

Measles elimination: progress, challenges and implications for rubella control

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Measles and rubella are major vaccine-preventable causes of child mortality and disability. They have been eliminated from the Americas and some other regions have also come close to elimination. In this paper, we review regional progress toward measles and rubella control/elimination goals, describe the recent epidemiology of these infections and discuss challenges to achieving the goals. Globally, measles vaccination is estimated to prevent nearly 2 million deaths each year. Despite this remarkable progress, large measles outbreaks have occurred in recent years, often involving older persons who were not vaccinated in earlier years. Such an occurrence would be particularly damaging for rubella control programmes as it could lead to peaks in congenital rubella syndrome. Challenges to achieving and sustaining high vaccination coverage include civil conflict, weak health systems, geographic, cultural and economic barriers to reaching certain population groups and inadequate monitoring and use of data for action. Countries and regions aiming to eliminate measles and control rubella urgently need to improve the implementation and monitoring of both routine and mass vaccination campaign strategies.

KEYWORDS: congenital rubella syndrome • epidemiology • measles • measles elimination • rubella • rubella elimination • vaccination

Before measles vaccine was introduced, measles was one of the most severe childhood illnesses leading to at least 2 million deaths per year [1,2], and it was a major cause of blindness in low income countries [3]. The acute illness is characterized by fever and rash with coryza, cough or conjunctivitis. Measles virus is a potent immune modulator and common complications that often require hospital care include pneumonia, diarrhea and dysentery. Clinical, virological and pathological features are reviewed elsewhere [4]. Since licensure of live attenuated measles vaccine 50 years ago, estimated global measles mortality has fallen to <7% of its pre-vaccination levels [5]. Elimination of measles is biologically feasible [6], and programmatic feasibility has been demonstrated in the Americas, where the last indigenous case occurred in November 2002 [7].

Rubella infection is another cause of fever and rash in children which is usually mild when acquired postnatally [8] but may result in fetal loss or severe disability after primary infection in the first trimester of pregnancy [8–10]. Estimates of the global burden of congenital rubella syndrome (CRS) derive from models of the risk of infection

in pregnancy, using serological data on the age-specific prevalence of rubella antibodies. Based on literature reviewed in 1996, approximately 110,000 cases of CRS (uncertainty bounds ranging from ~14,000–308,000) were estimated to occur each year in developing countries which did not vaccinate against rubella [11], with highest numbers predicted in Africa and south east Asia. A review of data up to 2010 resulted in estimates of a similar order of magnitude [12].

Measles and rubella vaccines are live, attenuated viral vaccines [4,13] which are most effective when administered after maternal antibody is lost (this passively acquired antibody declines exponentially from about age 2–3 months onward and is undetectable in most infants by 9–12 months of age). They are available as separate or combined vaccines and administered by subcutaneous or intramuscular injection, although alternative routes of vaccination such as aerosol or intranasal have shown promise [13–18]. Sabin and colleagues pioneered the use of aerosol measles vaccines in Mexico in the 1980s [19]. Subsequently, trials in South Africa and Mexico showed that sero-responses and persistence of

boosted antibody levels were better following measles vaccination of school children by aerosol than subcutaneous vaccination [20–22] and some studies in infants have also shown good responses [14,17,18,23]. Aerosol administration of dry-powder measles vaccine is also being evaluated [24]. Cost-effectiveness analyses [24] and stakeholder opinion [25] suggest that the aerosol route could be efficient and help programs to achieve measles control goals. A recent pivotal Phase II/III trial conducted in India under the auspices of the WHO measles aerosol project, however, showed that following vaccination at age 9 months, the per-protocol seropositivity in the aerosol arm was 85.4% (95% CI: 82.5–87.9%) as compared to 94.6% (95% CI: 92.7–96.1%) in the subcutaneous arm, with the difference in seropositivity and the upper limit of the confidence interval both being greater than the non-inferiority margin of 5% defined in the study protocol. SAGE members concluded that the tested aerosol vaccine may not be suitable for primary vaccination of infants against measles but recommended that further research on measles-rubella (MR) aerosol be conducted [26].

Combination MR vaccines used in industrialized countries usually also include mumps vaccine, but the burden of mumps infection is poorly described in low income countries. Based on mortality and disease burden, WHO considers measles control and the prevention of CRS to be higher priorities than the control of mumps [27]. We therefore do not discuss mumps in this article.

A single dose of measles-containing vaccine (MCV1) induces antibody responses among 85–90% of infants at age 9 months and over 95% of infants vaccinated at age 11 months or above (reviewed in [28]). Field studies show median vaccine effectiveness (VE) of 84.0% (interquartile range [IQR]: 72.0–95.0%) and 92.5% (IQR: 84.8–97.0%) after vaccination at 9–11 and >12 months, respectively [29]. Infants may respond to vaccine at an earlier age, once most mothers have vaccine-induced rather than natural immunity, since the former results in lower antibody levels being transferred *in utero* [30]. In low transmission settings, it is feasible to vaccinate at the age of 15 months when effectiveness is higher [31,32]. By contrast, the WHO recommends vaccination at age 9 months in countries with ongoing transmission in which the risk of measles mortality among infants remains high [28,33,34]. To eliminate measles, a second dose of vaccine is recommended [33]; field studies show median VE for two doses of 94.1% (IQR: 88.3–98.3%) compared with no vaccination [29]. Responses to measles vaccine are lower in HIV-infected children [35–37], but their high mortality has reduced any resulting effect on population immunity [38,39]. The potential role of revaccination of HIV-infected children on antiretroviral therapy in low-income countries is under evaluation [40]. Rubella-containing vaccines (RCV) currently distributed in most countries contain the RA 27/3 strain prepared in human diploid cell culture [13]. Seroconversion rates of 94–98% have been reported after vaccination at the age of 9 months or older (reviewed in [41] and [42]).

Immunity is long-lasting among persons who develop a primary immune response to measles and rubella vaccines. Antibody levels wane after vaccination [43], but are boosted rapidly on exposure to infection which may be subclinical or associated with mild illness. For rubella, such re-infection of pregnant women has very low

risk of transmission to the fetus [44,45]. Antibody levels are boosted after revaccination of persons whose antibody levels have waned but fall again quickly [28].

Rubella vaccination is cost effective in industrialized and middle-income countries [46]. In 2010, however, over two-thirds of the global birth cohort lived in countries that did not include rubella vaccination in their national immunization programme, due to a lack of empirical data on disease burden (only a minority of cases are seen at medical facilities having the capacity to diagnose CRS [47,48]), the increased cost of combined MR vaccine compared to single-antigen measles vaccine, and concerns about potential increases in CRS if adequate coverage of rubella vaccination could not be assured and sustained [49].

As interest in measles elimination increases [50], there are calls to include rubella in measles control and elimination activities [51–53]. The GAVI alliance, a public-private partnership of charitable organizations, national governments and international organizations such as WHO and UNICEF, has supported the introduction of new vaccines in low-income countries for more than a decade and has also contributed funding for measles campaigns. There are currently 56 GAVI-eligible countries, although not all are available for all types of support [201]. Recently, GAVI has made funding available for MR catch-up campaigns in countries that can achieve 80% immunization coverage (via routine, or routine and campaigns); and can finance the introduction of rubella vaccine into their routine program immediately following the catch-up campaign [54]. GAVI will also fund second dose measles vaccine (MCV2) costs in eligible countries, though not the rubella component. In 2012, WHO and partners published the first global combined strategic plan for measles and rubella control and elimination [202]. In this paper, we briefly review some principles of measles and rubella vaccination and describe progress toward measles control and elimination and current challenges in different WHO regions. We then discuss the implications of the experience with measles vaccination programmes for rubella control and elimination.

Principles of measles & rubella control and elimination

The crucial factor determining the spread of infections transmitted person-to-person, such as measles and rubella, is the number of secondary cases caused by each infectious person [55]. The basic reproduction number, R_0 , is a measure of the transmissibility of an infection within a population, defined as the average number of secondary infections produced by a typical infective person in a totally susceptible population. It depends on the characteristics of the infectious agent (e.g., infectivity and duration of infectiousness) and of the population (e.g., population density and social mixing patterns). The R_0 of measles has been estimated as 14–18 in England and Wales, 12.5 in North America, and 10 in Niger [56]. The R_0 of rubella is generally lower (4–7) [57], however in high density settings (e.g., in Addis Ababa, Ethiopia) R_0 values as high as 11.8 have been estimated [58].

In the context of a vaccination programme, the effective reproduction number, R , is key for predicting and preventing outbreaks [55].

R is the average number of infectious individuals resulting from a single infective introduced into the population, given the population mix of vaccine-acquired and naturally acquired immunity at that time [59], and decreases as population immunity increases. If R is below 1, then the average case will give rise to less than 1 case and transmission will eventually cease. Consequently, elimination programmes aim to keep R below 1. Births and immigration increase population susceptibility (and hence R), while vaccination slows the rate of this increase. High vaccine coverage induces a period of low incidence termed the ‘honeymoon period’ [60] during which cohorts of susceptible children who were not immunized in the early years of the programme can reach older ages before being exposed. Susceptible persons gradually accumulate until ‘post-honeymoon’ outbreaks occur [61]. Although the proportion of cases in older children increases after vaccination, the absolute number of such cases may still fall because of the overall reduction in incidence. For rubella, it is crucial to achieve and sustain adequate coverage to avoid an increased incidence in adults, as discussed later in this paper.

Definitions of measles goals & targets

Measles elimination is defined as the absence of endemic measles transmission in a defined geographical area (e.g., region) for ≥ 12 months in the presence of a well performing surveillance system [62]. As of 2011, the WHO Region of the Americas had eliminated measles, and four of the remaining five regions had adopted a measles-elimination goal; the Americas and Europe included a rubella elimination goal. Standardized definitions and indicators have been developed to monitor progress towards elimination, including clinical, laboratory and epidemiological definitions which lead to 12 possible categories for classifying measles cases [62]. Similar indicators are likely to be developed and used for rubella elimination.

Progress in measles control & elimination

Progress in the Americas

The USA established its first measles elimination goal in 1966 [63]. Measles elimination appeared close in 1983, but subsequently outbreaks occurred among highly vaccinated school-age populations [64], leading to expensive outbreak control activities [65,66]. In 1989, a two-dose measles vaccination strategy was recommended [67]. From 1989–1991 there was a large measles resurgence in the USA (rubella and CRS also increased at that time) [68]. Almost one half of all measles cases and 90% of deaths occurred in unvaccinated preschool children [65,69,70]. Control required immense efforts to deliver the first dose on time [71], demonstrating the critical importance of achieving and sustaining high and timely routine coverage.

The goal of eliminating measles from the Americas was set in 1994, the year when the region was declared polio-free [7]. In Latin America and the Caribbean, routine services aimed to ‘keep-up’ high population immunity by vaccinating over 90% of each birth cohort and increasing the age for first dose to 12 months [53]. In the early 1990’s ‘catch-up’ campaigns, usually targeting children aged 9 months to 15 years were conducted, aiming to immunize all susceptible children who had accumulated over the previous

years of routine vaccination. After approximately 4 years, ‘follow-up’ campaigns were done among children aged 1–4 years, to sustain high population immunity. Both types of campaigns included community-based ‘mop-up’ activities in areas where monitoring showed that campaign coverage was below 95% [7]. Finally, once the goal of rubella elimination was added in 2003 [53], ‘speed up’ campaigns were done among adults (of both sexes in all but three countries) up to age 40 years, to quickly reduce transmission. Although rubella was the primary motivator for the speed-up campaigns, all countries used combined MR or MMR vaccines [53]. The age range for rubella vaccination campaigns was wider than that for measles as the lower R_0 of rubella meant that a larger number of adults had been susceptible to rubella than for measles. Programmes were guided by close monitoring of progress including routine coverage, campaign coverage, case-based disease surveillance and virus surveillance [7,53]. The last endemic case of measles was documented in November 2002, and that of rubella in 2009 [53].

Progress in other regions

The success of measles elimination in the Americas encouraged the adoption of measles elimination goals in the eastern Mediterranean (EMR, 1997), European (EUR, 1998), western Pacific (WPR, 2005) and African (AFR, 2011) regions, with varying target dates for elimination. The south east Asia region (SEAR) retains a measles mortality reduction goal, but elimination is under discussion.

By 2000, through global use of at least one routine dose of MCV, estimated measles mortality had fallen about 75% to 535,300 deaths (95% CI: 347,200–976,400). This fell to 139,300 (95% CI: 71,200–447,800) in 2010 through further increases in routine MCV1 coverage and campaigns [5]. The Measles Initiative, launched in 2001 with a goal of reducing measles mortality, reports that its assistance has led to vaccination of over a billion children in catch-up and follow-up campaigns in 47 GAVI-eligible countries at an average cost of just under one dollar per dose administered [203]. Reported measles incidence reached all-time lows in the European region in 2006, when cases were less than 1% of those reported in 1980, and in EMR in 2010, when cases were less than 3% of those reported in 1980 [204]. Despite this encouraging progress, no other regions have shown the uniformly high and sustained impact of the Americas on reported measles incidence (FIGURE 1).

In AFR, measles transmission may have been interrupted briefly in southern Africa [72] and Uganda [73], but since 2009 outbreaks have occurred across the region [74]. Large outbreaks were reported in the Democratic Republic of Congo (DRC: 133,802 cases, 2011), Malawi (118,712 cases, 2010), Burkina Faso (57,489 cases, 2009), Zambia (28,989 cases, 2010–2011) and Nigeria (18,843 cases, 2011). Of these, Malawi, Burkina Faso and Zambia reported both high routine coverage and regular measles vaccination campaigns. Vaccination and long lulls between outbreaks increase the average age of infections [75]. Between 2002 and 2009, the median age for a reported measles case was 36 months in countries with MCV1 coverage of less than 50%, vs

49 months in those with MCV1 coverage of 75% or greater [76]. In Burkina Faso, Malawi and Zambia there were large numbers of cases among teenagers and adults, and the majority of cases in Malawi's 2010 outbreak were over 5 years of age [77].

Nine countries in EMR reported measles incidence of <one case per million persons in the presence of a sensitive and well-functioning nationwide surveillance system in 2011 [78]. In 2011, however, a major resurgence of measles occurred in conflict-affected and poorer countries with 35,923 cases reported to WHO—more than in 1997. Of these, almost half were from Somalia, and between 2600–5600 from each of Afghanistan, Pakistan, the Sudan and Yemen [204]. In Somalia, low MCV coverage in areas where immunization services could not be provided for nearly 2 years led to a massive measles outbreak, primarily among children aged <5 years. Population movements led to measles virus transmission among refugees, and outbreaks in Ethiopia and Kenya [79].

In Europe, Finland implemented a two dose schedule early in the programme and is the only country to have sustained measles elimination [80]. Catch-up campaigns, some going up to age 40 years, were implemented mainly in central and eastern Europe (CEE) and the newly independent states (NIS). From 2004–2006 outbreaks in CEE and NIS involved a high proportion of older and previously vaccinated persons [81] whereas most transmission since then has been in unvaccinated persons. From 2009–2011, large outbreaks

occurred in western Europe, as well as Bulgaria and Ukraine, and outbreaks continue to occur in several countries at the time of writing. These often began among groups having low coverage such as Roma and Sinti communities, Irish Traveller communities, anthroposophic groups and ultra-orthodox Jewish communities [82–86] and spread to the wider population and to other countries [86–89]. The majority of cases were among the unimmunized population, in infants younger than one year, adolescents and young adults. Low vaccine effectiveness, possibly related to cold chain failures and/or use of a more thermo-labile vaccine, was reported in Ukraine [90] and nosocomial transmission contributed in France and elsewhere [86].

SEAR has implemented accelerated measles control strategies. India was the last country to offer a second opportunity for measles vaccination [202]. A routine second dose has now been implemented in states with reported MCV1 coverage $\geq 80\%$ [91]. In states with reported MCV1 coverage <80%, catch-up campaigns reportedly reached almost 40 million children aged 9 months to 10 years (86–89% of target) in 2010–2011, with the final phase of the campaigns scheduled for completion by April 2013. The two other large countries in the region, Bangladesh and Indonesia, have much higher routine coverage but gaps remain, particularly in Indonesia.

WPR reported by late 2012 that the region was approaching interruption of endemic measles transmission [91]. China has had 99% MCV1 WHO-UNICEF estimates of coverage (WUENIC)

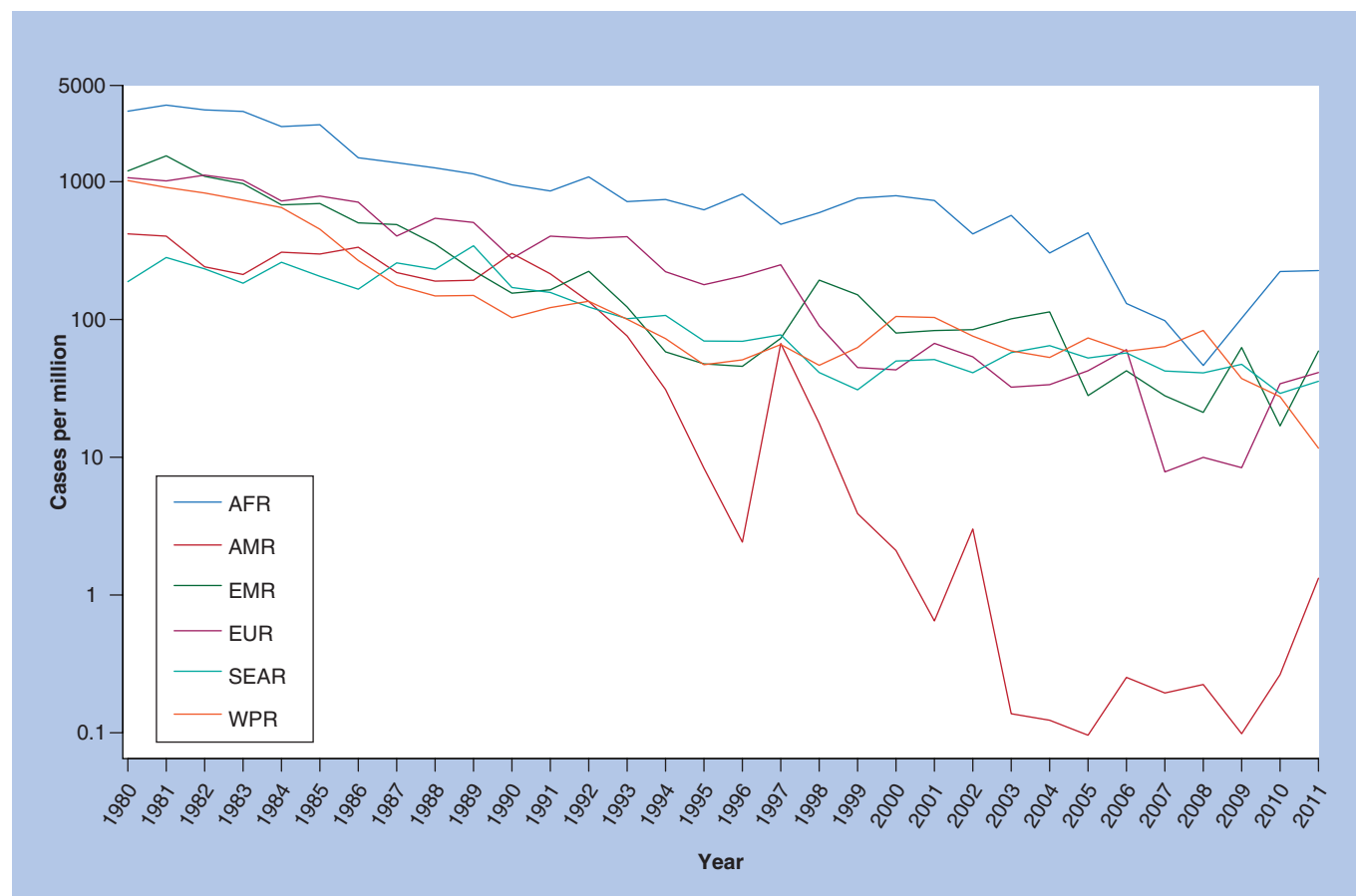


Figure 1. Reported measles incidence rates per million population by WHO region per year, 1980–2011.

AFR: African; AMR: Americas; EMR: Eastern Mediterranean; EUR: European; SEAR: South east Asia region; WPR: Western Pacific.

since 2010. It conducted subnational campaigns from 2003–2009 and a massive national catch-up campaign in 2010, reporting 95% coverage. China reported just under 10,000 cases to WHO in 2011 compared to 38000–131,000 cases per year in the previous decade and over a million cases in 1980 and 1981 [204]. Malaysia has relied chiefly on high routine coverage to control measles but regional heterogeneity in coverage, and delays in delivery of the second dose until age 7 years resulted in an outbreak in 2011 (FIGURE 2F) chiefly affecting <7 year olds. As elsewhere, an increased proportion of cases in WPR now occur among young infants and adults [92,93]. A 2008–2009 outbreak in Vietnam started among unvaccinated university students [92]. Vietnam conducted a campaign targeting 7–20 year olds in key provinces in 2008, and another in 2010 targeting 1–5-year-olds, and case numbers remain very low in 2012 [204]. Laos also implemented wide age range campaigns targeted at 9 month to 19 year olds in 2011. Measles genotyping indicates considerable measles introductions both between countries in the region, but also from outside [93].

The occurrence of outbreaks in countries after years of low incidence is due to the accumulation of susceptible persons. This is attributed to various challenges facing vaccination programmes, as illustrated below.

Current challenges to measles elimination

Inadequate routine coverage

When catch-up campaigns were conducted in the Americas about 20 years ago, WUENIC showed median routine MCV1 coverage of about 84–86% [205]. Impact was sustained by further increasing coverage to over 90% since 1997, with only Haiti having persistently low coverage since then. By contrast, WUENIC of MCV1 in AFR was only 54% in 2001, and remained far below target at 75% in 2010–2011. In 2011, half the countries in AFR had coverage below 80% (including the three largest countries – Nigeria, Ethiopia and DRC). Only a handful of small countries (Botswana, Cape Verde, Eritrea, Mauritius, Rwanda, Seychelles and Swaziland) sustained coverage above 90% from 2007–2011. Worryingly, routine MCV1 coverage tends to be lowest in countries with high birth rates (FIGURE 3). Over two-thirds of the countries in AFR have birth rates over 40 per 1000 population. This combination of low MCV1 coverage and a rapidly growing population provide ideal conditions for sustaining measles transmission.

In EMR, just over half the population lives in six countries which have multiple challenges to achieving and sustaining high coverage, including civil conflict, low median income/capita, low female literacy and high birth rates; their median WUENIC MCV1 coverage in 2011 was 73.5%. In the European region, 11–16 countries reported less than 90% nationwide MCV1 coverage each year during 2003–2008. All countries in EUR have a routine two-dose schedule, and 4–12 countries and 3–7 countries reported MCV2 coverage <90 and <80%, respectively; each year in this period 11 or more countries did not report MCV2 coverage [81]. In SEAR, regional coverage increased from 62% in 2001 to 79% in 2011. Here, seven out of 11 countries have sustained coverage over 90% but the two largest countries, India and Indonesia, have yet to reach 90% [205]. In WPR, coverage has been high

since 2005 in most countries, exceptions being some small island populations, Laos (though it has increased greatly here), Papua New Guinea and in the Philippines (where MCV1 coverage was over 90% from 2005–2010 but only 79% in 2011) [205].

At subnational level, low coverage in certain geographic areas or population groups is important in shaping measles epidemiology. In India, substantial diversity in routine vaccination coverage within the country is mirrored by variable age patterns of infection, seasonality and genotypic diversity [94,95]. In Nigeria, coverage in northern states is about half that of southern states and is lower in rural than urban areas [96]. Migrants, travellers [82–86,97], and certain castes, ethnic or religious groups often have lower coverage [98]. The 2009 outbreak in Bulgaria occurred despite estimates of around 95% MCV1 coverage since 1995 and for MCV2 since 2005 [81]. Most cases (97%) were reported from north-eastern Bulgaria, particularly in Roma populations and in persons who had received less than two doses of MCV [99]. Areas affected by conflict and those receiving refugees are also at risk not only of low coverage but of high mortality when outbreaks occur [100,101].

Variable impact of catch-up campaigns

Implementation and monitoring of catch-up campaigns have varied substantially between countries. In southern Africa, reported coverage ranged from 71% (Lesotho) to 114% (Malawi). Elsewhere in AFR most countries reported well over 90% (and often over 100%) coverage in catch-up campaigns but this has generally not been validated. In EMR, most of the nine countries that reported <90% coverage in their catch-up campaign were affected by conflict, however Egypt only achieved 78% coverage in 2001 [102] and later repeated catch-up campaigns. In the European region, unfounded vaccine safety concerns in 2008 contributed to only 50% campaign coverage in Georgia and led to the suspension of the planned campaign in Ukraine [81]. WPR reports that recent campaigns have had considerable impact on measles incidence, for example China in 2010 (despite parts of the migrant populations eluding specific efforts to target them [103]); Cambodia, in 2011; and Japan [93]. Past campaigns in the Philippines had inadequate coverage (indicated by the age profile of incidence observed after the 2007 campaign). A repeat campaign was done in 2011 with extensive rapid coverage assessments.

The impact of catch-up campaigns on reported incidence is often difficult to quantify. At regional level, the lack of synchronisation of catch-up campaigns between countries may have obscured impact (FIGURE 1), since resurgences were beginning in some countries before campaigns had been done in others. At country level, other factors complicate interpretation of trends, as illustrated in (FIGURE 2). In Burkina Faso and Malawi, catch-up campaigns seem to have contributed to lengthening the subsequent inter-epidemic period (FIGURE 2B & E), although it is difficult to disentangle campaign impact from that of concurrent increases in routine coverage in the former. In others, the campaign coincided with, or immediately followed, a large epidemic (FIGURE 2A,C,F&G), and thus low incidence after the campaign reflects a mixture of vaccine-induced and natural immunity. In DRC, catch-up campaigns had no demonstrable impact on reported measles cases (FIGURE 2D).



Figure 2. Country examples of the difficulty in assessing campaign impact through trends in reported measles cases per year. Percentage vaccinated = WUENIC MCV1. Grey shaded areas indicate period before campaigns included in WHO database. Catch-up campaigns covered 9 months–14 years and follow-up campaigns covered 9–59 months except: *catch-up covered 9 months–10 years; **follow-up covered 7–14 years; ***catch-up covered 7–15 years; ****catch-up covered 9 months–13 years.

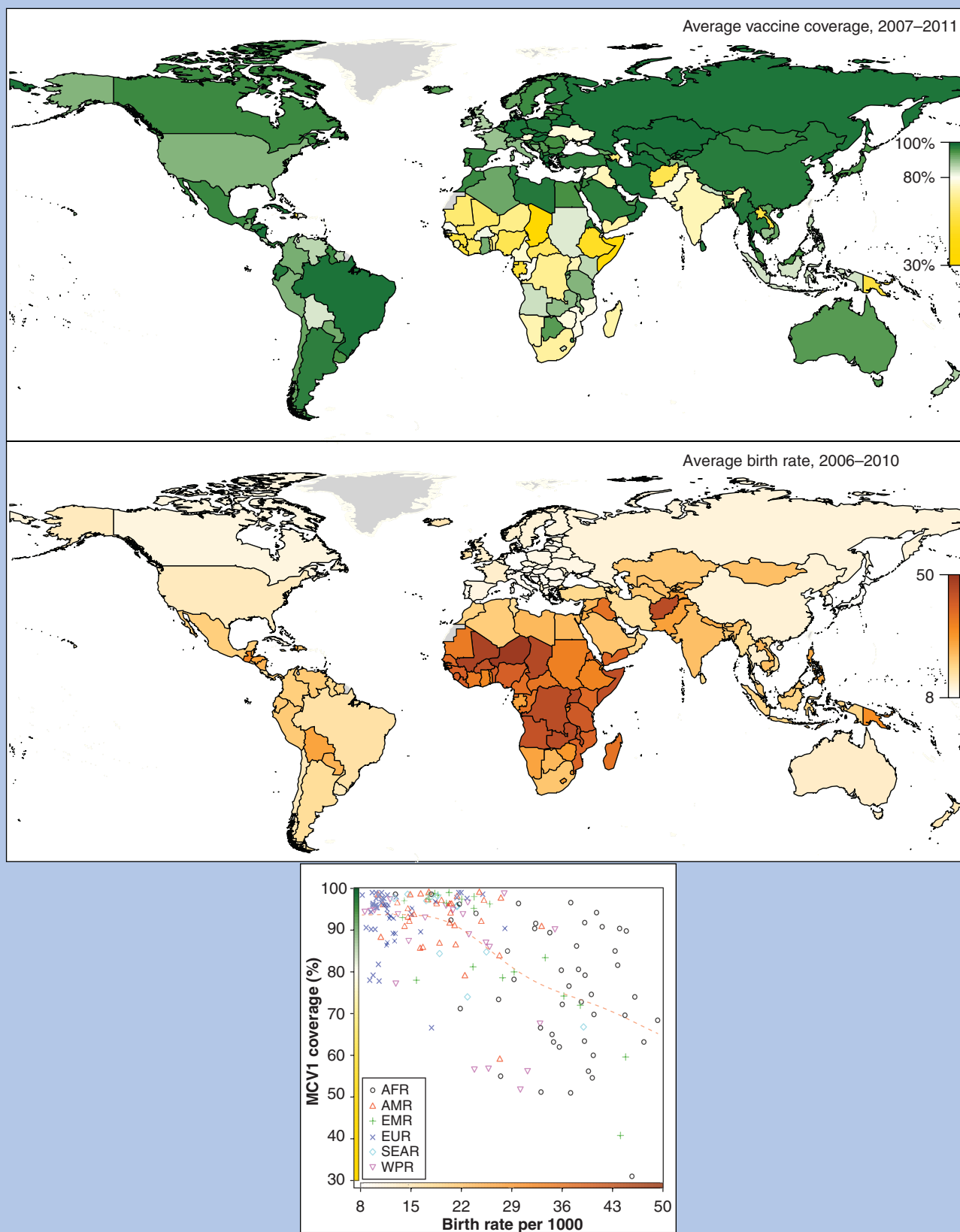


Figure 3. Average birth rates per 1000 population 2006–2010 and WUENIC measles vaccine coverage 2007–2011 by country. AFR: African; AMR: Americas; EMR: Eastern Mediterranean; EUR: European; SEAR: South east Asia region; WPR: Western Pacific.

Suboptimal or delayed implementation of follow-up campaigns

WHO recommends that follow-up campaigns are repeated regularly to sustain high population immunity until >90–95% immunization coverage has been achieved at the national level for both MCV1 and MCV2 for at least 3 consecutive years, and that data on the degree of heterogeneity of coverage among districts and on the epidemiology of measles should be reviewed by a national committee before stopping campaigns [33]. The higher the birth rate and lower the routine coverage, the more frequently campaigns need to be repeated [33,104–106]. Follow-up campaigns have not been adequate to maintain high rates of immunity in many countries, however. Postponement of planned campaigns has contributed to outbreaks, for example Kenya in 2005–2006 [107]. Outbreaks with a large proportion of cases in children <5 years of age that have occurred in countries such as Angola, Nigeria, the Philippines and Zimbabwe within 1–2 years after a follow-up campaign suggest suboptimal implementation of the campaigns [108]. In Botswana, South Africa, Swaziland and Zimbabwe, the outbreaks were partly related to vaccination refusals from some religious groups. Heterogeneous coverage in campaigns is problematic, as it is for routine coverage [96].

Suboptimal monitoring & surveillance

Monitoring of immunization coverage is one of the weakest links in measles control and elimination [109,110]. For example, Uganda reported 85–90% routine MCV1 coverage from 2004–2007, after its 2003 catch-up campaign reportedly reached 99.5% of children aged 9 months to 14 years [111]. A measles resurgence began in 2006, and most confirmed cases were in under 5-year-olds [111]. Problems with reported routine coverage were shown by data quality self-assessments and by a national survey which estimated only 76% MCV coverage of children aged 12–23 months [205]. The 2009 outbreak in Burkina Faso occurred within 2 years of a follow-up campaign which reported 102% coverage and when WUENIC was 90% for routine coverage; administrative reports of coverage have been only 63% for 2010–2011 [205]. Of the 28 countries in AFR with outbreaks from 2009–2010, 15 had implemented a follow-up campaign within 24 months prior

to the outbreak; and all reported ≥90% coverage in their most recent measles campaign [74].

Monitoring of MCV-2 coverage is done less rigorously than that of MCV-1 coverage, and campaign coverage has rarely been validated. Target population (denominator) figures are often projections from old census data and inaccurate [108]. Reports of over 100% coverage of campaigns reflect under-estimates of the target population, vaccination of children outside the target age-group, or inaccurate recording practices. Without reliable coverage figures for all routine doses and campaigns, it is impossible to estimate *R* accurately and thus to plan appropriate and timely action.

As well as the need for accurate coverage data, high-quality surveillance is essential to be able to detect increases in incidence early and respond appropriately [52,62]. WHO proposes identification of at least two cases of non-measles febrile rash per 100,000 population as an indicator of adequate surveillance. Although an increasing number of countries meet this criteria [91], measles is grossly under-reported, with some regions reporting fewer cases than there are estimated measles deaths (TABLE 1). Reporting completeness appears lowest in EMR and SEAR, with little improvement between 2000 and 2010. Insensitive surveillance may be used to evaluate trends if sensitivity remains constant [106] but it is inadequate for planning actions to sustain measles elimination. Surveillance of rubella and CRS is even more limited—even in Europe, Belgium, France and Germany do not have rubella surveillance systems with national coverage.

Serological surveillance is another potentially important but under-utilized tool to indicate problem areas, identify which age groups should be included in campaigns, and evaluate the contribution of campaigns to reducing population susceptibility [112–116]. It contributed to a decision to implement a catch-up measles-mumps-rubella campaign of schoolchildren in England and Wales in 1994 [117], which is believed to have avoided an outbreak [113]. The European region has set age-specific targets for measles antibody prevalence and monitors progress through a co-ordinated European Sero-Epidemiology Network [112,118]. Analysis of data from 1996–2004 showed that seven countries (Belgium, Bulgaria, Cyprus, England and Wales, Ireland, Latvia

Table 1. Ratio of estimated measles deaths to reported measles cases by region, 2010 and 2000.

Region	2010			2000		
	Reported cases [204]	Estimated deaths [5]	Ratio of deaths to cases (%)	Reported cases [204]	Estimated deaths [5]	Ratio of deaths to cases (%)
AFR	186,675	50,000	27.8	520,102	337,000	64.8
AMR	247	<100		1755	<100	
EMR	10,072	10,100	100.3	38,592	48,600	125.9
EUR	30,625	100	0.3	37,421	400	1.07
SEAR	52,529	76,000	144.7	78,558	136,200	173.4
WPR	49,460	3100	6.3	177,052	13,100	7.4
Global	329,608	139,300	42.3	853,480	535,300	62.7

AFR: African; AMF: Americas; EMR: Eastern Mediterranean; EUR: European; SEAR: South east Asia region; WPR: Western Pacific. Adapted with permission from [5], Copyright 2012, with permission from Elsevier.

and Romania) were at risk of epidemics due to low antibody prevalence in children and, in some, in adults [118]. Had these findings been acted on more quickly, some of the recent outbreaks in these countries might have been avoided.

The need for early & effective outbreak response

Until 2009, the WHO-recommended response to measles outbreaks focused on case management rather than outbreak response vaccination (ORV). In 2009, based on epidemiological analysis and evaluations of ORV [119], the recommendations changed to include ORV campaigns when specific criteria are met [206]. ORV campaigns have been conducted in several African countries [77,108,119–121]. The impact of ORV on reducing the likely magnitude or duration of the outbreak depends on how early ORV is implemented in the course of the outbreak, epidemiologic and demographic factors [119] and whether resources allow vaccination of a wide enough age group according to the local epidemiology [77].

Measles outbreak investigations provide an important opportunity to identify problems with a country's measles control activities. The distribution of measles cases by age, vaccination status and location may reveal populations that are missed by routine vaccination and campaigns, reduced vaccine effectiveness, and the accumulation of susceptibility in older age groups [77,122]. Such problems must be addressed to avoid a repeated resurgence of measles which may otherwise follow the post-outbreak honeymoon period.

Implications for rubella control & elimination

To date, rubella control or elimination programmes have mostly been restricted to countries with low or moderate birth rates (FIGURE 4), in which routine infant vaccine coverage levels of 80% or less are predicted to be adequate to interrupt transmission [123]. Two

exceptions are Guatemala (in the Americas which has a regional rubella elimination goal) and Iraq (in EMR). Funding from GAVI is now available for MR catch-up campaigns in eligible countries (which mostly have high birth rates), with the aim of interrupting transmission, following which routine vaccination is expected to sustain low incidence levels and indirectly protect any remaining susceptible adult women [207]. To apply, countries must demonstrate that they can achieve and maintain routine coverage of 80% or greater. WHO advises that countries introducing RCVs implement strategies to vaccinate women of childbearing age [51,124]. This was done in Latin America through campaigns and in North America and Europe through routine adolescent and/or post-partum vaccination, but so far GAVI has not proposed to fund such strategies. This situation will need close monitoring because 80% coverage may not be adequate to sustain rubella elimination in countries where birth rates are over 30/1000 [123], especially if coverage of catch-up campaigns and routine vaccination shows substantial heterogeneity, as has been seen for measles.

In Costa Rica, RCV was introduced for infants and over 80% coverage achieved from 1984 onwards. A catch-up campaign of MMR was conducted reaching 93% of children aged 9 months to 14 years in 1993 and follow-up campaigns in 1994 and 1997. The total burden of CRS was probably reduced over the course of vaccination (the pre-vaccination burden is not known) but in a large rubella outbreak in 1998–1999, incidence rates were highest among those aged 25–34 years. In response, a campaign was conducted targeting adolescent and young adult women in affected districts and subsequently a national MR campaign reached 98% of all adults in 2001 [125].

A perceived benefit of rubella vaccine introduction efforts may be reinforcement of existing measles programmes [125]. It will be

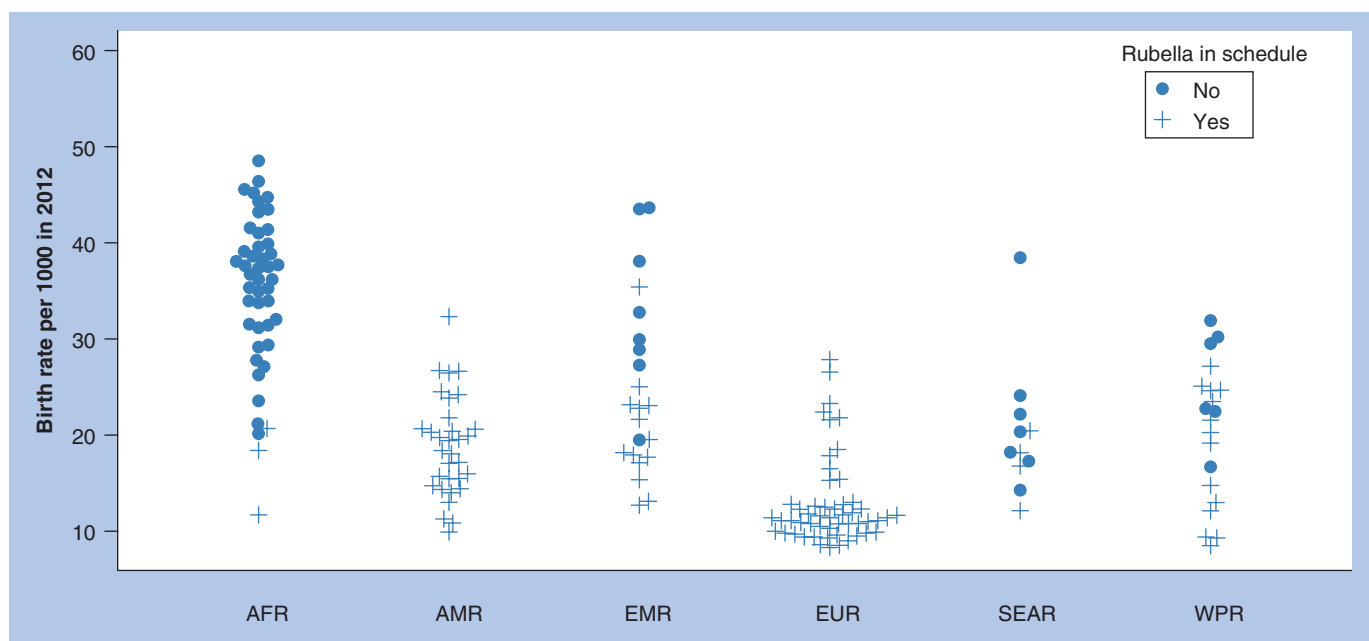


Figure 4. Number of countries with and without rubella vaccine in their national vaccination schedule in 2011, by region and birth rate.

AFR: African; AMR: Americas; EMR: Eastern Mediterranean; EUR: European; SEAR: South east Asia region; WPR: Western Pacific.

vital to ensure that this indeed occurs. The persistence of sub-populations with very low coverage and extinction–recolonization dynamics [126] can reinforce inequities in coverage, with poorly served districts experiencing a higher burden of CRS than they would have done if no vaccination had occurred, while other districts reap the benefits [127]. Past profiles of immunization coverage can be used to design catch-up strategies [128] but this will require improving data on the quality and coverage of campaigns and routine vaccination, and the ability to act on data [129].

Conclusion

Measles mortality reduction is highly cost-effective and substantial progress has been made. Estimated mortality in 2010 was <7% of that in the pre-vaccine era. Most of the estimated reduction was due to increases in routine coverage with at least one dose of measles vaccine [130]. CRS is a major preventable cause of severe disability and there should be low marginal costs to including rubella in measles elimination activities. The MRI plan aims to achieve measles and rubella elimination in at least five WHO regions by 2020 [208]. The strategy has five components, including achieving and maintaining high coverage with two doses of measles and rubella-containing vaccines, establishing effective surveillance and outbreak response, building public confidence in and demand for vaccination, and conducting operational research. To date, however, most funding has been allocated for campaigns, and GAVI funding appears to reinforce this tendency.

In the Americas, the routine programme spearheaded measles and rubella elimination and emphasis has consistently been placed on improving routine immunization to reach all communities and monitoring the equity of coverage in routine and campaign strategies [7,53,131]. Regional and national advisors have invested time and effort in improving program monitoring and in taking corrective action when problems are identified [132,133]. In the western Pacific, the announcement of an ambitious hepatitis B control goal concurrently with the measles elimination goal helped to ensure that countries strengthen integrated services [134] and both goals appear to be within reach [209].

By contrast, specific funding has not been provided to enable low income countries to strengthen routine MR vaccination programs and their monitoring. This is particularly worrisome given recent analyses which suggest that broad-scale vaccine coverage goals are unlikely to have the same impact on the interruption of measles transmission in all demographic settings and that target vaccine coverage should be scaled positively with either population size or the size of the birth cohort [135]. Routine MCV coverage in many low income countries, and in particular those with large birth cohorts such as DR Congo, Ethiopia, parts of India, and Nigeria, has stalled at levels far below those needed for measles elimination and the estimates of coverage are probably inflated in many countries [110,136]. This, together with the lack of externally validated data on the quality and coverage of campaigns and low completeness of measles surveillance makes it very difficult to plan appropriate strategies to sustain low transmission. The MR laboratory network has expanded remarkably over the last decade [137] but this needs to

be accompanied by strengthened field investigations and timely data-driven action.

Follow-up campaigns are expected to compensate for low routine coverage but the degree to which they reach children missed by the routine programme varies substantially between and within countries. Follow-up campaigns in the Congo reported 82% coverage in 2010 and 78% in 2011 (routine coverage is estimated at 90%), Equatorial Guinea reported 50% in 2011 (routine 51%); Senegal reported 81% in 2010 (routine 81%); Somalia reported 70% coverage in a national campaign in 2010 and 36% in a subnational campaign 2011 [210] and a survey in Karachi reported that only 17% of children had received measles vaccine in the 2011 campaign [138]. Elsewhere campaigns reported unfeasibly high coverage rates which were belied by subsequent outbreaks involving unvaccinated children in the cohorts eligible for the campaign. If measles and rubella are to be eliminated, there needs to be a drastic improvement in program implementation and monitoring.

The recent measles resurgence has been accompanied by a shift in age distribution to older children and adults, who were missed by vaccination efforts in earlier decades, and in infants too young to be vaccinated. This raises several concerns. First, the assumption that catch-up MR campaigns will interrupt rubella transmission is optimistic based on past experience with measles in AFR and EMR. Second, no funding is earmarked for vaccination of those in most need of protection like women of childbearing age, who may continue to be exposed to infection through migration to, or importations from, countries which do not use RCV. Third, unless routine coverage improves dramatically and campaigns are conducted to much higher standards, susceptibles will accumulate again after the catch-up campaign and resurgences of rubella involving older persons and cases of CRS will occur in the future [123]. Since there are no robust data on trends in CRS incidence pre-vaccination in low-income countries, outbreaks could lead health workers and communities to believe that vaccination has been ineffective or worse, whether or not overall incidence has truly increased [139]. Fourth, sustaining elimination in countries and regions which have eliminated measles and rubella is expensive in the face of frequent importations [140,141] and new strategies are needed to reduce importations.

Although measles and rubella elimination is biologically feasible, its attainment will require a dramatic shift in political will and commitment. Despite initial optimism about eradicating major infections after the success of smallpox eradication, the failure to achieve the dracunculiasis and poliomyelitis elimination goals set 25 or more years ago highlights the extent of the challenges to elimination of other infections [142]. The diversity of obstacles to achieving and sustaining high routine coverage even in high income countries, the delays in implementation of campaigns due to political and economic barriers, the inability of some countries to reach all children even via campaigns, the paucity of reliable data on coverage and the political and social turmoil in many countries raise major challenges to achieving the required population immunity. Routine immunization has been the backbone of MR elimination in the Americas and surveillance is a vital component of effective disease control [7]. Investment and

intensive action to strengthen immunization systems and their monitoring are urgent if the goals are to be achieved in all regions.

Expert commentary

Success in the Americas and some countries outside that region proves that measles and rubella transmission can be interrupted for long periods of time. Coverage of at least one dose of measles vaccine, delivered through routine services and mass campaigns, has been increasing in the last decade across most of the rest of the globe, resulting in considerable reductions in childhood morbidity and mortality. However, measles outbreaks continue to occur in much of the world, either due to constitutively low coverage (e.g., in conflict affected countries, or areas with weak health care systems), suboptimal routine two dose coverage (e.g., many countries in Europe), or reliance on campaigns that have not achieved adequate coverage, combined with inadequate monitoring of immune status (e.g., many countries in Africa). When outbreaks occur after a long period of low incidence, there is often a shift in the age distribution of cases towards older or very young individuals, with concomitant challenges for surveillance and control. Where rubella-containing vaccine has been introduced (mostly in low or moderate birth rate settings), late age rubella outbreaks have also been observed, of considerable concern for the burden of congenital rubella syndrome (CRS). Achieving and sustaining low or absent transmission of measles and rubella requires especially high coverage in countries with large birth cohorts and high birth rates which lead to large numbers of new susceptibles entering the population each year. While the experience in the Americas proves that elimination is possible, coordinated and sustained efforts by all countries and their global partners will be required to reach these goals.

Five-year view

Prospects for measles and rubella elimination over the next 5 years differ markedly at a global scale. For Europe, challenges to be addressed include disruptions to health services through reorganizations and the economic downturn, low priority given to measles vaccination by many health professionals and parents, difficulties in reaching travelling groups and vaccine refusal in others, and

pockets of susceptibility in wide age groups including adults. In the Americas, sustaining elimination will require continued high coverage and rapid response to importations of the infections, and public education in the presence of changing attitudes about measles vaccination among those who have never experienced the disease. Outside of Europe and the Americas, the key is strengthening routine infant immunization and improving the use of mass vaccination campaigns to reach those unreached by routine services; clearly this will be particularly difficult in countries affected by conflict. After over a decade of mass vaccination campaigns and increasing routine coverage leading to reductions in measles transmission, individuals have reached older ages before being exposed to measles. The immunity profile of populations in different settings is often difficult to predict due to past deficiencies in accurate monitoring of coverage and disease incidence and assumptions about the distribution of susceptibility that may no longer hold. Serosurveys and serosurveillance may play a greater role in informing policy. For countries where rubella continues to circulate, the concerning signature of wider age-ranges of incidence for measles highlight the importance of improving strategies and emphasizing surveillance and use of data for action after the introduction of rubella-containing vaccines.

If the polio endgame is achieved, it is likely that energies will turn toward measles and rubella. Innovations in how campaigns are effectively planned and deployed, perhaps in combination with a mixture of case-based and serological surveillance, changes in funding toward improved monitoring and strengthening of routine vaccination, and taking action to ensure adequate immunity in all age groups will be essential to make this a success.

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Key issues

- Measles and rubella have been eliminated from the Americas, and four of the five other WHO regions have established measles elimination goals.
- Despite impressive progress globally in reducing measles mortality via vaccination, large outbreaks have recently affected multiple countries around the world, often involving wide age groups including adults.
- Challenges to reaching and sustaining high enough routine vaccination coverage include weak or conflict-affected health systems, especially in some large countries with high birth rates, and barriers to reaching certain population groups even in high income countries.
- Mass vaccination campaigns have been used extensively in the last decade but their monitoring has been inadequate and impact often uncertain.
- Few low-income countries have introduced rubella vaccine because of the unrecognised disease burden, higher cost of the combined vaccine and concerns about a paradoxical increase in congenital rubella syndrome if adequate coverage is not ensured. Now that GAVI funding is available for measles-rubella vaccine catch-up campaigns, more countries are introducing rubella vaccine.
- Well-implemented campaigns may interrupt rubella transmission but women of childbearing age may continue to be exposed to infection through migration to, or importations from, countries which do not vaccinate against rubella.
- Countries and regions aiming to eliminate measles and control rubella urgently need to address past deficiencies in the implementation and monitoring of both routine and campaign strategies and in the use of data for action.

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