

The end of measles and congenital rubella: an achievable dream?

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Key words: Measles, rubella, congenital rubella, elimination Italy

Parole chiave: Morbillo, rosolia, rosolia congenita, eliminazione, Italia

Abstract

Background. Despite substantial progress towards measles and rubella control, outbreaks continue to threaten elimination goals worldwide.

Study design. This paper aims to document progress towards the global eradication of measles and rubella. In particular, it investigates the major challenges faced by Italy in reaching the elimination goals.

Methods. A review of the most important literature was carried out. Furthermore, a systematic review of the scientific literature on measles and rubella in the Italian setting was performed for the period 2000-2016.

Results. In the National Plan 2010-2015, Italy renewed its commitment to eliminate measles and rubella by 2015. However, Italy recently experienced a high measles burden (2,205 cases in 2013, 1,694 in 2014). Between June 2015 and May 2016, 515 cases were reported, accounting for 28% all cases in Europe. Immunization coverage decreased in recent years, with no Region reaching the 95% target. The systematic review included a total of 175 papers, with an upward trend in the number of published articles, which demonstrates an increasing interest in the field of measles and rubella. The review highlights the need to improve the commitment of the Italian Regions to the elimination goals; to promote Supplementary Immunization Activities (SIAs); to improve the communication skills of health care workers; to improve the health literacy of citizens; and to enhance integrated measles and rubella surveillance.

Conclusions. Elimination of measles and rubella in Italy will require a substantial improvement in both commitment of the 21 Regions and activity of the whole country towards the WHO goals.

Introduction

Measles and rubella are highly contagious, but vaccine-preventable, viral diseases, which can have a serious impact on an individual's health. Infection with measles virus can lead to serious complications,

especially in infants and adults, and it is a leading cause of death worldwide in children < 5 years (1). Before the widespread use of measles vaccination, almost everybody was infected in early childhood and acquired life-long immunity against measles. In the 1980s, measles killed an estimated

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2.6 million children worldwide each year (2). Before the widespread use of measles vaccination, almost everyone was infected in early childhood and acquired life-long immunity against measles. The widespread adoption of the measles vaccine in National Immunization Programs (NIPs) following the establishment of the Expanded Programme on Immunization (EPI) in 1974 resulted in a decrease in the number of reported cases. With increasing immunization coverage, the number of measles deaths worldwide was estimated to have been reduced to about 548,300 in 2000 (immunization coverage of 72%), and to an estimated 157,700 deaths, mostly children, in 2011 (immunization coverage of 84%) (3).

The attenuated live measles vaccine is highly effective, yielding seroconversion rates of 95% or more in persons over 12 months old. Almost all children who fail to respond to the first dose will respond to the second dose, thus ensuring seroconversion rates after two doses of 95% or more if the first dose is given at nine months, or 99% or more if the first dose is given at 12 months or older. As a result of the high transmissibility of the measles virus, the herd immunity threshold is very high, and consequently very high coverage ($\geq 95\%$) is necessary to interrupt virus transmission. Providing all children with two doses of measles-containing vaccine (MCV) is now the standard for all NIPs, with the second dose delivered either through vaccination campaigns or through routine health services, depending on which approach attains the highest coverage (4).

Rubella is generally considered to be a mild rash illness; however, it is more severe in infants and adults. If infection occurs during the early stages of pregnancy, the rubella virus can cause multiple birth defects, including congenital rubella syndrome (CRS), and may result in foetal loss or stillbirth. Congenital malformations have been reported in up to 85% of children born

to women with confirmed diagnoses of rubella during the first trimester of pregnancy. Before widespread rubella vaccination in the Region of the Americas, it was estimated that approximately 20,000 CRS-affected children were born there each year. In 1996, it was estimated that in developing countries approximately 110,000 children were born annually with CRS (4).

Many countries have introduced rubella vaccine and this has proven highly effective as $>95\%$ of persons vaccinated with a single dose are protected against both clinical rubella and viremia for at least 15 years (4). However, by 2008, very few countries in Africa, South-East Asia and the Western Pacific (areas at higher risk of rubella infection) had deployed the vaccine and therefore the burden of CRS in these areas is thought to be similar to that estimated for 1996 (1).

Both measles and rubella meet all the requirements for potential eradication: they are caused by genetically stable microorganisms, humans are critical for the transmission and there are no environmental or animal reservoirs for either virus, the period of infectiousness is short, infection confers lifelong immunity, and both accurate diagnostic tests and safe, effective vaccines are available (5).

This paper is an attempt to document progress towards the global eradication of measles and rubella with a specific focus on Europe, and Italy in particular, for which a systematic review of the literature with descriptive purposes was performed.

Measles and rubella vaccination programs throughout the world

Since the mid-1970s, the widespread establishment and implementation of the EPI has led to remarkable progress in controlling vaccine-preventable diseases worldwide (6). The considerable success of the global

smallpox eradication program, which was intensified from 1966 to 1977, demonstrated that universal access to immunization was possible.

The initial emphasis of the EPI was on increasing and measuring immunization coverage against targeted diseases, with immunization coverage of infants with the third dose of diphtheria–tetanus–pertussis vaccine – DTP3 – as a key program performance indicator. DTP3 coverage rose from 20% in 1980 to 75% in 1990. The attainment of high levels of immunization coverage, together with the success of smallpox eradication, stimulated the addition of specific disease control objectives to the EPI through global and regional resolutions of the WHO governing bodies. The resolution for worldwide eradication of poliomyelitis, adopted by the World Health Assembly (WHA) in May 1988, is a prominent example of the development of the EPI (6).

EPI programs were progressively strengthened throughout the '80s, particularly in the Americas. During this decade, measles vaccination resulted in decreased disease incidence and lengthening of interepidemic intervals. By the early 1990s, several countries pioneered a strategy recommended by the Pan American Health Organization to deliver measles vaccine to all children between 9 months and 14 years old in a catch-up campaign. The strategy appeared to be capable of interrupting endemic measles transmission (7).

The goal of eliminating measles from the Americas was set in 1994, the year when the region was declared polio-free. In the early 1990s, 'catch-up' campaigns, usually targeted at children between 9 months and 15 years old, were conducted, aiming to immunize all susceptible children who had accumulated over the previous years of routine vaccination (6, 7). After approximately four years, 'follow-up' campaigns were carried out among children

aged 1–4 years to sustain high population immunity. Both types of campaign included community-based 'mop-up' activities in areas where monitoring showed that the campaign coverage was below 95% (7, 8). Finally, after the goal of rubella elimination was added in 2003, 'speed-up' campaigns were carried out among adults (of both sexes, in all but three countries) up to 40 years old to quickly reduce transmission. Programs were guided by close monitoring of progress including routine coverage, campaign coverage, case-based disease surveillance and virus surveillance. The last endemic case of measles was documented in November 2002, and that of rubella in 2009 (8).

The success of measles elimination in the Americas encouraged the adoption of measles elimination goals in the eastern Mediterranean (in 1997), European (1998), western Pacific (2005) and African (2011) Regions, with varying target dates for elimination. The South-East Asia Region retains a measles mortality reduction goal, but elimination is under discussion (6, 8).

In 2000, the WHA adopted a resolution to reduce global measles deaths by half compared with 1999 levels during the period 2000–2005. This goal was achieved following the implementation of a five-year strategic plan to increase coverage of measles vaccination through routine immunization and supplemental immunization activities (SIAs) (9). Following this achievement, the Measles and Rubella Initiative supported a five-year strategic plan in 2006 with a more ambitious goal to reduce estimated measles mortality by 90% by 2010 compared with 2000 levels. Considerable progress was achieved by 2010: about 9.6 million deaths were averted as a result of measles immunization during 2000–10, and, with the exception of the South-East Asia Region, all WHO Regions achieved at least a 75% reduction in measles mortality in 2010 compared to 2000 (9, 10). The 90% measles mortality reduction goal was not achieved

in India and Africa largely due to delayed implementation of measles control activities and the occurrence of large-scale measles outbreaks, respectively (9).

By 2011, all 194 WHO Member States had introduced or begun the process of adoption of a two-dose measles vaccination strategy delivered through routine immunization services and/or SIAs. According to WHO and UNICEF estimates, global routine coverage with a first dose of measles vaccine (MCV1) increased from 72% in 2000 to 85% in 2010. By the end of 2010, the routine immunization schedules of 139 countries included two doses of MCV (10).

Similarly to measles, a safe, heat-stable, effective and inexpensive rubella vaccine exists, and substantial progress has been made towards rubella control. However, rubella infection remains one of the leading causes globally of preventable congenital birth defects. As of December 2010, 131 of the 194 WHO Member States included rubella-containing vaccines (RCVs) in their routine immunization programmes (9).

In May 2012 the WHA adopted the Global Vaccine Action Plan (GVAP) for the 2011-20 Decade of Vaccines. Recognizing the significant health and financial benefits provided by vaccines, the GVAP aspires to create a world “in which all individuals and communities enjoy lives free from vaccine-preventable diseases” by extending the full benefits of immunization to all people by 2020 and beyond (11). The GVAP represents one of the largest and most ambitious public health projects ever initiated, and it includes achievement of the existing disease eradication and elimination goals for polio, neonatal tetanus, measles, and rubella by 2020. Specifically, regional goals included elimination of measles in four of the six WHO Regions (Eastern Mediterranean by 2015, European by 2015, Western Pacific by 2012, and African by 2020), reducing measles mortality by 95% in 2015 compared with 2000 levels in the South-East Asia

Region, eliminating rubella in the European Region in 2015, and pursuing accelerated rubella control with a CRS prevention goal in the Western Pacific Region in 2015 (9, 11). Unfortunately, progress has been slow.

Between 2010 and 2014, global routine measles vaccine coverage stagnated at 85% – well below the 2015 target of $\geq 90\%$. Three of the six WHO Regions sustained MCV1 coverage above 90% (Region of the Americas, European Region and Western Pacific Region), one Region achieved coverage between 80 and 90% (South-East Asia Region) and two Regions achieved coverage below 80% (African and Eastern Mediterranean Regions). The number of Member States achieving the global MCV1 coverage target at the national level remained the same in 2014 as in 2010: 122 Member States achieved the $\geq 90\%$ MCV1 national coverage target (12).

Since 2010, global reported measles incidence has decreased by 19%, from 50 cases per million population in 2010 to 40 in 2014, with only one Region (Region of the Americas) meeting the global 2015 target of fewer than five cases per million population. During the same period, there was a decrease in the number of Member States (95 Member States in 2014 compared to 114 Member States in 2010) meeting the global 2015 incidence target. In 2014, 154 (79%) Member States had introduced a second dose of MCV (compared to 136 (70%) in 2010) and MCV2 global coverage was 56% (compared to 40% in 2010). Between 2000 and 2013, estimated measles deaths decreased by 73% (from 544,200 to 145,700) and all Regions reported substantial reductions in estimated measles mortality. However, the progress since 2010 has been too slow (from 69% mortality reduction in 2010 to 73% in 2013) making it highly unlikely that the target of 95% mortality reduction could be achieved by the end of 2015 (12).

Many countries regularly employ SIAs in addition to routine vaccination programs.

SIAs vaccinated approximately 197 million children in 33 Member States in 2013 and an additional 215 million children in 28 Member States in 2014. Among 34 countries that conducted SIAs between 2012 and 2014 and that conducted a coverage evaluation survey of the SIAs, fewer than half (16 Member States) were able to reach the target of 95% national coverage (10, 12). Given these gaps in coverage and population immunity, it is not surprising that outbreaks continue to threaten elimination goals in all six WHO Regions.

As of December 2014, 140 (72%) Member States had introduced RCVs, a 49% (46 countries) increase from 2000. Average coverage globally has gradually increased from 41% in 2010 to 46% in 2014. However, it varies from 12% in the South-East Asia Region to 94% in the European Region. In 2014, the global incidence of rubella was estimated to be 4.6 per million population (averaged over 158 Member States). It must be noted that the total number of Member States reporting rubella incidence to the WHO has diminished in recent years, from 176 (91%) in 2012 to 158 (81%) Member States in 2014, which explains why rubella incidence appears to be diminishing. The same trend can be seen with CRS reporting. The very low reported incidence is probably more a sign of the almost non-existent CRS surveillance systems outside the Americas and a few other Member States than a reflection of true disease burden (12).

Immunization activities in Europe

To put the GVAP into action, the WHO Regional Office for Europe launched the European Vaccine Action Plan, with all 53 Member States making commitments to eliminate the endemic transmission of measles and rubella by 2015 (13). Although the Region has not met the 2015 measles and rubella elimination goal, many of the

Member States have provided evidence for absence of endemic measles and/or rubella transmission for at least three years (14).

The reported incidence of measles and rubella in the WHO European Region has declined dramatically over the past two decades. With improving disease surveillance, the annual average number of reported measles cases fell from more than 200,000 in the period 1990-99 to fewer than 30,000 in 2010-14. Despite this, significant measles outbreaks occurred in 2013 and 2014 in Azerbaijan, Bosnia and Herzegovina, Georgia, Germany, Italy, Latvia, the Netherlands, the Russian Federation, Turkey, Ukraine, and the United Kingdom. In 2015, the target year for elimination in Europe, large outbreaks occurred again, with 300 cases in Austria and more than 2,500 in Germany, which accounted for 62.1% of all cases reported during this period. The average annual number of reported rubella cases fell from more than 300,000 in 2000-09 to fewer than 20,000 in 2010-14. Rubella outbreaks in Poland and Romania accounted for the majority of the recently reported cases (13).

Continuing the trend of recent years, approximately one-third of reported measles cases occurred in individuals aged twenty years and older between 2013 and 2015. However, there are substantial differences across Member States in the age distribution of reported cases. The majority of cases occurred among unvaccinated or incompletely vaccinated individuals, including many older people with unknown vaccination status, infants younger than one year, adolescents and young adults (13). The most recent outbreaks began among groups having low coverage such as Roma and Sinti communities, Irish Traveller communities, anthroposophic groups and ultra-orthodox Jewish communities, with consequent spread to other populations and other countries. In some countries a substantial number of

measles and rubella cases have been reported among HealthCare Workers (HCWs). Measles outbreak investigations provide an important opportunity to identify problems with measles control activities in individual countries. The distribution of measles cases by age, vaccination status and location may reveal populations that are missed by routine vaccination and campaigns, with reduced vaccine effectiveness and the accumulation of susceptibility in older age groups (8).

In 2013, following a global technical consultation on the feasibility of global measles eradication, the WHO developed and published technical guidance on the regional process for verifying measles and rubella elimination. This guidance was shaped in agreement with the process for certifying poliomyelitis eradication and 2012 was selected as the first year in which evidence on elimination would be gathered. Since 2012, Member States are required to provide evidence each year on the status of endemic measles and rubella transmission in their country (14). A standardized annual report form is used to assist each National Verification Committee (NVC) in compiling and documenting evidence along the following five principal lines: the epidemiology of measles, rubella, and CRS; the performance of measles, rubella, and CRS surveillance; the molecular epidemiology of measles and rubella viruses; population immunity; and the sustainability of the national immunization program (4, 14). The key components are interrelated; therefore, it is necessary to provide evidence that the data are valid, complete, representative and that there is consistency among the different information sources.

In 2015, the Regional Verification Commission (RVC) for Europe reviewed documents submitted by NVCs for 2012, 2013 and 2014 to assess the status of endemic measles and rubella transmission for 2014, as well as to determine in which Member States measles and rubella could

be considered eliminated for the three-year period. Several documents are missing from a few countries with functioning NVCs (13, 14).

Based on the Elimination Status Reports submitted for 2014, the RVC verified that 32 Member States (60%) provided evidence of the interruption of endemic measles transmission in 2014, 18 (34%) remained endemic for measles transmission, while 3 (6%) did not submit any document. Similarly, 32 Member States (60%) provided evidence of the interruption of endemic rubella transmission, 18 (34%) remained endemic for rubella transmission, while 3 (6%) did not submit any document. Sixteen Member States (30%) had endemic transmission of both measles and rubella in 2014 (14).

Despite progress in some countries, the goal of measles and rubella elimination in the WHO European Region by the target date of 2015 was not met. This is an unexpected outcome in a region where sufficient resources are available. Unless and until progress toward genuine political commitment, increased technical capacity, and universal public awareness of the benefits of measles and rubella elimination (especially in Western Europe) is urgently accelerated, this important public health initiative will remain unfulfilled (13).

The situation in Italy

A monovalent measles vaccine became commercially available in Italy in 1976. This was replaced in the early 1990s by the combined measles–mumps–rubella (MMR) vaccine, but only since 1999 has vaccination with MMR been included in the NIP (15). Since 2003, when Italy approved the first National Plan for the Elimination of Measles and Congenital Rubella (PNEMoRc) 2003–2007, a two-dose schedule of MMR vaccine was adopted in all Regions starting with the 2002 birth cohort, with the first dose at the

13th to 15th month of life and the second at the age of 5–6 years. In all Regions, MMR vaccination is now offered free of charge to children and susceptible adolescents and adults (16).

During the implementation of the PNEMoRc, measles and rubella surveillance has been strengthened to monitor progress towards elimination of the diseases and prevention of CRS. Laboratory investigation of all suspected cases, with special attention to rubella cases in pregnant women, started in 2005, when CRS became a statutory notifiable disease, and a catch-up campaign to administer MMR vaccine to school-aged children (7–14 years old) was conducted in all Regions (1).

The overall incidence of measles has decreased in Italy since the measles vaccine was introduced from a mean incidence of 150 cases per 100,000 population in the 1970s to 81 cases per 100,000 in the 1980s and 41 cases per 100,000 in the 1990s. In the past decade, large epidemics occurred in the years 2002, 2003 and 2008, with 18,020 reported cases (incidence 32/100,000 population) in 2002 and 5,312 cases in 2008 (8.9/100,000 population). Another resurgence of cases was then observed in December 2009. All the above outbreaks mainly affected adolescents and young adults (15). Measles transmission was also reported among HCWs in various settings, including hospitals, emergency rooms and ambulatory care units. Outbreaks also occurred in Roma communities, especially among children (17).

From October 2010 to December 2011, 5,568 possible, probable or confirmed cases were reported, giving a national cumulative incidence in the 15-month reference period of 9.2 per 100,000 population. The highest incidence was seen in the age group 15–19 years, followed by the age group under one year. Sixty-two per cent of cases were aged 15–44 years. Factors contributing to this upsurge include suboptimal routine

vaccination coverage (<95%) and, in particular, the large numbers of susceptible adolescents and young adults born in the 1980s and 1990s, when uptake of measles vaccine was very low and the second dose had not yet been introduced (15).

In 2011, Italy renewed its commitment to eliminate measles by approving a new national elimination plan. The plan, which once again addressed all components of the WHO elimination strategy, was approved by the State-Regions collegial body (Conferenza Stato Regioni), which means that all 21 Regions committed to the objectives and strategies included in the plan. Following approval of the elimination plan, a national task force of representatives of the Ministry of Health, the National Health Institute and five regional health authorities was established to define priorities, coordinate activities, prepare technical documents, promote sharing of information and best practice between the different Regions, and implement elimination strategies in all Regions (15, 18). Through the implementation of the new PNEMoRc 2010–2015, the goal of measles elimination and incidence reduction of CRS cases was postponed from 2007 to 2015. However, despite every effort, the objectives of the National Plan have not yet been achieved (1).

To help Italy accelerate progress towards the elimination of measles and rubella, a delegation of the European Regional Measles/Rubella Verification Commission visited the country on 10–11 March 2015. This visit represented a follow-up to the meeting of the RVC in Copenhagen in October 2014 which, among other things, recommended that all countries that did not submit a timely or complete annual status report, in accordance with the procedures established for the verification of disease elimination, should receive a visit. The team focused on the process of achieving and documenting interruption

of endemic transmission, including the need for high-quality surveillance and immunization coverage data and the roles and responsibilities of the various parties involved (19). A set of recommendations was

made (20) (see Box 1). After the site visit in Rome, the Ministry of Health decided to change the whole NVC, which submitted the two annual status reports for 2013 and 2014 by the end of July 2015.

Box 1. The WHO recommendations made for Italy at the end of the country visit in March 2015 (20)

Consistent with the renewed commitment in Italy to eliminate measles and rubella and to prevent CRS, the WHO mission to Italy generated a number of policy and technical recommendations, which were submitted for consideration by the Ministry of Health.

Political commitment

Currently there is an improved political commitment at the national level, but there is a need to carry this forward to the regional and local levels. In particular, it is urgent that the 21 Regions mobilize to forge a stronger commitment to shared ownership, and responsibility for, the national elimination goals.

National Plan of Action

The National Plan of Action for the elimination of measles and rubella should be updated and extended in collaboration with the regional health authorities and other stakeholders including professional associations. These professional associations have already been instrumental in harmonising the national immunization schedule and can help to achieve the targeted goals. In addition, civil societies have the potential to contribute to the achievement of these goals.

Vaccination campaign

Achieving two-dose MMR coverage of at least 95% in all Regions, a requirement for elimination, will be highly challenging. Therefore, to achieve herd immunity through the immunization of remaining susceptible individuals in all age groups in the population, there is a need to implement a high quality, wide age-range vaccination campaign. The target population for the campaign should take into account the epidemiology of both measles and rubella. Such a campaign requires comprehensive micro-planning at all levels, including vaccine supply, human resources, waste disposal, adverse events monitoring, social mobilization, communication and messaging.

Rubella elimination

To ensure elimination of rubella and congenital rubella syndrome, the importance of rubella needs to be elevated. Components that need to be strengthened include rubella surveillance and laboratory confirmation, CRS surveillance, investigation of rubella outbreaks, and reporting of rubella cases to the appropriate international surveillance institutions.

Health workers

WHO recommends that all health workers should be immune to measles and rubella to protect themselves and to prevent nosocomial transmission, which can cause severe disease or death, especially among hospitalized patients.

Surveillance and outbreak response

There is a need to further enhance integrated measles and rubella surveillance through the formalization of a national network of MR laboratories compliant with the WHO MR LabNet standards. The establishment of an appropriate mechanism and tools for optimal EPI surveillance and laboratory collaboration will allow timely linkage of case-based epidemiological and laboratory data and prompt outbreak responses.

Advocacy and communication

Italy should develop a comprehensive communication and social mobilization plan for measles and rubella elimination. This should include clear national policies for handling media relations and responding to the urgent need to disseminate public information following an adverse event allegedly associated with the administration of a vaccine. Clear communication strategies to promote vaccination across the population are also essential. Furthermore, there is a need to proactively educate the media on vaccination issues and to engage medical professionals and other scientific groups to advocate for and promote elimination efforts.

Based on the reports submitted, the RVC concluded that 2,205 cases of measles (41 per million population) and 66 cases of rubella (1 per million population) occurred in Italy during 2013. Adolescents and young adults were especially affected, with 75% of reported cases occurring in individuals >15 years of age. Almost all Regions were affected. During the same period, two cases of CRS occurred. MMR vaccination coverage was 90% for the first dose and 84% for the second dose (13, 14).

In 2014, measles incidence was 27 per million population, with a considerable number of outbreaks (193) occurring all over the country. Most reported outbreaks were limited to two cases. All ages were affected, but 57% of cases were subjects >20 years old. Rubella incidence was 0.4 per million, occurring in 11 Regions. No CRS cases were reported. MMR vaccination coverage for 2014 was 87% for the first dose, and 83% for the second dose (14).

None of the Regions met the 95% vaccine coverage target; all but two Regions reached coverage rates greater than 80%, the regional-level range being 68.8% to 90%. In the overall period 2012-2014, measles vaccine coverage in Italy decreased by 3.7%, with declining trends reported in all but one Region. In 11 Regions, the percentage reduction was greater than 5%. A similar pattern was observed for rubella vaccine coverage, for which national level coverage rates decreased by 3% from 2012, with declining trends in all but one Region, and a percentage reduction >5% in 10 Regions (21).

In 2015, the incidence of measles decreased to 3.9 per million population (253 cases), whereas the incidence of rubella remained stable (0.4 per million population: 24 cases). MMR coverage data are a matter of concern (85% for the first dose and 83% for the second dose). None of the 21 Italian Regions reached the 95% target, and all Regions but two were below the 90% coverage (Figure 1). Between 1st June 2015

and 31st May 2016, Italy reported 515 cases, accounting for 28% of the EU/EEA cases in the 12-month period. Most of the Italian cases (365) were reported between January and May 2016 (22).

Systematic review of the literature: the scientific evidence in Italy (2000-2016)

To describe the scientific activity on measles and rubella in Italy, a systematic review of the literature was performed for the period 2000-2016. We searched electronic databases: Medline, Embase and Scopus from 2000 to June 2016. We used the following search terms: “measles* OR rubella* AND Italy*”. A manual review of references from eligible studies was also performed. Titles, abstracts and full texts of the resulting papers were examined and discrepancies were resolved by consensus. Articles were considered eligible if the studies focused on the topic of measles and/or rubella, were conducted in the Italian setting and added information about the current status of such diseases. We excluded papers not relevant to measles or rubella, not involving humans, and brief reports (e.g., abstracts, letters, and/or editorials) that did not provide sufficient detail.

A total of 314 studies were retrieved from electronic databases after removing duplicates; a further two articles were obtained from a review of references cited in the studies initially identified. After screening for title/abstract, 210 full-text articles were assessed for eligibility and 175 papers that met the inclusion criteria, 167 primary and 12 secondary studies (reviews or systematic reviews), were included (1, 13, 15-17, 23-192). Figure 2 summarizes the literature search process and results. Figure 3 shows the distribution of the studies included by year, with numbers of publications ranging from two studies published in 2001 to 19 in 2015. Overall,

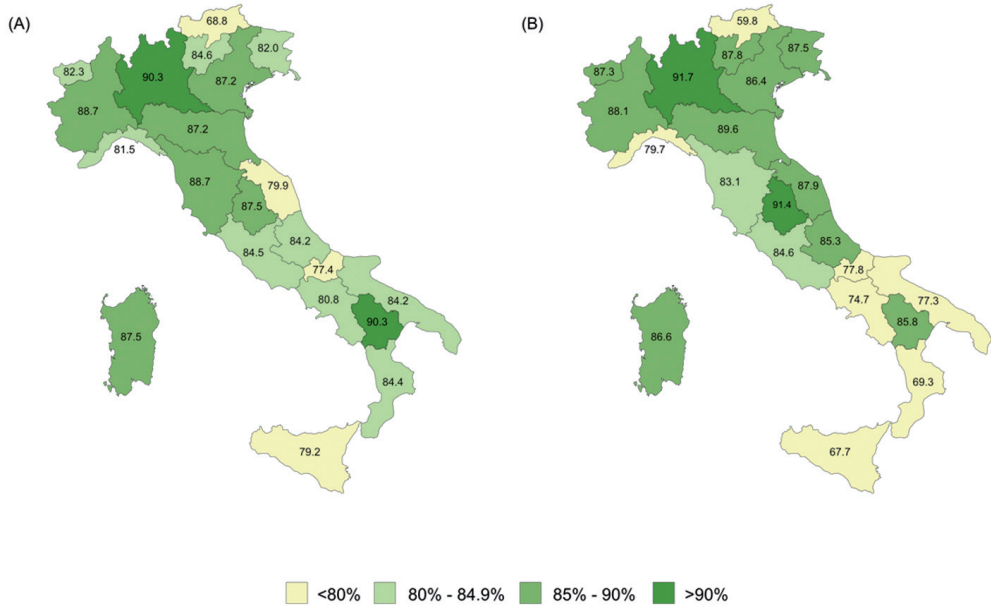


Figure 1 - Measles vaccination coverage, 1st dose (A) and 2nd dose (B), 2015

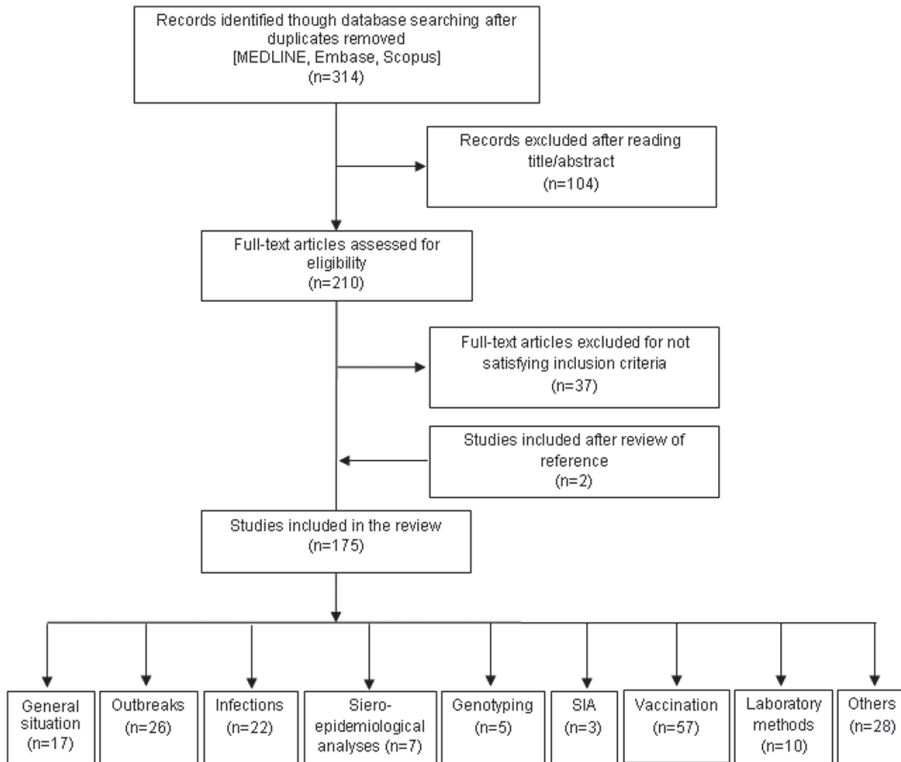


Figure 2 - Flow diagram for selection of studies focused on measles and rubella in Italy.

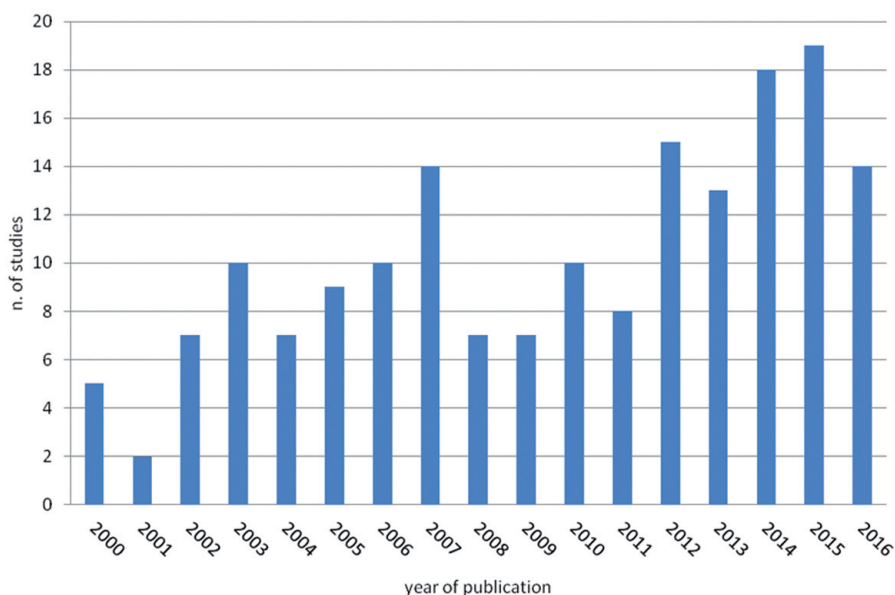


Figure 3 - Distribution of the included studies on measles, rubella and congenital rubella syndrome (CRS) in Italy by year of publication.

there was an upward trend in the number of published articles on measles and rubella. From 2000 to 2008 the average number of published articles per year was almost half that in the following eight years [7.89 (SD 3.41) vs 13.00 (SD 4.41)], although a peak was recorded in 2007 (14 studies). This increase is likely to be due to the interest and findings resulting from the first five-year strategic plan on measles vaccination by WHO, which ended in 2005. Given the considerable heterogeneity of the studies, a categorization of the articles according to specific subtopics was performed and each category is described separately below. We identified nine categories: (a) general situation (epidemiology and surveillance system); (b) outbreaks; (c) seroepidemiologic analyses; (d) genotyping analyses; (e) infection (complications, risk association); (f) SIAs; (g) laboratory methods; (h) vaccination (efficacy and safety, uptake, coverage, at-risk subpopulations, complications, vaccination strategies); (i) others.

(a) General situation (epidemiology and surveillance system). Seventeen studies provided information on two relevant aspects of the Italian situation: the epidemiology of infection and complications related to measles and rubella, and the performance of the national notification system. Six articles described the incidence of infection and complications of measles (40, 86, 180) and rubella (79, 169) or both (34) in Italy, during defined time periods. Four articles included data on infection incidence among the general population (34, 79, 86) or pregnant women and newborns (169) using data from the notification system. Two papers provided the incidence of measles complications in the general population using hospitalization data (40, 180). Eleven articles included information on the Italian notification system (15, 29, 30, 45, 66, 80, 92, 95, 149, 163, 172). Three were published by the National Health Institute and described the correct laboratory process defined for measles surveillance (15, 149, 172). Seven studies reported data on

the performance of the notification system for measles (45, 92), congenital rubella (66, 95, 163) and measles and rubella (30, 80), specifically addressing the problem of underreporting. One study reported the first steps in the adoption of a European network system (29).

(b) Outbreaks. Twenty-six studies provided information on Italian outbreaks: 24 on measles and two on rubella (17, 39, 52, 64, 65, 74, 76, 77, 83, 85, 94, 101-104, 109, 110, 112, 117, 138, 139, 143, 146, 167, 187, 191). Nine of the studies on measles (74, 101, 102, 104, 110, 112, 138, 187, 191) and one on rubella (103) outbreaks also included data on genotyping. One article on measles also considered the economic impact of hospitalization due to a large outbreak (77). Three studies on measles outbreaks targeted at-risk populations such as the Roma/Sinti (17, 187) and HCWs (117).

(c) Seroepidemiologic analyses. There were seven seroprevalence studies, which evaluated the proportion of susceptible populations (26, 91, 96, 118, 119, 122, 190). Two studies considered the prevalence of anti-rubella virus IgG (119) or anti-rubella virus IgG and IgM (122) in pregnant women in southern Italy and northern Italy, respectively. Two other studies focused on rubella, the first considering the prevalence of IgG and IgM anti-rubella antibodies in women of childbearing age (96), and the other evaluating anti-rubella antibodies in the general population (26). Two studies described the seroepidemiological situation for measles in the general population (91, 190), and one of these studies using anti-measles IgG antibodies to measure seroprevalence (190). In one article the presence of both anti-rubella and anti-measles IgG antibodies was used to evaluate the prevalence of measles and rubella in the general population (118).

(d) Genotyping analyses. Five articles included information on the genotyping of circulating virus over a time period covering

more than a single outbreak (46, 72, 126, 144, 188). Four studies used measles genotyping to determine the circulation of measles viruses in Italy, over different periods of time (72, 126, 144, 188). The first study showed co-circulation of B3-variants in 2014 (188), while the second documented the co-circulation of genotypes D4 and D8 as endemic genotypes, and sporadic cases associated with genotypes D9 and B3 in Italy during 2010 (144). The third article focused on a longer period (2002-2007) and showed that the D7 genotype was predominant from 2002 to 2004, but was then replaced by the D4 and B3 genotypes in the years 2006-2007 (126). The fourth article focused on virus circulation in the Liguria Region in different periods, showing that genotype D4 was present in 2003, genotype D8 in 2004 and 2005, and genotype D4 in 2006 (72). Only one study analyzed the molecular epidemiology of rubella virus (46), documenting that, in the period between 1991-1997 in northern Italy, most viruses belonged to rubella genotype I and genotype II.

(e) Infection (complications, risk association). This category included 22 articles focused on two different issues of measles and rubella infection: complications directly related to infection (27, 41, 44, 57, 68, 73, 97, 105, 114, 131, 145, 148, 152, 157, 173), and clinical manifestations linked to increased post-infection susceptibility (23, 37, 54, 69, 111, 129, 130).

Concerning complications, 15 studies analyzed possible complications associated with viral infection (27, 41, 44, 57, 68, 73, 97, 105, 114, 131, 145, 148, 152, 157, 173). Six articles described different measles-related complications: Guillain-Barré Syndrome (148), acute disseminated encephalomyelitis (114), respiratory distress syndrome (105), secondary pulmonary complications (97), interstitial pneumonia (41) and acute meningitis (27). One study considered the mortality associated with

measles complications from 1990 to 2010 (145). Eight articles studied complications due to rubella infection (44, 57, 68, 73, 131, 152, 157, 173). Six focused on CRS in newborns (44, 68, 73, 131, 157, 173), one on IUGR (intrauterine growth restriction) as a consequence of rubella infection in pregnancy (152), and another described the Guillain-Barré Syndrome as a complication of rubella infection in adults (57).

The development of a measles or rubella infection can be associated over time with an increased risk of neoplastic disorders, and neurodegenerative or other diseases. Seven studies considered diseases in adults not directly related to measles and rubella (23, 37, 54, 69, 111, 129, 130). Five articles studied the association with leukemia and non-Hodgkin's lymphoma (129), non-Hodgkin's and Hodgkin's lymphoma (69), type 1 diabetes (37, 130) and multiple sclerosis (23). Two studies focused on the exposure to virus in utero and the risk of developing anorexia nervosa (111) or attention-deficit/hyperactivity disorders (54) during life.

(f) Supplementary Immunization Activities (SIAs). Three studies described the implementation of SIAs in different contexts (56, 115, 120). One article focused on a campaign in a large hospital in the Lombardy Region for unprotected HCWs (120). The other two articles described interventions in Roma/Sinti camps (56, 115).

(g) Laboratory methods. Ten studies compared laboratory methods for the diagnosis of measles or rubella (42, 87, 90, 93, 106, 135, 142, 150, 160, 165). Concerning measles, two studies compared chemiluminescent immunoassay (CLIA) and enzyme immunoassay (EIA) (142, 150), one CLIA and enzyme-linked immunosorbent assay (ELISA) (165), and another focused on a new ELISA method (42). For rubella, one study evaluated the characteristics of an automated immunoassay for rubella IgG and IgM using the Abbott ARCHITECT analyzer (106), and another compared the VIDIA assay

to the VIDAS, AXSYM and LIAISON assays for rubella virus IgG and IgM detection (90). Four studies focused on seroimmunological analysis for rubella in pregnancy (87, 93, 135, 160), and one of these (135) evaluated two TORCH survey systems.

(h) Vaccination (efficacy and safety, uptake, coverage, at-risk subpopulations, complications, vaccination strategies). Fifty-seven published articles described various aspects of vaccination, as shown in the subtitle. Seven studies gave information on the efficacy or safety of vaccines (24, 55, 59, 124, 125, 155, 182). Two articles focused on the evidence of effectiveness and the unwanted effects associated with MMR (59, 124), two other studies focused on the efficacy and safety of combined or co-administrated MMR and varicella vaccine (125, 182), while one article analysed the immunogenicity and reactogenicity to a new MMR vaccine (24). Two articles considered specific situations in which the vaccine could be administered: the first showed the safety and immunogenicity of MMR vaccine in children with congenital T-cell defect (55), while the second focused on the correlation between individual genetic variation and the efficacy of vaccines (155).

Six studies investigated the problems connected with poor adherence to a vaccination program, and they focused on different reasons that should be interfered in a vaccination program (28, 121, 174, 175, 184, 189). Three articles investigated the factors that could affect the parental decision to vaccinate their children (28, 175, 189). One study underlined the interplay of public intervention and private choices in determining the outcome of, and adherence to vaccination programs (121). The parental perspective on psychological empowerment in the MMR vaccination decision was covered in one report (184), and another studied a different approach to vaccination, underlining the moral requirement for preventive intervention measures (174).

Twenty-two studies described vaccination coverage for measles, rubella or both (33, 36, 48, 50, 51, 62, 70, 71, 82, 84, 98, 100, 128, 137, 151, 161, 162, 168, 177, 178, 185, 186). Five studies focused on the measles and rubella coverage in HCWs to assess the level of immunization in this group (33, 82, 98, 100, 168), while one article described the MMR vaccine coverage in students taking university courses for the medical professions (70). Two articles described measles and rubella coverage in the general population of northern Italy (62, 161). Two reports considered vaccination coverage in children aged < 24 months (36, 50). One study examined measles coverage in Naples in 2001-2002 (51). Four articles (71, 178, 185, 186) described vaccination coverage in very specific categories, such as adopted children (71, 178) and children living in Italian foster homes (185, 186). Four articles focused on patients with specific pathologies and evaluated measles and rubella coverage in different target populations: HIV-1 infected patients (177), children with chronic disease (128), children with autism spectrum disorders (137), and patients with inborn errors of metabolism (162). Three studies focused on rubella coverage in the general population (48, 84) and in women of childbearing age (151).

Concerning at-risk subpopulations, four articles focused on indications for vaccination in groups with health problems (63, 136, 147, 158). One study provided specific recommendations on vaccination for paediatric, haematological and oncological patients (147), while another analysed vaccination in patients with disorders of the muscles and neuromuscular junctions (136). One article focused on the need to improve the timeliness of vaccination for preterm infants, for whom immunization is considerably delayed (158). Another article demonstrated that MMR vaccination is compatible with egg allergy (63).

Nine studies described possible

complications relating to vaccine administration; such complications were highly variable (25, 99, 108, 134, 140, 141, 159, 179, 183). Five articles focused on autoimmune manifestations induced by the MMR vaccine (99, 108, 134, 159, 183): two were specifically on the development of immune thrombocytopenic purpura in children (99, 134), two case reports described neurologic manifestations (159, 183) and one article described autoimmunity induced by vaccination (108). Other articles described measles infection as the consequence of vaccination (179), febrile seizure after measles vaccination (140), development of opsoclonus-myoclonus syndrome after anti-rubella vaccination in a young woman (25), and epilepsy after vaccination (141).

Nine studies gave an overview of vaccination strategies (1, 32, 47, 58, 75, 89, 107, 113, 132). Two articles focused on health care workers: one assessed prevention with vaccination as a powerful instrument for health care workers in a hospital (107), while the other described the delivery of MMR vaccine to HCWs in the Lombardy Region and also evaluated the possibility of extending it to critical patients (75). Two articles described measles vaccination policies implemented in the Italian Regions (47) and the effect of regional organisation and management of vaccination programs (113). One article investigated the effectiveness of the vaccination program in the Latium Region in reducing cases of infection (32), while another study described the strategies proposed by the National Plan 2010-2015 to eliminate measles and rubella (1). Two articles reported vaccine strategies in different contexts (89, 132). One article underlined the role of economic evaluation of the implementation of vaccination strategies (58).

(i) Others. We retrieved a further 38 articles not included in the above-mentioned categories. The main topics were: history of measles and rubella infection (176)

and vaccination (153, 156, 164, 171); structural characterization of measles and rubella viruses (88, 166, 181); new drugs for infected patients (31, 35, 43, 78, 81); correct procedures for congenital rubella diagnosis and treatment (67, 133); analysis of measles and rubella elimination strategies for European countries and Italy (13, 16, 49, 116, 127, 154, 170, 192); simulation models to estimate various issues of measles and rubella infection, such as epidemiological trends, costs of measles incidence and the impact of the elimination plan (38, 53, 60, 61, 123).

Conclusions

The success achieved in a number of countries against measles and rubella shows that elimination is technically possible with the vaccines available and with targeted vaccination strategies. The current paradox in prevention is that immunization programs can become victims of their own success. Some vaccine-preventable diseases have become so sporadic that people, and even healthcare professionals, fail to appreciate the benefits of vaccination. In Western Europe, measles and rubella are not perceived as a serious problem and anti-vaccine movements have gained popularity in the last decades, dangerously publicizing unfounded vaccine safety concerns (1). Moreover, it is well known that prevention loses consideration in times of economic crisis: there is much evidence that Italian Regions with financial problems devote less attention and fewer resources to prevention activities (193-198).

Italy is still at the stage of limited control of measles, especially as far as adolescents and young adults are concerned, and women of childbearing age are not adequately protected against rubella infection. Several priorities can be identified.

First, there is need to increase the commitment of the 21 Italian Regions.

There is some evidence that the institutional devolution introduced in Italy has influenced the regional organization and performance in managing vaccination programs (113). To strengthen their ownership of the elimination goals, the Regions should clearly understand their situation in the elimination process. Since the annual status reports permit the documentation of progress across the whole country, and not just of a single Region, one potentially effective strategy could be to produce regional annual reports to provide Regions with feedback about their own progress towards elimination. Furthermore, regional reports could be instrumental in identifying those Regions with major problems, which must be supported as a priority through appropriate interventions such as audit and site visits.

Second, SIAs are needed for population groups with levels of immunity that are inadequate to interrupt endemic measles and rubella transmission (15, 199). Susceptible population groups should be defined by evaluating existing epidemiological data on measles and rubella cases, by assessing historical vaccine coverage data or, in some circumstances, by conducting serosurveys (4). Several seroepidemiological surveys have been performed in Italy (91, 118, 190). These surveys discovered pockets of susceptibility to measles and rubella, and identified target populations requiring MMR vaccination catch-up programs, such as adolescents, young adults, adults (particularly fertile women), and hard-to-reach groups with poor access to health care and health promotion (e.g. the Roma/Sinti communities) (91, 118, 190).

Additional immunization efforts should be targeted at susceptible groups such as health care workers. It is well known that HCWs are at higher risk of exposure to measles than the general population and a HCW with measles will inevitably come into contact with large numbers of high-risk patients and expose them to the virus

(15). Nosocomial transmission of measles has frequently been reported in Italy and has a major role in the epidemiology of the disease (117, 167, 187). It can have serious consequences since the virus might be transmitted to immunocompromised patients, young children, pregnant women, or other persons at high risk of severe complications (98). The PNEMoRc 2010–2015 strongly recommends vaccination of susceptible adults at risk of contracting and transmitting disease, such as health professionals (18). However, immunization coverage among HCWs has often been reported as very low (168). Misconceptions regarding the severity of measles or the safety of MMRV persist not only among parents, but also among HCWs. Inadequate knowledge of the advantages of vaccination among HCWs can have substantial negative effects on vaccination coverage. Therefore, it is fundamental to raise awareness about the disease and fill any knowledge gaps among health care workers, providing them with evidence-based information on vaccines and educating them to communicate effectively with patients and parents (200). This will enable HCWs to address misinformation and vaccine hesitancy, maximizing their potential roles in promoting elimination efforts.

Another priority is the need to improve the health literacy of citizens in the field of vaccination. The low immunization rates highlight the importance of identifying and understanding the factors that affect the uptake of recommended childhood immunizations, so that proper interventions and public health policies can be instigated with the aim of increasing vaccine compliance; various studies have been carried out in Italy on this topic (175, 189). Furthermore, risk perception is highly influenced by anti-vaccination movements, which are particularly efficient at spreading their views on the Internet. As well as ignoring or avoiding scientific evidence, such groups have also been offering tropes

(mottos or phrases used recurrently) to create fear, uncertainty and doubt about vaccines (201). To counteract the misinformation on vaccines, the adoption of innovative tools should be encouraged. An effective example is the website “VaccinarSI”, promoted by the Italian Society of Hygiene, which aims to address the lack of information on the web and at the same time to demonstrate the validity of vaccination (202). It is also important to engage the healthcare operators and the general population in spreading the use of communication channels among peers, such as the “Italian Paper for the Promotion of Vaccinations”, born from the collaboration with existing initiatives –as the portal “VaccinarSI”- and with groups of the population. It represents a call to action to be offered to all those people who desire to take the opportunity to sustain and spread the importance of vaccines (203, 204). Finally, civil society organizations could play an important role in improving the sustainability of the vaccination programs: innovative and effective new approaches could communicate the benefits of vaccination by means of public events, messages from celebrities, and social media blogs. By working with experts, civil society organizations can also be an important bridge between the scientific community and the lay public (205).

To interrupt the circulation of measles and rubella viruses, public health institutions should also prioritise the strengthening of surveillance and outbreak control systems. A prompt and accurate laboratory diagnosis, including molecular characterization of the measles virus, is essential to identify imported viruses, to define import-related outbreaks and to understand transmission patterns (126, 138, 149, 172, 188). Sensitive virological surveillance can be guaranteed by integrated measles and rubella surveillance. In Italy, laboratory surveillance is performed by the National Reference Laboratory (NRL) for Measles and Rubella and by several subnational laboratories. Experience at

regional level has shown that molecular characterization of measles viruses enriches epidemiological investigation since it allows researchers to observe the change in virus genotypes over time in a particular Region. This helps document the interruption of virus transmission and provides an important method for assessing the effectiveness of vaccination programs (1, 92, 103, 104, 161, 191). However, to improve the quality of surveillance data, there is a need to strengthen collaboration between laboratories and to formalize a national network of MR subnational laboratories compliant with the WHO MR LabNet standards. This will allow timely linkage of case-based epidemiological and laboratory data and ensure a prompt outbreak response (20).

In conclusion, the epidemiological situation for measles and rubella in Italy, including the vaccination coverage rates, is of great concern. All the above-mentioned priority actions should be pursued to reach the goal of measles and rubella elimination; indeed, these actions have already been included in two major projects financed by the Ministry of Health in support of the PNEMoRc. Without sustained political commitment, increased investment and accelerated actions, the eradication of measles and rubella will remain an unrealized dream.

Acknowledgements

Funding: none. Competing interest: none declared. Ethical approval: not required.

Riassunto

L'eradicazione del morbillo e della rosolia congenita: un sogno realizzabile?

Premessa. Nonostante progressi sostanziali siano stati fatti nel controllo del morbillo e della rosolia, diversi focolai epidemici continuano a mettere a rischio gli obiettivi dell'eliminazione in tutte le Regioni dell'OMS.

Disegno dello studio. Questo studio documenta i progressi verso l'eradicazione nel mondo e in Europa, con un'attenzione specifica sull'Italia, individuando le sfide principali del Paese nel raggiungere gli obiettivi di eliminazione.

Metodi. È stata effettuata una revisione della più significativa letteratura relativa al morbillo e alla rosolia. È stata condotta inoltre una revisione sistematica della letteratura relativa al contesto specifico italiano.

Risultati. Con il Piano Nazionale 2010-2015 l'Italia ha rinnovato il suo impegno nella eliminazione del morbillo e della rosolia per il 2015. Tuttavia il peso del morbillo in Italia negli ultimi anni è stato elevato (2.205 casi nel 2013, 1.694 casi nel 2014). Nel periodo giugno 2015-maggio 2016 si sono verificati 515 casi (28% di tutti i casi in Europa). Le coperture vaccinali sono in diminuzione, al di sotto del 95% in tutte le Regioni. La revisione sistematica della letteratura ha evidenziato un totale di 175 articoli pubblicati tra il 2000 e il 2016, con un trend crescente che mostra un incremento di interesse nei confronti del morbillo e della rosolia. Le principali azioni prioritarie da implementare comprendono l'aumento dell'impegno politico delle Regioni; l'implementazione di attività supplementari di immunizzazione; il miglioramento delle capacità comunicative del personale sanitario; la crescita dell'alfabetizzazione sanitaria dei cittadini; il rafforzamento della sorveglianza integrata.

Conclusioni. Sono necessari ulteriori sforzi per assicurare il pieno impegno dell'Italia nei confronti degli obiettivi di eliminazione.

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