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Measles, Rubella, and Tetanus Vaccinations: a Brief Global Review

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Abstract

Purpose of Review The study aims to review the prevention efforts for vaccine preventable diseases.

Recent Findings Significant progress in global vaccination coverage has been made since World Health Organization established the Expanded Programme on Immunization to ensure that all children have access to routinely recommended vaccines. Global coverage with vaccines to prevent tetanus, poliomyelitis, or measles has increased from < 5 to ≥ 85% in multiple countries, and for the first time, in 2016, global estimated measles deaths were fewer than 100,000. However, vaccination rates for the third dose of polio vaccine, diphtheria, tetanus toxoids, and pertussis-containing vaccine and first dose of measles-containing vaccine have remained unchanged at 84–86% since 2010, demonstrating a need for new strategies to improve immunization rates especially in low-income regions.

Summary In addition to political commitment from governments, disease surveillance efforts should be strengthened. In developed countries, vaccine refusal should be continuously addressed. In this review, tetanus, measles, rubella, and polio vaccinations are discussed with their unique success stories and challenges.

Keywords Measles elimination · Tetanus elimination · Rubella · Polio · Vaccine preventable diseases

Introduction

Of all the contributions made to global health in the past centuries, immunization continues to be one of the most cost-effective interventions, preventing 2 to 3 million deaths every year [1]. Expanded Programme on Immunization (EPI) by the World Health Organization (WHO) developed in 1974, and later, the Global Alliance for Vaccination and Immunization (GAVI) developed in 2000, not only enhanced the global coverage of vaccination but also reduced the pediatric hospitalization rates, overall disease burden, and childhood mortality of vaccine preventable diseases [2, 3]. Taking these significant successes into account, the fourth United Nations Millennium Development Goal was adopted in 2000 and set a target to reduce the child mortality by two thirds by 2015. Currently, the new set of Sustainable Development Goals which span from 2015 to 2030 fit into a global development framework, and among other goals included the reduction of inequality within and among countries, one of the main determinants of vaccine access.

There are numerous examples of advances that have been made in development and expansion of vaccinations leading to increased coverage. The coverage for three doses of the diphtheria-tetanus-pertussis (DTP) vaccine rose from 52% in 2000 to 76% in 2015 in the African WHO region [4]. The rotavirus vaccine was introduced in 90 countries by the end of 2016 with significant coverage, and the MenAfriVac (meningitis A), only 6 years after its introduction, has been given to over 260 million people living in the African meningitis belt [5]. The first dengue vaccine (CYD-TDV) was registered in Mexico in December 2015 to be used in 9- to 45-year-old individuals living in high-risk areas, and the RTR S/AS01 malaria vaccine is being evaluated in pilot studies in sub-Saharan Africa to determine its risk/benefit profile before being added to the core malaria prevention package [6, 7].

Optimizing the full benefits of immunization has been challenging despite the obvious progress and benefits, especially

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in regard to the availability, access, acceptability, and optimal delivery in many regions. The global vaccination coverage for the diphteria-tetanus-pertussis (DTP) vaccine was 86% in 2016, a number that has barely changed since 2010, and is still suboptimal especially in children who are born in low- and middle-income countries [8]. Vaccine preventable diseases remain among the leading causes of mortality in children less than 5 years of age in some regions of the world [8]. The immunization rates show a great global disparity between countries, and within richer and poorer areas of the same country [8]. As of 2016, eight countries had less than 50% immunization coverage including Central African Republic, Chad, equatorial Guinea, Nigeria, Somalia, South Sudan, Syrian Arab Republic, and Ukraine. Worldwide, 19.5 million infants are still missing basic vaccines, and estimates from 2016 showed that 1 out of 10 infants had not received any vaccines [9].

The inequalities in vaccination coverage brought the global health community to call for a Decade of Vaccines (DoV) in 2010. The objectives of DoV were to extend and optimize the benefits of immunization worldwide by 2020. The Global Vaccine Action Plan (GVAP) was then developed by WHO and United Nations International Children's Emergency Fund (UNICEF) to allow a more equitable access to existing vaccines for all populations by strengthening the national immunization programs. To date, the targets set by the GVAP are still far away. The 2017 GVAP assessment report concluded that there is a need to continue focusing on (a) strengthening the power of national immunization programs, (b) reinforcing the alignment between emerging global health agendas and immunization, (c) strengthening international cooperation by recognizing common interests, (d) growing towards applying immunization beyond childhood, and (e) strengthening the dialog with other sectors [8].

There are many vaccine preventable diseases that remain important global health problems. Among these, the eradication of measles, rubella, and maternal and neonatal tetanus remain a priority for GVAP and will be addressed individually in this review. Polio eradication is almost achieved, setting a remarkable example, but efforts for its eradication go in hand with measles and tetanus control; hence, we will review it briefly here as well. Some of the other vaccine preventable diseases and their current situation have been summarized in Table 1.

Maternal and Neonatal Tetanus

Introduction

Despite the availability of tetanus toxoid-containing vaccines (TTCV) since 1924, tetanus continues to be a global health problem, affecting the most disadvantaged populations [28]. In areas such as Africa and Southern and East Asia where TTCV coverage has not been achieved, women give birth to newborns that are not protected against tetanus contributing to the maternal and neonatal tetanus burden. The WHO first called for the elimination of neonatal tetanus in 1989. The Maternal and Neonatal Tetanus Elimination Initiative (MNTE) was launched by UNICEF and its partners in 2000 [29, 30]. Its main strategies include improving immunization coverage of pregnant women and women of childbearing age, birth hygiene promotion, and optimizing surveillance systems [29]. In 2002, mortality from neonatal tetanus was estimated at 180,000 worldwide, which represents a 78% reduction since the 1980s [31]. Between 2000 and 2017, 44 countries eliminated maternal and neonatal tetanus and more than 150 million women have been immunized with two or more doses of TTCV. Despite these progresses, unfortunately, an estimated 34,000 neonates died from tetanus in 2015 [31], and as of December 2017, 15 countries have not yet achieved tetanus elimination [18]. The initiative's goal is to achieve less than 1 case of neonatal tetanus per 1000 live births in every district of every country by 2020.

Epidemiology

Tetanus is caused by the spores of toxigenic strains of *Clostridium tetani* and usually presents with increased muscle tone and spasms. Whereas tetanus is usually wound associated in other populations [28], inadequate maternal immunity and unhygienic perinatal practices represent the main risk factors for the development of tetanus in newborns and mothers [32]. In addition to unhygienic umbilical cord care, maternal tetanus can occur after unhygienic practices during delivery, miscarriage, or abortion.

Most of the reported tetanus cases worldwide occur in newborns in low-income countries. Case fatality rates for tetanus could be as high as 80% without appropriate inpatient care [33] and around 50% with reported hospital care [34]. Limited treatment options due to the lack of effective drugs combined with scarcity of resources contribute to the high mortality rates. Newborn deliveries outside of health care settings and overall poor reporting hamper surveillance reports, and the real incidence of neonatal tetanus is not known in many regions. Studies have indicated that only 2–5% of cases may be reported, making planning and assessment of elimination programs difficult [33]. Despite these challenges, considerable progress has been made towards global elimination of neonatal tetanus, with most recent figures reporting that 38 of the targeted countries have now eliminated the disease with a reduction in incidence to 58,000 cases a year (Fig. 1) [33].

Table 1 Vaccine type, WHO immunization recommendations, current situation, and goals by disease

Disease	Vaccine type	Vaccine regimen recommended by WHO	Immunization coverage	Mortality and current situation	Goals
Measles [10–15]	Live attenuated	First dose at 12 months (nine in countries with high rates of transmission), and second dose at 15–18 months	MCV1 85% MCV2 64–85% of WHO member states have introduced MCV2 in their schedules	Mortality: 89,780 (2016) Cases reported: 117,115 (2017)	Eliminate measles and rubella in 5 WHO regions by 2020
Rubella [13, 16]	Live attenuated	1 dose at 9–12 months, with measles vaccine 1 dose in adolescent girl or woman of childbearing age if not vaccinated before	152 of 194 countries have introduced rubella vaccines, but national coverage ranges from 13 to 99% (2016)	11,675 rubella cases reported (2017) > 100,000 babies estimated to be born with CRS (2010)	
Mumps [16, 17]	Live attenuated	2 doses, with MCV (integrate strategies with measles/rubella; use of MMR is strongly encouraged)	Introduced in 121 countries by 2016	583,199 cases worldwide (2016), mainly Western Pacific and African regions	
Polio [16, 17]	Inactivated (injectable) Live attenuated (oral)—being discontinued	3–4 doses, at least one of IPV with DTP	85% receiving 3 doses (2016)	Polio has been stopped in all countries except for Afghanistan, Pakistan, and Nigeria Polio-free countries have been infected by imported virus	Eliminate polio by 2018
Rotavirus [16, 17]	Live attenuated (oral)	Rotarix: 2 doses with DTP Rotateq: 3 doses with DTP Recommended for all countries, but for countries where diarrhea accounts for ≥ 10% of childhood deaths, it is strongly recommended	Introduced in 90 countries by 2016, coverage estimated at 25%	Mortality: 527,000 children < 5 years (2004)	
Tetanus (*Clostridium tetani*) [18, 19]	•Toxoid-containing vaccines •Single antigen vaccine or in combination	•3 rounds of TTCV for WCBA and pregnant woman in high-risk areas •3 primary (start at 6 weeks, with minimum intervals of 4 weeks) + 3 boosters (12–23 months of age (DTP), 4–7 years of age (Td), and 9–15 years of age (Td)[a]	•86% (DTP3) •72% reported TT2 + coverage (among pregnant women) •27% of countries reached ≥ 80% DTP3 coverage in all districts (2016)	•Mortality: 34,019 neonates (2015) •Maternal and neonatal tetanus is still a burden in the poorest regions •15 countries have NOT yet eliminated MNT (December 2017)	•MNT elimination Other preemptive measures: -Birth hygiene -Appropriate wound care -Surveillance
Diphtheria (*Corynebacterium diphtheriae*) [20]	•Inactivated bacterial toxoid (DTP, pentavalent, Td)			• 7097 cases (2016) •Mortality > 10% in infants • Sporadic cases or small outbreaks	•The objective of the GVAP is to obtain 90% or more DTP3 vaccination coverage at the national level and 80% or more in all districts
Pertussis (*Bordetella pertussis*) [8, 21]	•Whole-cell vaccine (wV) or acellular vaccine (aV)	•3 primary doses (initiated at 6 weeks of life and no later than 8 weeks), 1 booster dose (at 1–6 years, and ≥ 6 months after last primary dose) •National programs may consider vaccination of pregnant women with one dose of Tdap[b] (in the		•Endemic in all countries with epidemic cycles every 2–3 years •The main aim of vaccination is to reduce risk of severe pertussis in infants and	

Table 1 (continued)

Disease	Vaccine type	Vaccine regimen recommended by WHO	Immunization coverage	Mortality and current situation	Goals
		second or third trimester and preferably at least 15 days before the end of pregnancy) as a strategy additional to routine primary infant pertussis vaccination in countries or settings with high or increasing infant morbidity/mortality from pertussis		young children due to high mortality and morbidity •Mortality < 5 years: 63,000 (2013)	
H. influenzae (HIB) [22, 23]	•Conjugated vaccine •Multiple formulations	•From 6 weeks to 6 months: 2–3 doses with intervals of at least 4 weeks •Alternatives: 3 primary doses, 2 primary + 1 booster, or 3 primary + 1 booster •If booster dose is given, it must be ≥ 6 months after last primary dose	•70% global (2016) •WHO regions of Americas 90%. Western Pacific 28% •Introduced in 191 countries as of 2016	•90% of cases of invasive HIB disease occur in children < 5 years of age • Children infected with HIV have increased risk of HIB invasive disease	•Vaccines are the only public health tool capable of preventing the majority of serious HIB disease • HIB vaccines are safe and efficacious even when administered in early infancy •WHO recommends inclusion of conjugate HIB vaccines in all infant immunization programs
Streptococus pneumoniae [24]	•Conjugate vaccines (PCV 10 and 13) •23-valent polysaccharide vaccine (PCV23) (numbers indicate the number of serotypes included in the vaccine)	With conjugate vaccines: •3 doses, with DTP or •2 doses before 6 months of age, plus booster dose at 9–15 months of age	•42% global (2016) •Introduced in 134 countries by the end of 2016	• < 5 years of age in 2008, WHO estimated that 476,000 (333,000–529,000) of the deaths were caused by pneumococcal infections [23] •Disease rates and mortality are higher in developing than in industrialized settings, with the majority of deaths occurring in Africa and Asia •Children with HIV infection are at substantially increased risk of serious pneumococcal disease	•WHO recommends the inclusion of PCVs in childhood immunization programs worldwide. In particular, countries with high childhood mortality (mortality rate of > 50 deaths/1000 births in children younger than 5) should make the introduction of these multicomponent PCVs a high priority
Neisseria meningitidis (A, B, C, X, W, and Y) [25, 26]	•Polysaccharide or conjugate (A, C, W135, Y), (A, C, W135), (A, C) •Protein based: B •No vaccines for X	•Countries with high (> 10 cases per 100,000 population/year) or intermediate (2–10 cases per 100,000 population/year) endemic rates and/or frequent epidemics of invasive meningococcal disease: large-scale meningococcal vaccination programs		•No reliable estimates of disease burden due to poor surveillance in certain areas •> 50% mortality if untreated •Observed worldwide •The most affected region sub-Saharan Africa (meningitis belt): from Senegal to Ethiopia (26 countries), were around	•To control invasive, group A disease in all countries in the African meningitis belt •Optimize disease surveillance and vaccination program evaluation in high-incidence areas

Table 1 (continued)

Disease	Vaccine type	Vaccine regimen recommended by WHO	Immunization coverage	Mortality and current situation	Goals
		•Countries with low incidence: vaccination recommended for defined risk groups		30,000 cases are still reported each year	
Meningococcus A (Men A) [27]	•Polysaccharide-protein conjugate vaccine	•Complete mass vaccination campaigns with 1 dose in individuals aged 1–29 in the African meningitis belt •1 dose between 9 and 18 months as routine childhood vaccination	•280 million persons have been vaccinated with the Men A vaccine in 2016 African belt countries		

TTCV tetanus toxoid-containing vaccines; *WCB* women of childbearing age; *DTP* diphtheria, tetanus, and pertussis vaccine; *Td* tetanus and low-dose diphtheria toxoid; *TT2+* two or more doses of tetanus toxoid-containing vaccines; *MNTE* maternal and neonatal tetanus elimination; *Tdap* tetanus, low-dose diphtheria toxoid and acellular pertussis; *PCV* pneumococcal conjugate vaccine; *GVAP* Global Vaccine Action Plan

[a] To further promote immunity against diphtheria, diphtheria toxoid and tetanus toxoid rather than tetanus toxoid alone should be used when tetanus prophylaxis is needed following injuries

[b] In children > 7 years of age and pregnant woman, acellular vaccines should be used

The Maternal and Neonatal Tetanus Elimination Initiative

The strategies of the MNTE initiative include

A) Improving immunization coverage of mothers

In high-incidence settings, where most deliveries occur at home, interventions to improve immunization coverage are crucial [34]. It has been estimated that neonatal tetanus mortality can be reduced by 94% (95% CI 80–98) by immunizing woman of childbearing age (WCBA) and/or pregnant woman [35]. The main strategies to achieve these goals in high-risk regions for maternal and neonatal tetanus (MNT) include (a) implementation of routine childhood immunization schedules (three primary and three booster doses, one per decade), (b) strengthening routine immunization practices in pregnant women, and also (c) mass campaigns through supplementary immunization activities (SIA). This involves global vaccination of woman of childbearing age living in high-risk areas with three rounds of TTCV. This strategy has proven to be cost-effective and to improve coverage in otherwise unreached population [28, 36]. The main WHO objective is to protect newborns and mothers until the six-dose childhood/adolescent schedule reaches high coverage, and future WCBA are protected [19].

B) Birth hygiene

Interventions that advocate improving hygienic practices during the delivery and adequate perinatal care are effective in reducing neonatal tetanus mortality and should be promoted [34, 37]. In China, maternal and neonatal tetanus was successfully eliminated in 2012 primarily by providing universal clean services and increasing in-hospital delivery rates [38]. WHO advocates using six hygienic measures: clean birth surface, clean hands, clean perineum, cord cutting, cord tying, and cord care. Skilled birth attendants (SBA) and hygienic umbilical stump practices have shown to reduce the risk of neonatal tetanus (NT) and neonatal mortality [39, 40]. Recent evidence suggests that provision of clean delivery kits for home deliveries can decrease neonatal mortality, independent of SBA [41].

C) Surveillance

Many cases of NT occur outside of health facilities and are never recorded. Tetanus is a non-communicable disease unlike other vaccine preventable diseases. Optimizing surveillance is crucial to understand the real disease burden and to evaluate the effectiveness of interventions. To determine whether a country had met the NT elimination definition, a formal survey method has been developed [42]. There have

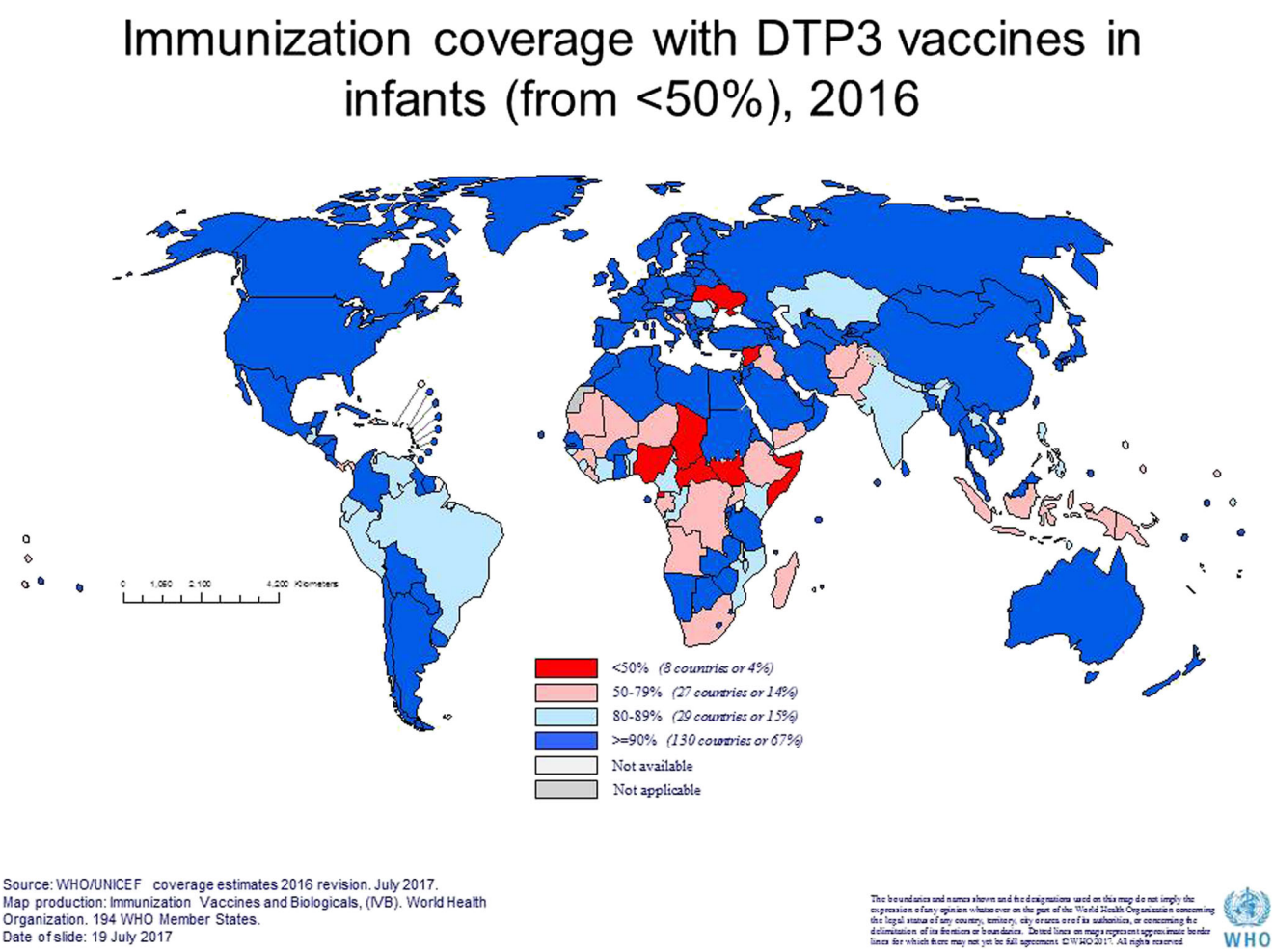


Fig. 1 "Developing" countries with percent of districts achieving at least 80% DTP3 coverage, 2014

also been significant efforts towards identifying high-risk areas requiring supplementary immunization activities and closely monitoring the results of the vaccination campaigns [32]. WHO recommends routine monthly surveillance and retrospective record review at least once a year at major health facilities to identify unreported cases [43].

In summary, there are still several challenges that will require a join effort from the different global health associations, stakeholders, and communities for elimination of MNT. Lack of disease knowledge, poor hygiene practices of local communities, and misinformation about the objective of the vaccine campaigns have been some of the socio-cultural problems encountered in countries like Pakistan, Kenya, or Mexico [44].

Measles

Introduction

Measles is one of the most contagious infections with serious complications including pneumonia, diarrhea, keratoconjunctivitis, and encephalitis [45]. Case fatality rates vary from 0.1% in developed world to 15% in the developing countries, with deaths usually due to pneumonia or diarrhea [10]. Diarrhea is more severe in children with underlying malnutrition and resource poor settings with limited access to health care and rehydration strategies.

When the Expanded Programme on Immunization (EPI) was launched in 1974, measles vaccine was one of the six vaccines included in the basic package recommended for all children in developing countries. Measles was unique among the proposed vaccine preventable diseases with high transmission rates. It has been shown that population immunity of 92–95% is necessary to stop measles transmission [10].

In 2001, the Measles Initiative, a coalition led by UNICEF, WHO, Center for Disease Control and Prevention (CDC), United Nations Foundation (UNF), and the American Red Cross, was formed, spearheading a more aggressive approach to measles control (increasing first- and second-dose vaccine coverage with SIAs). This strategy was initially very successful and resulted in a reduction of estimated measles mortality

by 74% in 2010 relative to 2000. However since then, the gains have slowed down [46].

In 2010, the World Health Assembly (WHA) set three milestones for measles control by 2015: (1) increase routine coverage with the first dose of measles-containing vaccine (MCV1) among children aged 1 year to ≥ 90% at the national level and to ≥ 80% in every district, (2) reduce global annual incidence to less than five cases per million population, and (3) reduce global measles mortality by 95% from the 2000 estimate [11].

In 2012, the initiative, now targeting measles and rubella (Measles and Rubella Initiative), published the "Global Measles and Rubella Strategic Plan 2012–2020" to achieve elimination of both diseases by 2020 in at least five WHO regions [46].

Epidemiology

Before the introduction of measles vaccine in 1963 and widespread vaccination, major epidemics occurred approximately every 2–3 years, and measles caused an estimated 2.6 million deaths each year [47]. Virtually, every person acquired measles before adulthood. In the USA, before implementation of vaccine, measles occurred in epidemic cycles, and for every 1000 reported measles cases, approximately 1 case of encephalitis and 2–3 deaths resulted [12]. In USA, the rates significantly declined, but unfortunately, in low- to middle-income countries, measles continues to be a huge burden and disease is often more severe with case fatality rates as high as 25%. In USA, measles has been continuing to cause outbreaks in communities where vaccination rates have been low due to vaccine refusal as well as following overseas travel to measles endemic areas. The Center for Disease Control and Prevention reported outbreaks in 2008, 2011 (mainly related to imported cases from Europe), 2013, 2014 (related to unimmunized Amish population in Ohio), 2015 (linked to a traveler visiting an amusement park in California—the virus from this outbreak was identical to the one identified in the 2014 Philippines outbreak), two in 2016 (Tennessee and Arizona), and the most recent one in 2017 (Minnesota) [48]. This last outbreak occurred in a Somali-American population with low vaccine coverage (declining since 2007) due to parental concerns for association of MMR vaccine and autism [49].

Physicians in low-risk areas are not familiar with measles presentation and rash. In a recent cluster observed in Hawaii, measles cases were seen following a late diagnosis of an infant who traveled to the Philippines during a community outbreak [50]. Significant measles increase was reported in Europe since 2011, especially in France [48]. Outbreaks were reported in 2013 and in 2014 in Azerbaijan, Bosnia and Herzegovina, Georgia, German, Italy, Latvia, the Netherlands, Russian Federation, Turkey, Ukraine, and the United Kingdom [46]. Groups of unimmunized people pose major programmatic challenges. For example, in Italy, where measles vaccination is recommended but not mandatory, a new outbreak has been observed since early January 2017. Italy is currently one of 14 European countries with ongoing endemic transmission [51].

The disease remains one of the leading causes of death among young children globally, despite the availability of a safe and effective vaccine, because vaccine coverage is not universal. Approximately 89,780 people died from measles in 2016—mostly children under the age of 5 years [47].

Most affected regions to date continue to be in the African region and the South East Asian region, mostly in developing countries with high infant mortality rates. The 2017 yearly WHO report shows countries with the highest number of cases as India (55,226), Nigeria (10,795), and Indonesia (6583) (Fig. 2) [13].

Rubella

Introduction

Rubella, another vaccine preventable (VPD) but mild disease, is primarily a concern because infection during pregnancy can result in severe birth defects named congenital rubella syndrome (CRS) including severe heart defects, cataracts, deafness, cleft palate, and mental retardation [46].

Epidemiology

Rubella was common in the USA before the licensure of live, attenuated rubella vaccines in in 1969, and rubella epidemics occurred every 6–9 years. Majority of patients were young children, with a peak incidence among children 5 to 9 years. During the last rubella epidemic in 1964–1965, an estimated 12.5 million rubella cases occurred in USA, resulting in approximately 2000 cases of encephalitis, 11,250 fetal deaths attributable to spontaneous or therapeutic abortions, 2100 infants who were stillborn or died soon after birth, and 20,000 infants born with CRS [12].

Unfortunately, vaccine coverage is not optimal especially in developing countries in the African region and the Southeast Asian region, where CRS rates are highest. Reported rubella cases declined 97%, from 670,894 cases in 102 countries in 2000 to 22,361 cases in 165 countries in 2016. In 2010, more than 100,000 babies with CRS were estimated to be born globally [46].

Measles and Rubella Laboratory Network

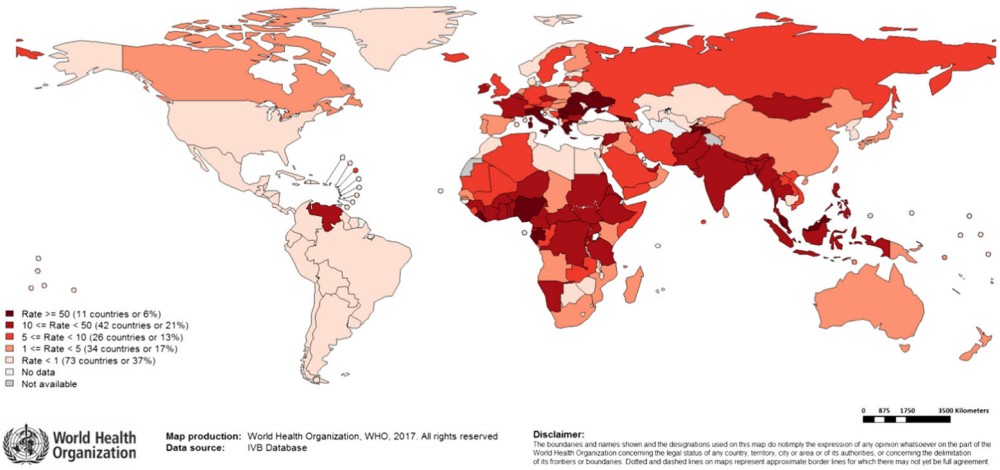
The global Measles and Rubella Laboratory Network (LabNet) was developed based on the successful model of

Measles Incidence Rate per Million (12M period)

World Health Organization

Top 10**		
Country	Cases	Rate
India	51626	38.99
Nigeria	10391	55.87
Indonesia	7790	29.83
Ukraine	7758	174.58
Pakistan	6151	31.84
China	5492	3.91
Italy	5041	84.82
Romania	4474	226.21
Bangladesh	3225	19.79
Serbia	2827	320.52

Other countries with high incidence rates***		
Country	Cases	Rate
Liberia	1041	225.63
Gabon	394	199.01
Greece	1851	165.51
Georgia	379	96.55
Malaysia	2227	71.41
Tajikistan	539	61.71



Measles cases from countries with known discrepancies between case-based and aggregate surveillance, as reported by country			
Country	Year	Cases	Data Source
DR Congo	2017	45,165	SITUATION EPIDEMIOLOGIQUE DE LA ROUGEOLE EN RDC, Week of 27/3/2018
	2018	5143	
Somalia	2017	23,353	Somali EPI/POL Weekly Update Week 14, 2018
	2018	4294	

Notes: Based on data received 2018-04 and covering the period between 2017-03 and 2018-02 - Incidence: Number of cases / population* * 100,000 - * World population prospects, 2017 revision - ** Countries with the highest number of cases for the period - *** Countries with the highest incidence rates (excluding those already listed in the table above)

Fig. 2 Measles incidence rate per million in 2017, modified from WHO data report [51]

the global polio laboratory network, and as of 2013, 696 laboratories have been established in 164 countries, majority as part of WHO laboratory network [52]. LabNet provides results for measles and rubella immunoglobulin M (testing of suspected cases) and share virus sequencing information (confirmed cases). This network provides valuable global information about the circulation of measles and rubella infections and is a vital resource for immunization programs to monitor virus transmission patterns and help document successful elimination strategies [53].

Progress Towards Elimination

Measles vaccines are highly effective. One dose of the MMR vaccine is 95% effective at preventing measles and 92% effective at preventing the spread of measles to household contacts [45]. A small percentage of people do not mount effective response to first dose of MCV1 and outbreaks can continue to occur, so providing a second dose of measles-containing vaccine (MCV2) has been recommended to overcome this gap [47].

Significant gains towards measles elimination have been made in the past 17 years. Between 2000 and 2016, 87% decrease in reported measles incidence and 84% reduction in estimated measles mortality were achieved (from 550,100 (95% CI = 374,000–896,500) in 2000 to 89,780 (95% CI = 45,700–269,600) in 2016) [11]. Measles vaccination prevented an estimated 20.4 million deaths during this period [11]. Measles has been eliminated from the USA in 2000 and from the entire WHO region of the Americas in 2002. However, as stated above, measles cases and outbreaks associated with importation of the virus in contact with susceptible (unimmunized) groups continue to occur [12, 47].

During 2012–2015, the number of WHO member states/countries providing MCV2 nationally through routine immunization services increased from 131 (68%) to 154 (79%). Estimated global MCV2 coverage increased from 48 to 56%. By the end 2015, Regional Verification Commissions (RVCs) in the American, European, and Western Pacific

regions had verified elimination of measles in 61 member states (34 of 35 in the Americas, 21 of 53 in Europe, and 6 of 27 in the Western Pacific) and elimination of rubella in 67 member states (35 of 35 in the Americas, 20 of 53 in Europe). All six regions included in these surveys have measles elimination goals by 2020 and two have rubella elimination goals. However, none of the regions except the Americas has yet achieved its 2015 milestones [46].

As measles is one of the most contagious VPD and virtually all infections clinically manifest with rash and fever, it is usually the first recognized VPD to infect population clusters of susceptible persons. For these reasons, measles incidence rates are recognized as markers of the success of immunization systems and of overall health systems [46].

Despite all the progress made, in 2017, there have been 117,115 measles cases and 11,675 rubella cases reported worldwide [13].

The decrease in measles mortality was one of five main contributors to (along with decreases in mortality from diarrhea, malaria, pneumonia, and neonatal intrapartum deaths) progress towards the UN Millennium Development Goal of improvement in overall child mortality worldwide, but continued work is needed to help achieve measles elimination goals. Of concern is the possibility of drawback in the progress made due to decrease in funding after polio eradication is achieved. Countries with highest measles mortality rely most heavily on polio-funded resources. Improved implementation of elimination strategies is needed with focus on increasing vaccination coverage, surveillance systems, and securing political commitment [11].

Polio

Introduction

Polio is a highly infectious disease invading the nervous system, and can cause total paralysis in a matter of hours. The polio virus is transmitted by person-to-person spread mainly through the fecal-oral route and multiplies in the intestine. It mainly affects children under 5 years of age. One in 200 infections leads to irreversible paralysis. Among those paralyzed, 5–10% die because of inability to breath. There is no cure available, but vaccination is effective [54].

Epidemiology

Polio cases have decreased by over 99% since 1988, from an estimated 350,000 cases in more than 125 endemic countries to 37 reported cases in 2016.

Of the three strains of wild poliovirus (type 1, type 2, and type 3), wild poliovirus type 2 was eradicated in 1999 and no case of wild poliovirus type 3 has been found since the last reported case in Nigeria in November 2012 [54].

Progress Towards Elimination

Global Polio Eradication Initiative

In 1988, the World Health Assembly adopted a resolution for the worldwide eradication of polio. It marked the launch of the Global Polio Eradication Initiative (GPEI), spearheaded by national governments, WHO, Rotary International, the US Centers for Disease Control and Prevention (CDC), UNICEF, and supported by key partners including the Bill & Melinda Gates Foundation.

Since the GPEI was launched, the number of cases has fallen by over 99%. The WHO regions that have been certified polio-free are the following: Americas (1994), Western Pacific region (2000), European region (2002), and South-East Asia (2014). Currently, 80% of the world's population live in certified polio-free regions but endemic transmission is continuing in Afghanistan, Nigeria, and Pakistan [54].

An estimated 1.5 million childhood deaths have been prevented through the systematic administration of vitamin A during polio immunization activities.

The strategies for polio eradication work when they are fully implemented. However, failure to implement strategic approaches leads to ongoing transmission of the virus. Failure to stop polio in the last remaining areas could result in as many as 200,000 new cases every year, within 10 years, all over the world [54].

Much of the gains towards improving vaccine coverage for measles, rubella, diphtheria, and tetanus have been greatly influenced by the success of polio campaigns. As polio nears its end, efforts to maintain progress achieved in all of these diseases need to be emphasized. Effective re-direction of funds and strategies towards measles and tetanus/diphtheria vaccination need to be a priority.

Vaccine Refusal

Despite constant efforts to achieve better vaccine coverage and control of VPDs, there have been ongoing challenges brought by vaccination refusers. This in part has led to several of the recent outbreaks we have been facing.

Parental concerns include supposed association between autism and vaccines (disproved by scientific evidence), concern for weakened immune system due to multiple vaccines, and thinking that it is better to develop immunity from natural disease, supposing the disease severity is low, religious reasons or preference for complementary or alternative medicine [51]. These are mainly based on false information obtained from Internet or from peers rather

than evidence-based data from credible sources or discussions with clinicians [48].

The idea of a link between vaccines and autism has a long history but the thought that specifically, MMR vaccine may cause autism gained attention by the publication of an article by Andrew Wakefield in 1998. The article has been discredited and withdrawn by *The Lancet*. Since that time, many studies have found no evidence of a link between autism and MMR [45].

During the previously mentioned Minnesota measles outbreak (April 2017), the state and local health departments increased outreach to encourage vaccination (with culturally appropriate educational materials and interpreters). By the second week of May 2017, the average number of MMR vaccine doses administered per week had increased from 2700 doses before the outbreak to 9964, as reported by the Minnesota Immunization Information Connection [49].

Further discussion on vaccine refusal is beyond the scope of this article, but the authors consider it imperative to make health care providers aware of this growing problem and to encourage them to try address and discuss with parents all their concerns, providing appropriate evidence.

Conclusion

Despite vaccines being one of the most cost-effective public health interventions, ongoing and new challenges prevent countries around the world from optimizing the full benefits of immunization, and many children under 5 years of age still die from VPD. There has been an obvious effort from the global health community to address these challenges as seen by dramatic improvements in immunizations rates in the past decade; however, in the last few years, progress seems to have slowed down/stalled.

The poorest countries and regions are the most affected, having the highest mortality in children under 5 years of age and the lowest immunization coverage rates. Availability, access, acceptability, optimal delivery, and reliable surveillance programs are the main issues, requiring strategies that adapt to each region's political and social situation and therefore needing commitment from local governments.

On the other hand, developed countries that generally have no problem with access to vaccines, and where mortality due to VPD has been practically reduced to a few cases, have started to show increased incidence of VPD due to parental vaccine refusal.

Global immunization coverage is, and will continue to be, a challenge. Efforts should continue to address old and new challenges in order to achieve immunization goals, reduce child mortality, and ultimately, eliminate vaccine preventable diseases.

Compliance with Ethical Standards

Conflict of Interest Cristina Garcia-Mauriño, Cristina Tomatis Souverbielle, and Guliz Erdem declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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