995-2008



The WHO performance indicator expected rate is >1 notification of AFP per 100,000 population aged <15 years.

so. Of the 14 years that AFP surveillance has been undertaken in Australia, the targets for case ascertainment have been achieved in only five years (Figure) and the criteria for stool collection have never been met [10].

We have previously shown, at least for the state of Victoria and by inference for other Australian states, that it was not a lack of AFP cases that led to notification rates below the WHO target, but incomplete notification of cases [11]. Despite not meeting the WHO AFP surveillance criteria for the maintenance of the documentation of polio-free status, Australia, as a member state of the polio-free Western Pacific Region, is nonetheless acknowledged to have no circulating wild poliovirus.

Australia and measles

We have previously reviewed the body of evidence to demonstrate that Australia has eliminated the transmission of endemic measles [12]. Although we acknowledged that measles virus was still detected in Australia, we argued that the transmission of endemic measles virus has been eliminated, based on criteria we compiled using the evidence for Australia [12]:

- Absence of an endemic genotype since 1999,
- High proportion of cases imported or linked to an imported case since 1999,
- Containment of outbreaks without the re-establishment of a specific genotype since 1999,

TABLE 1

Australia's documentation of measles elimination compared with the criteria proposed by the WHO Western Pacific Regional Office, September 2007

Western Pacific Regional Office criterion for progress towards measles elimination	Criterion status in Australia
1. Confirmed measles cases <1 per million	Met in 2005 and 2007; not met in 2006 or 2008
2. Reported suspected measles cases >2 per 100,000	Not available at a national level; met in the state of Victoria since 1999
3. At least 80% of districts reporting >1 per 100,00 suspected cases	Data not collected at a national level
4. At least 80% of cases investigated within 48 hours	Data not available at a national level
5. At least 80% of cases with adequate blood samples collected	Data not available at a national level
6. At least 80% of cases with laboratory results within seven days	Data not available at a national level
7. At least 80% of clusters with samples for virus isolation	Data not available at a national level
8. Two-dose MCV coverage >95%	MCV1 >95% and MCV2 >90%
9. At least 80% of clusters with <10 cases	Data not available at a national level
10. Absence of endemic measles virus	No endemic measles virus since 1999

MCV: measles-containing vaccine; WHO: World Health Organization. Adapted from Heywood et al. [12].

TABLE 2

Alternative criteria for the documentation of measles elimination

Criterion	Justification
The absence of an endemic measles genotype for at least 12 months	Based on the criterion by which England and Wales declared the re-establishment of endemic viral transmission [18].
One dose MCV coverage >95% with the opportunity for a second dose.	One dose of MCV administered at the age of 12 months with coverage >95% was modelled to be more likely to maintain elimination status than a two-dose regime [19]. The failure to maintain high measles vaccine coverage led to measles becoming again endemic in England and Wales [18].

MCV: measles-containing vaccine.

- Maintenance of an effective reproductive number for measles <1 since 1999,
- Serological evidence of population immunity >90% since 2002,
- Consistently high two-dose vaccination coverage since 2004: >95% for the first dose of measles-containing vaccine (MCV) and >90% for the second dose of MCV,
- <1 notified confirmed endemic case per million population since 2005.

We examined Australia's ability to meet the criteria proposed by the Western Pacific Regional Office (WPRO) in 2007 for the documentation of progress towards measles elimination in member states of the Western Pacific Region (Table 1) [12,13].

The first WPRO criterion requires a national incidence of less than one confirmed measles case per million population. A confirmed case includes laboratory-confirmed cases, cases epidemiologically linked to a laboratory-confirmed case, or clinically confirmed cases; imported cases are excluded. In Australia, national surveillance data are not adequate to demonstrate the proportion of cases that are imported. In both 2005 and 2007, less than one case per million was reported in Australia, inclusive of imported cases. However, an importation leading to a widespread outbreak in 2006 resulted in a notification rate exceeding six cases per million population. Cases in 2008 also exceeded one case per million population. We are unable to quantify the number of confirmed measles cases in 2006 and 2008 that were not imported or directly related to importation [14].

In the first quarter of 2009, 78 cases of measles were notified in Australia, of which 17 were related to importation [15]. Large outbreaks occurred in Queensland and Victoria and smaller outbreaks occurred in other states. In the three months from January to March alone, the number of indigenous cases exceeded an annual notification rate of one per million inhabitants. However, extensive case follow-up and genotyping confirmed that the outbreaks were due to several different genotypes (D4, D8, D9 and H1) and that no one genotype has been circulating for more than 12 months.

The next six WPRO criteria relate to setting surveillance standards for suspected case investigation. Australia is unable to meet any of these criteria (Table 2). The final three criteria refer to vaccine coverage ($\geq 95\%$ two-dose MCV coverage), proving that 80% of outbreaks have fewer than 10 cases and demonstrating the absence of an endemic measles genotype. Australia meets only the third of these criteria. However, in addition to the WPRO criteria, Australia has demonstrated a measles immunity exceeding 90% in the population in serological surveys [12], and a number of disease modelling studies have consistently estimated that the reproductive number for measles was less than one in a number of studies from Australia, indicating that endemic measles transmission cannot be sustained [12].

Measles elimination in other countries

In order of the year of declaration, nine countries – Finland, Cuba, England and Wales, Brazil, Mexico, Canada, the United States (US), South Korea and Australia – have publicly declared measles elimination using a variety of criteria (listed in Table 2 of the paper by Heywood *et al.* [12]). However, unlike the other countries in this list, the Australian government has not formally ratified the declaration of measles elimination in Australia. The mode and median number of the 10 WPRO criteria that these countries satisfied was two (range: one to eight). South Korea,

which satisfied eight of the 10 criteria, and Australia, which satisfied only two, are the only two nations in the Western Pacific Region whose declaration might be constrained by WPRO criteria. Finland, which has remained measles-free for 25 years, reports only the two criteria of low incidence and high vaccine coverage [16].

It is clear that disease elimination cannot be declared in the absence of high quality laboratory-enhanced surveillance. Reflecting this, the WPRO criteria for progress towards measles elimination include a number of specific laboratory indicators for high quality surveillance. In countries such as England and Wales, the US and Australia, specific WHO performance indicators for surveillance are difficult to satisfy. These countries were approaching measles elimination prior to the publication of the WHO elimination criteria, and development of national surveillance systems preceded the smallpox and polio eradication programmes. Collating and summarising surveillance data from different state and local sources at a national level is often difficult. Some developed countries such as the US, did not attempt to justify their polio-free status through AFP surveillance [2]. Surveillance systems in these countries were established outside the WHO framework, and do not have routine mechanisms to capture the surveillance process data specified by the WHO and reflected in the WPRO guidelines for the documentation of the eradication of polio or the elimination of measles. England and Wales declared measles elimination in 2003 prior to the establishment of formal elimination criteria [17]. The laboratory-enhanced measles surveillance system of England and Wales does not meet all the surveillance benchmarks specified by WPRO criteria. Despite this, the system rapidly detected the re-establishment of endemic measles in England and Wales in 2008 [18]. Furthermore, the experience of England and Wales demonstrates the critical fact that elimination is an ongoing task. While wild virus is circulating elsewhere, vaccine coverage needs to remain high to prevent the re-establishment of sustained transmission of measles virus.

Reviewing the evidence which England and Wales used to declare elimination before acknowledging the re-establishment of endemic measles transmission illustrates the relative importance of elimination criteria [17,18]. Measles elimination was declared in England and Wales using the following evidence [17], with the relevant WPRO criteria in brackets:

- MCV1 coverage of over 90% until 1998 (WPRO criterion: two-dose coverage at least 95%),
- Average number of measles cases of 1.8 per million inhabitants per year 1995-2001 (WPRO criterion: <1/million/year),
- Small number of large clusters, four clusters with 10-24 cases and four clusters with 25 or more cases (WPRO criterion: $\geq 80\%$ of outbreaks or transmission foci with <10 cases),
- 23% of sporadic cases and 43% of clusters linked to a known imported case (no specified WPRO criterion),
- Suspected measles case identification rate ca. 4.4 per 100,000 per year (WPRO criterion: $>2/100,000$) with 66% tested (WPRO criterion: $>80\%$ tested),
- Wide variety of genotypes with absence of previous endemic genotype (WPRO criterion: no endemic genotype),
- Effective measles reproductive number estimated as 0.5-0.7 by a variety of methods (no specified WPRO criterion).

England and Wales, as part of the WHO European region, are not bound by the WPRO criteria for assessing progress towards measles elimination, but other WHO regions are proposing similar criteria. The WPRO criteria are used here to illustrate the comparison

of evidence for elimination with published criteria for assessing progress towards elimination required in one WHO region. Moreover, it is reasonable to expect that a country that has eliminated measles should satisfy criteria assessing the progress towards elimination. The interim criteria from the WHO Regional Office for Europe that would guide member states in declaring elimination [5] include the following:

- Vaccination coverage: achieving and maintaining at least 95% coverage with MCV1 and MCV2 in all districts and nationally;
- Outbreak size: At least 80% of outbreaks should have less than 10 confirmed measles cases;
- Incidence: Achieving a measles incidence of less than one confirmed case per million population per year, excluding cases confirmed as directly imported;
- Endemic measles virus strain(s): zero cases of measles caused by an endemic strain for at least 12 months, i.e. evidence of the absence of endemic transmission by demonstrating zero cases of measles or zero cases with identical genotype sequence over a period of 12 months.

Guidelines for measles elimination criteria in the European region are currently in late draft form, but a recently published review of progress towards measles elimination in Europe confirms the inclusion of the vaccine coverage and measles incidence criteria [5]. A number of surveillance criteria have also been added to the elimination criteria:

- 100% of member states should report monthly to WHO on measles cases;
- 80% of member states should submit at least 80% of case-based reports each month, and submit at least 80% of reports on time.

When declaring measles elimination in 2003, England and Wales did not satisfy the criteria related to vaccine coverage or

measles incidence. In addition, the surveillance criteria were not reported at the time.

Measles elimination criteria: an alternative approach

The experience of all countries that have eliminated measles highlights a general problem with WHO criteria for progress towards elimination. It is not possible for most countries that have clearly eliminated measles to meet the criteria for progress towards elimination. This is a strange anomaly.

Since elimination criteria are yet to be finalised, we suggest that consideration be given to documenting measles elimination using only two criteria:

- The absence of an endemic measles genotype for at least 12 months,
- One-dose MCV coverage of at least 95% with an opportunity for a second dose.

In conjunction with suitable surveillance standards, these criteria could also be used for assessing progress towards elimination. Justification for these criteria is presented in Table 2.

Table 3 evaluates the two proposed alternative criteria for measles elimination against evidence presented by the nine countries declaring elimination. All countries reported on measles vaccine coverage targets and all except England and Wales satisfied this criterion. Only Finland and Mexico did not provide evidence of the absence of circulating genotypes, but would without doubt be able to report on these criteria on an annual basis.

Although not absolutely necessary, these criteria could be supported by the demonstration of a reproductive number of less than one for measles and the estimation of at least 90% population immunity. While low measles notification rates are important, we believe that a number of confirmed cases under one per million is

TABLE 3

Assessment of alternative criteria for measles elimination by countries declaring measles elimination

Country declaring measles elimination and year of declaration	Alternative elimination criteria	
	Absence of an endemic measles genotype for at least 12 months	One-dose MCV* coverage of at least 95% plus opportunity for second dose
Finland, 1994	Not reported	>97% two-dose coverage
Cuba, 1998	Reported absence of circulating virus	One-dose coverage 98% with catch-up campaigns
England and Wales, 2003	Variety of circulating genotypes confirmed	MCV1 coverage >90%; MCV2 introduced in 1996
Brazil, 2003	No endemic genotype	>95% two-dose coverage since 1997
Mexico, 2004	Not reported	>95% coverage at age 1-6 years since 1996; >97% coverage at age 6-10 years since 1999
United States, 2004	No endemic genotype	>90% coverage at age 19-35 months; 98% coverage at school entry; >92% of school children immune
Canada, 2004	No endemic genotype since 1998	MCV1 coverage >95%; MCV2 introduced in 1996
Republic of Korea, 2006	No endemic genotype	>95% two-dose coverage; 93% of school children immune
Australia, 2008 (declaration not endorsed by national authority)	No endemic genotype since 1999	MCV1 coverage >95% MCV2 coverage >90%

MCV: measles-containing vaccine.
Adapted from Heywood et al. [12].

not a necessary requirement for elimination to be declared, because of residual susceptibility in young adults documented in a number of countries [20-22] and because there is an increased risk of transmission within susceptible groups that may have religious or other objections to vaccination. It is, however, necessary to demonstrate that an importation of a specific measles genotype into a susceptible subgroup does not result in transmission of that measles genotype in the wider population over a period of more than 12 months, as has occurred in England and Wales. In Australia, 22 confirmed cases notified in a year will exceed the threshold of one confirmed case per million. Small outbreaks among young adults resulting from importations have regularly resulted in higher numbers of annual cases during the period when there was no endemic measles genotype [23]. These importations have not led to the re-establishment of endemic measles transmission in Australia.

Surveillance criteria are important for the documentation of the elimination of endemic measles transmission. Using the proposed alternative elimination criteria, it is only critical that cases and clusters are identified and that a suitable specimen is sent to a WHO-accredited laboratory for genotype identification. As already recommended by WHO, all suspected cases of measles should have a serum sample sent to an accredited laboratory for testing measles IgM by a commercial enzyme-linked immunosorbent assay. We further suggest that a suitable specimen for genotyping, preferably a nose/throat swab [24], should be collected from all serologically confirmed cases that are not part of clusters and from a minimum of two cases at the start and two cases at the end of any identified cluster. Placing the emphasis on identifying the absence of an endemic genotype over a 12-month period requires efforts to be focussed on genotype capture, rather than performing individual serological tests within a nominated time. If using the alternative criteria suggested here, it would not be necessary to confirm a case within seven days as is specified in the WPRO criteria. However it would still be necessary to collect a specimen suitable for genotype identification not more than two weeks after rash onset [24]. When countries do not have a national laboratory that is able to perform measles genotyping, appropriate specimens could be referred to a regional laboratory for genotyping, with all results reported to the WHO in order to monitor international transmission patterns [25].

The WPRO criteria related to outbreaks (criteria 7 and 9, Table 1) can be subsumed into the single criterion of complete absence of endemic measles genotype (criterion 10). While it may be difficult to find all cases that are not part of a cluster, all countries with an active surveillance system should be able to recognise clusters. In Finland, where measles has been eliminated for 25 years, it is noted that 'some sporadic imported cases may have escaped our attention, but clusters of secondary cases would almost certainly have been detected had they occurred' [16].

Conclusions

Despite best intentions and a considerable amount of effort, Australia has not been able to maintain WHO AFP surveillance criteria for the documentation of polio eradication [26]. However, it is accepted that Australia is free of circulating wild poliovirus, the single most important criterion for eradication. We have provided evidence to support our claim that Australia has eliminated measles transmission, but cannot satisfy the criteria for documenting progress towards elimination promulgated by the WHO WPRO. Neither has this evidence resulted in a formal declaration of measles elimination in Australia. Incidentally, we note that the WHO position on the status of measles elimination in Australia is not completely clear. *The WHO document Global measles and*

rubella laboratory network – update published in 2005 [27], prior to presentation of evidence for measles elimination in Australia, acknowledged measles elimination in Australia. Map 1 in that document states that 'Measles has been eliminated from the Western Hemisphere and Australia' [emphasis added] and did not include any countries from the western hemisphere or Australia on the map. The document also noted that multiple genotypes had been detected from imported cases [27]. However, a more recent WHO publication suggests that the Republic of Korea is the first and only country in the Western Pacific Region to have achieved elimination [28].

We believe it is appropriate to separate criteria for the documentation of measles elimination from surveillance performance and laboratory accreditation. We suggest it may be worth considering only two criteria for the documentation of measles elimination with an annual review of elimination status. Finally we suggest there are four principles that should guide the development of formal documentation of measles elimination:

1. Elimination criteria should be able to be met by countries that have eliminated measles;
2. Quality surveillance criteria are necessary but not sufficient to define elimination;
3. Quality surveillance criteria should be guided by elimination criteria, not the other way around;
4. Without good reason, elimination criteria should not differ by WHO region.

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