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Innovations in measles and rubella elimination in Africa

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It is estimated that more than 21 million deaths have been averted, globally, by measles vaccination since 2000. Despite this undeniable success, measles elimination is facing various challenges including the inability of health systems to reach more children. Measles vaccine coverage has plateaued over the past 10 years to levels incompatible with measles elimination goals, vaccine hesitancy sometimes fueled by increasingly vocal anti-vaccine groups is posing new challenges, rumors spread even faster than the disease through social media, outbreaks of various scales are reported in various countries in Africa as well as in countries of Europe and North America that had virtually eliminated measles. The special issue aims to documents innovations that have impacted or have the potential to help accelerate progress towards measles elimination targets by focusing on immunization service delivery, community demand for vaccination and advocacy, injection safety, supply chain management and cold chain, immunization financing, measles laboratory, measles and rubella campaigns planning an implementation, and more.

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Special feature

The African Region early experience with structures for the verification of measles elimination – a review

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Guest editors: Robert Davis, James Goodson, Raoul Kamadjeu

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Abstract

Substantial progress has been achieved in the last two decades with the implementation of measles control strategies in the African Region. Elimination of measles is defined as the absence of endemic transmission in a defined geographical region or country for at least 12 months, as documented by a well-performing surveillance system. The framework for documenting elimination outlines five lines of evidence that should be utilized in documenting and assessing progress towards measles elimination. In March 2017, the WHO regional office for Africa developed and disseminated regional guidelines for the verification of measles elimination. As of May 2019, fourteen countries in the African Region have established national verification committees and 8 of these have begun to document progress toward measles elimination. Inadequate awareness, concerns about multiple technical committees for immunization work, inadequate funding and human resources, as well as gaps in data quality and in the implementation of measles elimination strategies have been challenges that hindered the establishment and documentation of progress by national verification committees. We recommend continuous capacity building and advocacy, technical assistance and networking to improve the work around the documentation of country progress towards measles elimination in the African Region.

Introduction

The WHO global vaccine action plan 2011-2020 outlines a goal for the elimination of measles and rubella in at least 5 WHO regions by 2020 [1]. In the African region, the regional goal for measles elimination was adopted in 2011, with a target date for 2020 [2]. The regional strategies to achieve elimination include increasing access and coverage with routine immunization services in all districts; achieving high coverage during all measles Supplemental Immunization Activities (SIAs), as well as improving the quality of measles surveillance. The member states adopted a goal with the following targets: i) ≥ 95% coverage with the first dose of measles-containing vaccine (MCV1) at national and district levels; ii) ≥ 95% coverage in all districts during measles SIAs; iii) confirmed measles incidence <1 per million population in all countries; iv) Attaining high quality measles surveillance as evidenced by a non-measles febrile rash illness (NMFRI) ≥ 2 per 100,000 population annually and the collection of a blood specimen from at least 1 suspected measles case in at least 80% districts annually [2, 3]. As of April 2019, the African Region does not yet have a goal targeting rubella/Congenital Rubella Syndrome (CRS) elimination. However, countries in the region are using the opportunity of implementation of measles elimination strategies to introduce rubella vaccine and to document the epidemiology of rubella through the existing measles case based and lab-supported surveillance system. By the end of April 2019, a total of 29 of the 47 countries in the region have introduced rubella vaccine in their vaccination schedules [4]. Currently, only a limited number of countries have implemented sentinel surveillance and/or retrospective reviews of clinical records for Congenital

Rubella Syndrome (CRS) [5]. Substantial progress has been achieved in the last two decades with the implementation of measles control strategies in the African Region. By the end of 2017, 8 (17%) of the 47 countries have coverage ≥ 95% according to the WHO-UNICEF estimates for national MCV1 coverage; 32 (74%) of 43 countries attained ≥ 95% administrative coverage in their most recent measles or measles-rubella SIAs; 23 (52%) of 44 countries in the case-based surveillance network have met the targets for the two principal surveillance performance indicators. Reported incidence of confirmed measles is less than 1 per million population in 20 (45%) of the 44 countries reporting case-based surveillance data regularly [4]. Between 2000 and 2017, estimated measles mortality declined by 86% in the African Region of the WHO [6].

The framework for verification of measles elimination

Elimination of measles is defined as the absence of endemic transmission in a defined geographical region or country for at least 12 months, as documented by a well-performing surveillance system. The 3 criteria for verifying measles and rubella elimination include: i) the documentation of the interruption of endemic measles and rubella virus transmission for a period of at least 36 months from the last known endemic case; ii) the presence of a high-quality surveillance system; iii) measles virus genotyping information that supports interruption of endemic transmission [7, 8]. The global and regional frameworks for the verification of measles elimination require that countries establish independent structures charged with compiling the programmatic and epidemiological information necessary to assess progress and document measles elimination [8]. This includes the establishment of National Verification Committees (NVC) with the primary responsibility for guiding countries in the preparation of their documentation of progress towards the achievement of measles elimination, as well as the Regional Verification Commission (RVC), which validates and verifies elimination in each country and eventually in the Region.

The framework for documenting elimination outlines five lines of evidence that should be utilized in documenting and assessing progress towards measles elimination: 1) a detailed description of the epidemiology of measles and rubella since the introduction of measles and rubella vaccine in the national immunization program; 2) population immunity, presented as a birth cohort analysis with the addition of evidence related to any marginalized and migrant groups; 3) quality of epidemiological and laboratory surveillance systems for measles and rubella; 4) sustainability of the national immunization program, including resources for interventions to sustain elimination; 5) genotyping evidence that measles and rubella virus transmission has been interrupted [7, 8].

When evaluating the lines of evidence, NVCs and RVCs are expected to review all the available data at both national and subnational levels that can be assessed to determine whether elimination has been achieved. The five lines of evidence facilitate a comprehensive evidence-based assessment of population immunity at all levels, immunization program performance and the capacity to sustain elimination.

The WHO African regional standards for case-based measles surveillance have been in place since 2004, with an update in 2015 to include an optional elimination-standard surveillance which is recommended for countries with confirmed measles incidence approaching or less than 1 per million population. Elimination standard surveillance is expected to improve the sensitivity of measles surveillance by employing a broader suspect case definition requiring detailed active investigation of all suspected cases. As countries approach the elimination threshold, it will be critical to investigate each confirmed case of measles to determine sources of infection and reasons for lack of immunity. It will also be crucial to collect throat swab samples for viral genotyping, in addition to the serum specimens collected for serological confirmation. Elimination standard surveillance requires robust surveillance and laboratory capacity, as well timely and intensive investigation of sporadic as well as outbreak cases and is expected to be more costly to implement [9].

The sensitivity of measles surveillance and the quality of data generated is critically important in the verification process. Without adequate surveillance sensitivity consistently attaining the performance indicators including characterization of circulating viral genotypes, it is difficult to generate evidence required to verify elimination. For example, NVCs in some countries in the WHO European region have been unable to determine whether disease transmission remained endemic or was interrupted. Reasons included inadequate surveillance systems with low sensitivity producing incomplete surveillance data that could not be clearly interpreted to demonstrate evidence in support of elimination; as well as inadequate or incomplete evidence of population immunity [10]. In order to improve the quality of NVC documentation, Italy implemented subnational level assessment of progress and subnational compliance with the elimination criteria [11].

The measles verification framework shares similarities with the polio-free certification process. For a region to be certified polio free, the Regional Polio Certification Commission (RCC) will consider the following: i) the absence of wild poliovirus for at least 3 consecutive years from any source, in the presence of high quality, certification-standard AFP surveillance; ii) high routine immunization coverage with the third dose of oral polio vaccine (OPV3); iii) the completion of phase 1 poliovirus containment activities; iv) country readiness to respond to any poliovirus importation; v) the presence of a functional National Certification Committee to critically review, endorse and submit complete documentation to the RCC [12-14].

The establishment of measles verification procedures and structures in the African Region

In March 2017, the WHO Regional office for Africa developed and disseminated regional guidelines for the verification of measles elimination. Official communication was sent from the WHO regional office to 32 of the 47 countries in the region between May 2017 and February 2019, requesting them to establish an NVC and to commence the work of documenting progress towards elimination according to the regional guidelines and documentation template. WHO offered technical and financial assistance to establish NVCs. Not all countries were invited to establish NVC at the same time for several reasons. First, there is a limited number of technical staff from the WHO regional and sub-regional offices available to conduct briefings of the newly established NVCs. Second, countries were selected based on their relative progress towards the measles elimination targets in those countries nearing the elimination targets, and the potential advocacy value of NVCs to advance the implementation of elimination strategies in countries requiring significant improvement in their national immunization performance to advance towards measles elimination. A staged implementation of NVCs also allowed lessons to be learned from the initial country experiences.

The global framework and guidelines outline the process and requirements for the documentation of measles and rubella/CRS elimination. At present, in the absence of a formal regional goal of rubella/CRS elimination the African regional guidelines are limited to the verification of measles elimination. The regional verification framework, the process and the role of the verification structures was presented and discussed in various annual meetings of national immunization program managers' in 2018 and 2019. Additionally, an initial workshop was conducted in March 2018 to orient the members of the RVC. The first five countries to submit documentation of progress to the RVC were reviewed in May 2019. The status of establishment and functionality of NVCs as of April 2019 is summarized in Table 1.

Table 1: current status of establishment and functionality of NVCs in the African region, April 2019

Current status with NVC establishment	Countries
Countries requested to establish NVC; NVC not yet established	Benin, Botswana, Burkina Faso, Cameroon, Chad, Democratic Republic of Congo, Cote d'Ivoire, Eritrea, Ethiopia, Kenya, Lesotho, Liberia, Malawi, Mauritania, Mauritius, Mozambique, Sierra Leone, Togo
NVC established but not yet briefed	Cape Verde, Gambia, Niger
NVC established and briefed	Algeria, Eswatini, Senegal
NVC established, briefed and documentation started	São Tomé & Principe, Tanzania, Uganda
NVC submitted initial progress report to RVC	Ghana, Nigeria, Rwanda, Seychelles, Zimbabwe

Challenges

Despite the creation of NVCs and the organization of briefings for the NVC members, as of May 2019, only 8 countries in the region have begun to document progress toward elimination. A summary of the most common impediments in establishing NVCs and documenting country progress is detailed below.

Challenges with the establishment of NVCs

Inadequate awareness: national immunization program managers do not fully understand the purpose and function of NVCs. The justification and terms of reference for NVCs as well as the process of documentation of progress were presented in annual program meetings. However, misconceptions persist including the opinion that countries need to establish NVCs only when they get closer to claiming measles elimination status. Actually, the process of documenting progress with NVC oversight is expected to help weak performing countries to critically review their data, improve program performance and benefit from the advocacy of the NVC with national authorities and partners.

Multiplicity of committees: discussions with various national immunization program managers have revealed concern about the existing multiplicity of national committees and advisory groups to support immunization. There is a limited pool of dedicated and available scientists and experts to engage in such voluntary work, especially in the smaller countries. WHO AFRO has indicated that countries may opt to utilize the expertise in the current national polio certification committees for the purpose of measles verification if practical. However, it is necessary to amend the terms of reference and nomenclature of the committee and conduct a technical briefing of the committee members.

Availability of technical experts: WHO recommends that the membership of NVCs include specialists from various fields (clinicians, laboratory experts, epidemiologists, etc.) who will participate in the committee on a voluntary basis. However, in smaller countries, the available pool of high-level expertise from academic, research and clinical settings is often limited. In addition, available experts often have multiple professional responsibilities and engagements, and often are already engaged as members of NITAG, National Polio expert committee, national polio certification committee, or national polio containment taskforces.

Prioritization of verification work: national immunization program staff handle numerous programmatic priorities and are fully engaged in a multitude of activities, including the development of annual and multiannual plans, development of GAVI application documentations, new vaccine introductions, SIAs, program assessments and appraisals, outbreak response activities and responding to the effects of civil conflict and natural emergencies. The NVCs require the attention, time and dedicated support of the national immunization program team, and the WHO country office immunization team to be fully functional.

Inadequate human resources at regional level: there is a limitation of program staff in the WHO regional and sub-regional offices responsible for the overall coordination of measles and rubella elimination work. For this reason, it was not possible to quickly scale up and establish NVCs in multiple countries, conduct initial briefings and provide continuous to support the work of the NVC including associated work with data management and regular follow-up of the verification documentation at country level.

Inadequate funding to support country level NVC activities: WHO provides catalytic funding for the establishment and functioning of the NVCs at country level. These funds cover costs related to the organization of technical meetings, joint working sessions to analyze data and prepare the country progress reports, supply stationery material and cover costs related to in-country travel when necessary. Currently, the WHO Regional office has limited committed funding to support NVC activities, requiring prioritization in the support to countries to establish NVCs.

Challenges with the implementation of elimination strategies and data quality

Data quality: in many countries in the African region, vaccination administrative data overestimates the levels of population immunity as compared to survey and WHO UNICEF estimates of coverage. This discrepancy also exists in data at the subnational level. As a result, unless there are recent coverage surveys done to estimate subnational levels of coverage, it is often difficult to assemble accurate information regarding population immunity levels [15, 16]. The measles strategic planning (MSP) tool can provide national measles immunity profiles across multiple age cohorts to better estimate population immunity. However, the utility of the MSP tool is limited because it cannot consider subnational level coverage data [17].

Incomplete implementation of measles elimination strategies: as of April 2019, only 27 of the 47 countries in the region have introduced MCV2 in their routine immunization schedule. For countries having MCV2 for more than 3-5 years, the drop-out rate between MCV1 and MCV2 is more than 10% in 17 out of the 26 countries for 2017. This is a major programmatic weakness having a bearing on the documentation of one of the lines of evidence [4, 18]. In the case of large countries, like Nigeria or Ethiopia, there is a substantial difference at subnational levels in the implementation of elimination strategies that results in differential levels of progress towards elimination, which can be masked when viewed at the national level.

Surveillance funding gaps: forty four out of 47 countries in WHO African region have been implementing measles case based surveillance since at least 2006, with the support of a network of national and regional referral measles serological laboratories. However, over the past five years, the quality of case-based surveillance has not been improving across the region despite the fact that countries are approaching the 2020 target date for elimination [19]. This is compounded by coordination challenges when disease surveillance and immunization are under different divisions within Ministries of Health. Most countries do not allocate adequate funding to support measles surveillance activities. Mobilizing adequate funding is critical to scale up surveillance performance and to implement elimination-standard surveillance when nearing the elimination targets.

Stock out of lab test kits: the regional serological measles laboratory network consists of 49 national and subnational laboratories in 44 countries across the region. The network is supported by WHO to implement standardized testing methods, utilizes similar test kits and is supported with periodic external quality assurance and accreditation exercises. In the period from 2015 to 2017, nearly all the laboratories in the regional measles laboratory network experienced prolonged periods of stock-out of laboratory test kits as a result of delays in resupplying attributed to inadequate funding. This has seriously limited the surveillance system's sensitivity and its ability to generate high quality information for the purpose of verification [20].

Lack of genotypic data: despite the availability of services in the regional reference laboratories to perform molecular characterization of measles and rubella viruses, many countries have not yet made full use of this opportunity and therefore lack the baseline data required to assess endemic transmission patterns and distinguish them from importations that is important for the verification of elimination [20].

Inadequate data on CRS occurrence: CRS sentinel surveillance is established in only 9 countries across the region. However, several countries have some documentation from retrospective case reviews. CRS is often not recognized commonly as a clinical condition, and requires more specialized clinical skills and diagnostic equipment for initial case detection, there is lack of adequate documentation at country level [5].

Opportunities and successes

Previous experience with polio certification: countries across the region already have extensive experience with the process of preparing polio eradication progress reports and national certification documentation. The lessons from African regional certification of polio eradication are being utilized to ensure that the NVCs and the RVC establish robust processes from the outset [13, 14].

Functional regional commission: the regional director of the WHO African regional office has officially nominated the members of the Regional Verification Commission. The commission received its introductory briefing in March 2018. The second RVC meeting in May 2019 was used to review the progress reports from 5 countries. The RVC review of country documentation has helped to identify the strengths and weaknesses in country programs with regards to documenting the lines of evidence. The lessons from this exercise will be used to assist other countries, to use the opportunity to critically review their program data and the implementation of measles elimination strategies.

Advocacy value of verification committees: while the main objective of the NVCs and the RVC is to support countries to develop high quality documentation of progress towards elimination along the five lines of evidence, the terms of reference of the NVCs were designed to include advocacy as one of the key functions in their respective countries and at regional level for the RVC. The members of the committees are prominent clinicians, academicians and researchers whose professional reputations can garner support, visibility and influence policy makers in favor of measles elimination.

External technical assistance: to advance the work of verification of measles elimination, the WHO regional office received support from the US Centers for Disease Control (CDC) to complete a detailed analysis of programmatic data in Seychelles and Rwanda to compile their initial documentation submitted to the RVC. This work has helped to critically examine data quality and availability issues, as well as to refine the documentation template.

Country by country verification: the verification of measles elimination is assessed country-by-country, unlike the polio eradication program, where certification is done only on a regional basis. Such a country-focused approach gives high performing countries the opportunity to get official recognition for their progress and motivates others to strive to attain the elimination targets. In addition, when countries are presenting their progress report to the Regional Verification Commission, other NVCs and national immunization program managers are invited to participate and learn from the other country experiences.

Recommendations

In order to address these challenges and strengthen the ability of NVCs to document progress towards measles elimination, the following priority actions will need to be taken at regional and country levels.

Raise awareness: utilizing all opportunities to communicate to the national authorities and immunization program managers regarding the value NVCs can provide to assist countries with documenting progress towards measles elimination and advocating for better government ownership and partner support.

Document and disseminate progress: scaling-up the documentation of progress towards measles elimination among the high performing countries to help them verify elimination as early as possible and to document the advocacy work of NVCs.

Technical assistance: develop a regional pool of consultants that can assist countries in preparing the initial documentation of progress for review by NVCs.

Capacity building: WHO will continue to build the technical capacity and broader programmatic understanding of NVC members by engaging them as participants in immunization program technical meetings.

Networking: create opportunities and platforms for better networking and experience sharing among NVCs.

Funding: WHO and partners to allocate predictable funding to support the work of NVCs.

Sub-national documentation: in large countries, explore the possibility of NVCs monitoring and documenting progress toward measles elimination sub-nationally by province/State/Region level with their own documentation exercise. This will be a resource intensive exercise to be done in one or two countries, making sure not to burden national programs and in such a way as to carefully document lessons.

Competing interests

The authors declare no competing interests.

Authors' contributions

All authors have contributed to this work. All authors have read and agreed to the final manuscript.

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Brief

Control of measles in a juvenile custodial setting in the wake of the recent US outbreak

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Abstract

The recent US measles outbreak is the largest since 1992. It is just a matter of time before measles is introduced into a juvenile custodial setting. Are we prepared? Should we be prepared? This short article addresses steps institutional settings should take to prevent the spread of measles in a contained setting.

Brief

Measles is a contagious disease with a high rate of transmission in vulnerable populations. When introduced into a closed custodial setting such as jails, prisons, or juvenile detention centers, the number of potential new infections can rise exponentially depending on the immunization status of the inmates or residents. The US is experiencing the largest outbreak since 1992; according to the Centers for Disease Control and Prevention (CDC), over 1,000 infections have been reported from 28 states in 2019 [1]. Measles has a high reproductive number, meaning one infected person or resident has the potential to infect between 17-20 susceptible persons. Because of high infectivity, closed settings have to be prepared to rapidly identify, isolate and vaccinate vulnerable residents. We aim to address juvenile custodial setting outbreak prevention and immunity monitoring during the current high alert measles situation in the US measles can be introduced into a closed setting from external sources such as new detainees entering into the facility and staff, visitors, contractors or vendors working in or visiting the facility. Screening staff and residents for immunity, is cost effective and necessary to prevent measles introduction. The goal of screening will be to identify potential vulnerable residents and staff and in the event of an outbreak exclude them from work or isolate them to prevent disease transmission. Steps to follow in the event of an outbreak in a closed setting include the following: 1) Immediately isolate the suspected resident / inmate and implement contact precautions and post exposure prophylaxis (PEP). 2) Confirm diagnosis using clinical, and laboratory parameters see Table 1 for definitions. 3) Call your local health department upon suspicion; confirm disease using clinical and laboratory parameters (see definitions in Table 1). 4) Staff, visitors, and vendors exposed to measles who cannot readily show that they have evidence of immunity against measles should be offered PEP or be excluded from the facility. 5) To provide protection or modify the clinical course among susceptible residents/inmates, staff or vendors, either administer the MMR vaccine within 72 hours of initial exposure or immunoglobulin (IG) within six days of exposure. Do not administer the MMR vaccine and IG simultaneously, as this practice invalidates the vaccine. 6) If the MMR vaccine is not administered within 72 hours as PEP, the vaccine should still be offered in order to offer protection from any future exposures. Those who receive the MMR vaccine or IG as PEP should be monitored for signs and symptoms consistent with measles for at least one incubation period (7-21 days). 7) Infected inmates or residents should be isolated for four days after they develop a rash. 8) Work on logistics such as getting security clearance to enable local health department staff to enter the facility. 9) Stop the transfer of inmates or residents in and out of the custodial facility to reduce the risk of spreading measles to other parts of the facility.

According to the bureau of prisons immunization guideline, during a measles outbreak in an adult custodial setting, it is recommended that one dose of Measles-mumps-rubella (MMR) vaccine be given to persons identified to be at risk and to those who have no evidence of immunity to measles within 72 hours of exposure [2]. As of 2016, there are approximately 1,772 juvenile facilities of which 662 are detention centers. Annually, the detention centers remand an estimate average of 15,000 residents. To the best of our knowledge, there has been no report of a measles outbreak in a juvenile custodial setting; search of databases revealed a few reported measles outbreak cases in adult custodial settings [3-6]. The receipt of 2 or more MMR vaccines in the US is more than 90 percent among US adolescents aged 13 to 17 years across all ethnic groups, metropolitan statistical area, rural and non-rural counties and states, according to the national immunization survey [7]. The MMR vaccine update trend in the birth cohorts continues to remain high from 2008 through 2017, and we postulate that the high MMR vaccine rate might be a contributing factor to the paucity of the measles outbreak in juvenile custodial settings. Previous prison outbreak mitigation efforts demonstrated that mass vaccination following an outbreak is not always likely to prevent new infections among susceptible individuals; favorable mitigating factors include implementing opt-out testing, vaccination, and requiring full immunization of staff, contractors, and vendors [5].

Table 1: case definition and epidemiological classification[a]

Outbreak	**Measles outbreaks are defined as three or more cases**
Clinical description	An acute illness characterized by: Generalized, maculopapular rash lasting ≥3 days; and Temperature ≥101°F or 38.3°C; and Cough, coryza, or conjunctivitis.
Probable	In the absence of a more likely diagnosis, an illness that meets the clinical description with: No epidemiologic linkage to a laboratory-confirmed measles case; and Noncontributory or no measles laboratory testing.
Confirmed	An acute febrile rash illness with: Isolation of measles virus from a clinical specimen; or Detection of measles-virus specific nucleic acid from a clinical specimen using polymerase chain reaction; or IgG seroconversion or a significant rise in measles immunoglobulin G antibody using any evaluated and validated method; or A positive serologic test for measles immunoglobulin M antibody; or Direct epidemiologic linkage to a case confirmed by one of the methods above.
Internationally imported case	An internationally imported case is defined as a case in which measles results from exposure to measles virus outside the United States as evidenced by at least some of the exposure period (7–21 days before rash onset) occurring outside the United States and rash onset occurring within 21 days of entering the United States and there is no known exposure to measles in the U.S. during that time. All other cases are considered U.S.-acquired.
U.S.-acquired case	The patient had not been outside the United States during the 21 days before rash onset or was known to have been exposed to measles within the U.S.
Import-linked case	Any case in a chain of transmission that is epidemiologically linked to an internationally imported case
Imported-virus case	a case for which an epidemiologic link to an internationally imported case was not identified, but for which viral genetic evidence indicates an imported measles genotype
Endemic case	a case for which epidemiological or virological evidence indicates an endemic chain of transmission. Endemic transmission is defined as a chain of measles virus transmission that is continuous for ≥12 months within the United States.
Unknown source case	a case for which an epidemiological or virological link to importation or to endemic transmission within the U.S. cannot be established after a thorough investigation.
Internationally imported, import-linked, and imported-virus cases are considered collectively to be import-associated cases	
[a] council for state and territorial epidemiologist case definitions	

Competing interests

The authors declare no competing insterests.

Authors' contributions

All authors wrote and edited the manuscript. They all read and agreed to the final manuscript.

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Review

Measles and rubella microarray array patches to increase vaccination coverage and achieve measles and rubella elimination in Africa

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Abstract

The African Region is committed to measles elimination by 2020 but coverage with the first dose of measles-containing vaccine was only 70% in 2017. Several obstacles to achieving high coverage with measles and rubella vaccines exist, some of which could be overcome with new vaccine delivery technologies. Microarray array patches (MAPs) are single-dose devices used for transcutaneous administration of molecules, including inactivated or attenuated vaccines, that penetrate the outer stratum corneum of the skin, delivering antigens to the epidermis or dermis. MAPs to deliver measles and rubella vaccines have the potential to be a transformative technology to achieve elimination goals in the African Region. MAPs for measles and rubella vaccination have been shown to be safe, immunogenic and thermostable in preclinical studies but results of clinical studies in humans have not yet been published. This review summarizes the current state of knowledge of measles and rubella MAPs, their potential advantages for immunization programs in the African Region, and some of the challenges that must be overcome before measles and rubella MAPs are available for widespread use.

Introduction

Global measles vaccination coverage with the first dose of measles-containing vaccine (MCV1) has stagnated at about 85% for the past decade and global goals for reductions in measles incidence and mortality were not met [1]. Although the Region of Americas eliminated measles and rubella (the Americas lost their measles elimination status in 2018), no other World Health Organization (WHO) region has achieved measles elimination despite goals to do so by 2020 or earlier [2]. In 2011, the WHO African Region established a goal to eliminate measles by 2020 [3], but MCV1 coverage in 2017 was only 70% [2], far lower than what is needed for elimination. Numerous obstacles to measles and rubella elimination exist, including conflict, weak immunization systems, insufficient political will and resources and loss of confidence in vaccines leading to decreased demand. Despite regional differences in the underlying causes, the fundamental problem is the same across the globe: failure to achieve high coverage (> 95%) with two doses of measles vaccine. However, the tools to achieve high measles vaccine coverage have not changed much over the past several decades and better vaccine delivery platforms would be beneficial [4]. The only major advance in vaccine delivery since the beginning of the Expanded Program on Immunization in 1974 was the introduction of non-reusable syringes in 2000 [5].

Methods

We reviewed the published literature on microarray and microneedle patches for vaccine-preventable diseases, with a focus on measles and rubella vaccines. We did not conduct a systematic review of the literature.

Current status of knowledge

Microarray patches

Microarray array patches (MAPs), also known as microneedle patches, are single-dose devices used for transcutaneous administration of molecules, including inactivated or attenuated vaccines, that penetrate the outer stratum corneum of the skin, delivering antigens to the epidermis or dermis [6-8]. MAPs consist of an array of dozens to thousands of micron-sized needles on an adhesive backing (Figure 1). The needles may be solid or hollow, and coated or filled with the vaccine antigens. They can be fabricated from a variety of different materials, including polymers, colloidal silica, ceramics, steel, glass, sugar, hydrogel or alumina. Some array materials, such as polymers, are dissolvable on the skin and polymer blends mixed with vaccine antigens can deliver vaccine antigens to the dermis as they dissolve [9]. MAPs have the potential to be a transformative technology to substantially increase measles and rubella vaccination coverage, achieve regional elimination goals and facilitate global measles and rubella eradication [5, 7, 8]. MAPs offer several potential operational advantages when used for vaccine delivery, including thermostability, improved acceptance, decreased risk of infection, ease of administration, reduced supply chain requirements and medical waste and dose sparing. A critical advantage is the potential improved thermostability of vaccine antigens presented using MAPs because of the use of lyophilized vaccine. Enhanced thermostability could reduce cold chain requirements, minimize loss of vaccine potency and facilitate vaccine delivery in remote rural areas.

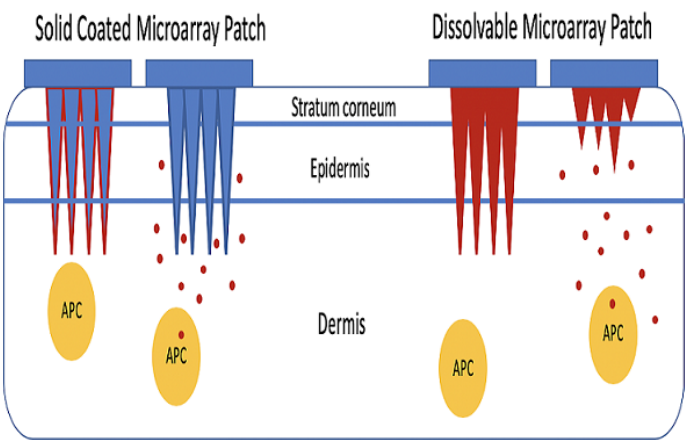

Figure 1: coated and dissolvable microarray patches for delivery of measles and rubella vaccines; APC: antigen presenting cell

Due to the potential for non-painful administration of vaccine antigens (by not stimulating pain receptors deeper within the skin), acceptability may be improved, especially among children. Although data on the acceptability of actual vaccination with MAPs are not yet available, end-user acceptability of a MAP for child immunization was evaluated in a multi-country study of 314 participants in Benin, Nepal and Vietnam using simulated vaccine administration and in-depth interviews [10]. Overall acceptability was 92.7%, but participants recommended that the technology first be introduced at healthcare facilities to establish confidence prior to use for outreach vaccination. In an unpublished study conducted in Ghana, simulated use of a dissolvable MAP by health care workers to vaccinate children and adult women demonstrated acceptability and feasibility, although the time needed to monitor complete vaccine delivery was noted as a potential operational challenge [8]. Another study examined the usability and acceptability of self-administered MAPs [11]. Participants received placebo MAPs three times by self-administration and once by an investigator, in addition to an intramuscular injection of saline to simulate standard vaccination practices. Self-administration was delivered by thumb pressure or a snap-based device. The best usability, as measured by skin staining, was seen with the snap device, with users inserting a median value of 93-96% of microarrays over three repetitions. Most participants (64%) expressed a preference for self-vaccination with MAPs.

Decreased risk of infection could result from the shallow penetration of the microarray needles, as well as the inability of MAPs to be refilled or reused [12]. The delivery technique is easy, requiring minimal training for administration. Importantly, persons not trained as healthcare workers may be able to safely and effectively administer MAPs, facilitating vaccination during mass vaccination campaigns (supplementary immunization activities), outbreaks and in disordered settings such as areas of conflict and other humanitarian emergencies. The logistical requirements for distribution and administration, from supply chain to disposal, may be reduced with MAPs. The volume and weight of shipments for distribution are expected to be lower than most current vaccine products, as no additional materials (e.g. needles, syringes, diluent for reconstitution) are required. Using HERMES modeling software, a simulation study was conducted to assess the impact of MAPs on routine vaccine supply chains in Benin, Bihar and Mozambique [13]. The conclusion was that a MAP would need to have a smaller or equal volume-per-dose than existing vaccine formulations and be able to be stored outside the cold chain for a continuous period of at least two months to provide additional benefits to these supply chains. Because no reconstitution is needed, cold chain requirements are expected to be further lowered and vaccine wastage should be reduced. Hazardous waste also is reduced, as no sharps or biohazardous materials remain after administration. There is potential for the complete absence of biohazardous waste, as dissolvable MAPs are made with water-soluble materials that release vaccine on dissolution [7]. Delivery of vaccine antigens through MAPs may improve immunogenicity, including more robust antibody and cellular response and longer duration of immunity, in part because of the presence of large numbers of antigen-presenting cells in the dermis and epidermis (e.g. dendritic cells) [7]. The potential enhanced immunogenicity of MAP vaccines could result in dose sparing, reducing the cost.

Studies of vaccine delivery using MAPs

Vaccines delivered through MAPs have undergone preclinical development and testing over the past decade in animal models for several vaccine-preventable diseases, including inactivated poliovirus vaccination in rhesus macaques [14], hepatitis B virus vaccination in mice and rhesus macaques [15], rabies virus vaccination in dogs [16], glycoprotein subunit Ebola virus vaccination in mice [17], formalin-inactivated respiratory syncytial virus vaccination in mice [18] and tetanus toxoid in pregnant mice [19]. Several of these MAP formulations were shown to have increased thermostability compared to currently used vaccines [20]. Although no microarray vaccines have yet been approved by the U.S. Food and Drug Administration (FDA), an FDA-approved solid microarray device can be purchased without vaccine or active ingredient. Much of the published studies using MAPs for vaccine delivery have examined the immunogenicity, safety and thermostability of influenza vaccines [21-24], in part because of the potential market in high-income countries. As an example, dissolving polymer microarray patches were shown in mice to induce antibody and cellular immune responses that provided protection against lethal challenge [22]. Vaccination using dissolvable MAPs resulted in more efficient viral clearance from the lung and enhanced cell-mediated recall responses after viral challenge than standard vaccination, evidence of enhanced immunogenicity when vaccine antigens are delivered into the dermis using MAPs.

Importantly, several published studies investigated influenza vaccination using MAPs in humans. A randomized, partly blinded, placebo-controlled, phase 1, clinical trial enrolled 100 non-pregnant, immunocompetent adults aged 18-49 years [25]. Participants were randomly assigned to four groups and received a single dose of inactivated influenza vaccine by MAP or intramuscular injection, or placebo by MAP, by an unmasked health-care worker. A fourth group received a single dose of inactivated influenza vaccine by MAP self-administered by study participants. The incidence of adverse events was similar across the vaccinated groups and consisted of mild tenderness (60%) and pain (44%) after intramuscular injection, and tenderness (66%), erythema (40%) and pruritus (82%) after vaccination by MAP. Geometric mean antibody titers and the proportion of participants who seroconverted were similar at day 28 between those who received influenza vaccination by MAP, including those who self-administered the patch, compared to intramuscular administration.

A second randomized, partly-blinded, placebo-controlled trial of influenza vaccination in healthy human volunteers was reported using a different MAP (NanopatchTM) [26]. Similar antibody responses were observed between those receiving influenza vaccinations, although sample sizes were small and adverse reactions were reported as mild or moderate. This included pruritis at the site of application, a potential adverse event related to MAPs that is likely due to the vaccine antigen or formulation. The cost-effectiveness of MAPs for influenza vaccination was evaluated in several published studies. A transmission model was coupled to an economic influenza outcomes model to assess the economic value of MAPs for influenza vaccination in the United States [27]. The model suggested that MAPs would be cost-effective or dominant (i.e., less costly and more effective) when administered by health care workers, and also cost-effective when self-administered if they increased compliance sufficiently to overcome any potential reduction in efficacy due to self-administration. Another study examined potential clinical outcomes and direct medical costs of an influenza vaccination program offering a MAP vaccine to children who declined intramuscular vaccine administration in Hong Kong [28]. These studies suggest the potential for MAPs to be cost-effective for influenza vaccination, but the full potential will not be known until MAPs are introduced into practice.

Measles and rubella vaccination using MAPs

An early study of transcutaneous measles vaccination using a patch in human adult volunteers failed to show induction of neutralizing antibodies, potentially due to the administration method or vaccine dose delivered [29]. However, several published studies have since demonstrated the immunogenicity of measles vaccination using MAPs in animal models. Although different measles MAPs have been developed and tested, the most promising consists of 100 microscopic water-soluble polymer cones, each the width of a human hair, that contain currently available, lyophilized, attenuated measles vaccine and that dissolve into the skin within several minutes of application. Following studies showing immunogenicity and safety in cotton rats [30], measles vaccine delivered via polymeric microarrays was shown to be immunogenic in rhesus macaques [31]. The dissolvable MAPs included the encapsulated, standard dose of the Edmonston-Zagreb vaccine strain (1000 TCID50) applied for 10 minutes, resulting in production of neutralizing antibody titers equivalent to those generated following standard subcutaneous vaccine administration with no adverse events except mild skin erythema. Importantly, the measles MAP demonstrated thermostability at 4-8oC for four months without unacceptable loss of potency, evidence of enhanced thermostability.

Because of the programmatic importance of concurrent administration of measles and rubella vaccines, a monovalent measles vaccine delivered by a MAP is unlikely to be widely used. Importantly, immunogenicity and safety were also demonstrated using the same MAP to deliver combined measles (Edmonston-Zagreb strain) and rubella (RA-27 strain) virus antigens in infant rhesus macaques [32]. Protective neutralizing antibody titers were detected in all infant macaques following vaccination with the measles-rubella MAP but in only 75% of infant macaques following subcutaneous vaccination, again evidence of enhanced immunogenicity. These antibody titers resulted in protection against wild-type measles virus challenge. Rubella neutralizing antibody titers were >10 IU/mL, the minimum protective level, for both groups of infant macaques. However, protective titers against measles were not achieved following either MAP or subcutaneous vaccine administration in macaques pretreated with immunoglobulin, simulating maternal antibodies, suggesting MAPs are not able to overcome the inhibitory effect of pre-existing, maternal neutralizing antibodies. These MAPs dissolved completely upon skin penetration and were thermostable for one month at 40oC, exceeding World Health Organization stability requirements. No adverse effects were noted.

The potential cost-effectiveness of a measles MAP was assessed using a spreadsheet model to compare the vaccination costs of MAPs with vaccine administration through needles and syringes, assuming MAPs would be more thermostable with less requirements for a cold chain [33]. Measles MAPs were estimated to cost US$0.95 per dose compared with US$1.65 for standard measles vaccine administered subcutaneously. Assuming these costs and 95% measles vaccine coverage with the first measles vaccine dose, MAPs were estimated to cost US $1.66 per measles case averted compared to US $2.64 per case averted with subcutaneous vaccination. The cost-effectiveness of MAPs will ultimately depend on cost, acceptability and effectiveness when implemented in immunization programs.

MAPs for measles vaccination in Africa

The use of MAPs for administration of measles and rubella vaccines in Africa could be particularly advantageous and potentially transformative [7, 8]. First, increased thermostability of a measles-rubella MAP could reduce cold chain requirements and facilitate transportation of the vaccine to remote areas in rural sub-Saharan Africa. Second, a measles-rubella MAP could be administered by minimally trained personnel (or even self-administered), making house-to-house measles and rubella vaccination campaigns possible using community health workers or other trained community members. Third, a measles-rubella MAP would not require reconstitution, obviating the need for needles and syringes and eliminating human error in reconstitution of the lyophilized vaccine (e.g. use of the incorrect diluent or volume, or bacterial contaminated diluent). Fourth, a measles-rubella MAP would overcome hesitation in opening a multidose vaccine for one or a few children, minimizing missed opportunities for vaccination and vaccine wastage. Fifth, a measles-rubella MAP would eliminate needle stick injuries and reuse of needles and syringes. Sixth, a dissolvable measles-rubella MAP would minimize biohazardous medical waste. Seventh, supply chain requirements could be reduced, due to lower cargo weight (no glass vials), lower cold chain volumes, and no need for consumable compatibility (e.g. needles and syringes that are compatible). Lastly, a painless measles-rubella MAP could improve acceptability in some communities.

The future of MAPs

Despite the potential advantages of MAPs for delivery of measles and rubella vaccines in sub-Saharan Africa, several challenges must be overcome before MAPs could be available for widespread use. The most significant obstacle relates to the value proposition of MAPs for measles and rubella vaccine delivery given the costs of development, manufacturing and use in immunization programs [8]. Thus, the product attributes of MAPs will need to confer substantial advantages to justify these investments, with a clear market demand to demonstrate the return on investment. MAPs can currently be produced on a small scale to support evaluation in early phase clinical trials but large scale production under Good Manufacturing Production (GMP) conditions will require a significant investment and several years from planning to production [8]. A key issue is whether MAPs need to be manufactured aseptically, as they are ultimately applied under non-sterile conditions, or whether demonstrated safety with low bioburden material would be acceptable [8]. Whether the investment in large-scale production facilities occurs concurrently with clinical trials of safety and efficacy, or is delayed until after phase 3 clinical trials are completed, will strongly determine the timeline as to when MAPs could be available for use in Africa.

There are also regulatory pathways that must be completed based on safety and efficacy data. A measles and rubella MAP would likely be considered a new product by regulatory agencies, despite the fact that currently used measles and rubella vaccine strains would comprise the antigenic components [8]. The measles and rubella vaccine formulations may need to be modified to optimize delivery through coated or dissolvable MAPs [8]. Because measles and rubella vaccines have generally accepted immunologic correlates of protection, demonstration of immunologic non-inferiority of a MAP (i.e. similar antibody titers within a pre-defined margin) compared to standard subcutaneous administration of measles and rubella vaccines may be sufficient. Ultimately, a MAP to deliver measles and rubella vaccines in sub-Saharan Africa will require WHO pre-qualification. The European Medicines Agency's Article 58, a regulatory pathway for innovative vaccines for diseases of public health importance, could facilitate prequalification by the WHO and registration in African countries [8]. Nevertheless, the financial, manufacturing, and regulatory hurdles mean that the availability of MAPs for measles and rubella vaccination is at least five years and probably longer from realization.

Importantly, to shorten this process as much as possible, the minimum and preferred attributes for a MAP to deliver measles and rubella vaccines are being developed by the WHO and an expert working group, leading to a target product profile. Efforts such as the Vaccination Innovation Prioritization Strategy, a partnership comprised of WHO, Gavi, the Bill & Melinda Gates Foundation, PATH and UNICEF, and PATH's Center of Excellence for Microarray Patch Technology, are critical efforts to accelerate the development of MAPs and provide guidance on research, regulatory pathways and manufacturing conditions. Hopefully, these efforts will expedite the development, testing, manufacturing, and implementation of MAPs for measles and rubella vaccination in immunization programs.

Conclusion

MAPs to deliver measles and rubella vaccines could play a critical role in achieving elimination goals in the African Region. Key stakeholders, including policy makers, ministers of health and finance, vaccine advocates, and immunization program managers, need to be aware of this potentially transformative technology and have a voice in moving the product development pipeline forward.

What is known about this topic

- Global MCV1 coverage has stagnated at 85% and is only 70% in the African Region;
- Currently used measles and rubella vaccines are safe, effective and low cost but several obstacles exist to achieving high vaccination coverage;
- These obstacles include the need to maintain a cold chain and use skilled health care workers, and the potential for missed opportunities and vaccine wastage.

What this study adds

- Microarray patches to deliver measles and rubella vaccines have the potential to be a transformative technology to achieve elimination goals in the African Region;
- Microarray patches for measles and rubella vaccination have been shown to be safe, immunogenic and thermostable in preclinical studies;
- Several obstacles must be overcome before MAPs are available for measles and rubella vaccination, including investment in large-scale production facilities and obtaining WHO pre-qualification.

Competing interests

The authors declare no competing interests.

Authors' contributions

The authors contributed equally to the writing of the manuscript. The authors have read and agreed to the final manuscript.

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PanAfrican Medical Journal

Research

The distribution and use of feedback bulletins among national immunization program management teams in East and Southern Africa

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Abstract

Introduction: immunization program monitoring includes numerous activities, some of which include monitoring of vaccination coverage, surveillance performance and epidemiological patterns. The provision of timely, high quality and actionable feedback is an essential component of strengthening health systems. Within the African region of the WHO, various bulletins are produced and disseminated regularly to provide feedback on the performance of immunization programs and vaccine preventable disease control initiatives.

Methods: the 2019 annual national immunization program managers' meeting for countries in the eastern and southern African subregion was held in Asmara from 18 - 20 March 2019. A survey questionnaire was administered to the participants representing the national programs and in-country partners across the 20 countries.

Results: on average, the 75 respondents receive 1.8 e-mailed feedback bulletins monthly. Twenty-three (31%) respondents receive 3 or more written feedback bulletins per month, and 72% receive the bulletins regularly. On a scale of 1 - 5 (from lowest to highest), 87% participants rated the relevance of the bulletins they receive at 4 - 5. Only 19% of the respondents responded that the results are discussed within the national immunization program, and 14% stated that action points are generated based on the feedback received. Fifty-nine (79%) respondents want to receive more frequent feedback on routine immunization performance. Among the EPI program managers and the EPI program data managers, the access to these feedback bulletins was quite limited. Even though the primary objective of the bulletins is to initiate discussions and action based on the provided feedback, such discussions do not happen regularly at country level. The programmatic use and advocacy value of the bulletins is not optimal.

Conclusion: we recommend integrating program feedback, regularly updating the distribution lists, the additional use of instant messaging platforms for distribution, as well as online posting of the bulletins for wider availability.

Introduction

The African Regional Strategic Plan for Immunization 2014 - 2020 (RSPI) maps out ambitious goals for improving access to vaccines and to eliminate targeted vaccine preventable diseases. The plan acknowledges the need to position strong immunization systems as an integral part of well-functioning health systems, and recommends corresponding actions for countries, one of which is to enhance the collection, triangulation and use of administrative, surveillance, risk assessment and vaccine safety data to improve performance of immunization services and complementary actions in tackling the disease burden [1]. Immunization program monitoring is done regularly by recording and tracking service data, including the number of doses of antigens provided to persons in the target population. Immunization coverage data needs to be interpreted alongside information from vaccine preventable disease surveillance systems in order to provide a more complete understanding of the performance and impact of immunization programs in the control of vaccine preventable diseases. The monitoring and use of data for action is one of the five pillars of the "Reaching Every District" approach used to address common obstacles to increasing immunization coverage [2]. At the district level, regular review of program and health worker performance has been recognized as one of the key drivers of improvement of routine immunization systems in the African setting [3]. The development of feedback mechanisms that facilitate access to timely, feasible, cost-effective and actionable performance data is an essential component of strengthening health systems. Feedback mechanisms in health systems provide opportunities for learning, and help build accountability into the system [4]. The provision of feedback is essential to motivate health workers, assure adherence to standards, track progress towards national and regional goals, provides corrective actions and to align and prioritize technical support. Feedback may be provided using various approaches including during supervisory visits, periodic program performance review meetings, using written bulletins, among others [3-6]. In disease surveillance systems, feedback is considered one of the core activities [7-9]. One of the core functions of the World Health Organization includes monitoring the health situation and assessing health trends [10]. In the area of immunization and the control vaccine preventable diseases, countries regularly report coverage and disease incidence data through the WHO country and Regional offices. One important example of monitoring from the WHO global level is the compilation of national reported data through the WHO-UNICEF joint reporting form, and subsequent generation of antigen-specific annual estimates of coverage for each country, often referred to as the WHO-UNICEF estimates of national coverage [11].

Using programmatic data generated at the national level, the WHO African Regional immunization and polio eradication programs provide regional programmatic overview and feedback to national immunization programs during annual meetings, and periodic monitoring and evaluation exercises, in the form of written program summaries, presentations and reports. In addition, regular feedback bulletins are produced to monitor country progress against the targets and to present a comparison of performance between different countries. The primary aim of these bulletins is to provide a regular and transparent assessment of country performance, with a view to encourage progress, and indicate the need for course correction where needed. Within the African region of the WHO, the provision of written surveillance feedback is a recognized legacy of the polio eradication program [12-14]. Various feedback bulletins are produced and disseminated regularly highlighting information on routine immunization performance and vaccine preventable disease control initiatives. The emailed feedback bulletins destined to reach the countries in the East and southern subregion include: Regional: a) Weekly African Regional polio updates; b) Weekly Regional polio lab feedback tables; c) Monthly African Regional immunization bulletin; d) Monthly Regional measles-rubella surveillance feedback summary bulletin. Sub-regional: a) Polio Surveillance Weekly Updates for East and Southern Africa; b) Monthly integrated EPI feedback bulletin for East and Southern Africa subregion; c) Monthly sub-regional Integrated Supportive Supervision Feedback; d) Quarterly sub-regional feedback bulletin on Rotavirus and Pediatric Bacterial Meningitis sentinel surveillance. Even though efforts are made to ensure the relevance of these feedback products, not much is known with regards to exactly how this information is received and utilized at country level. This study attempts to shed light on the utility of the written programmatic feedback in countries in eastern and southern Africa.

Methods

National immunization and disease control programs regularly share immunization coverage and disease surveillance databases with WHO. Country program data on acute flaccid paralysis (AFP) surveillance, polio virology laboratory as well as measles case-based surveillance and serological lab data is shared weekly, while other vaccine preventable disease (VPD) surveillance databases (eg., neonatal tetanus surveillance, meningitis surveillance, sentinel surveillance for pediatric bacterial meningitis and severe childhood diarrhea) and immunization coverage monitoring data is shared monthly. The immunization program data management team at the sub-regional office of the WHO aggregates, cleans and analyses the data regularly with the relevant program officers in order to provide interpretation, prepare and disseminate feedback bulletins. These bulletins include tabulation, maps and charts as well as narrative descriptions covering data quality, immunization coverage, surveillance and laboratory performance, as well as epidemiological trends.

The WHO African regional immunization program develops and disseminates more detailed and specialized feedback bulletins summarizing Regional performance across the 47 countries. These comprise of the weekly feedback from the polio program on the Acute Flaccid Paralysis surveillance performance and Polio Laboratory performance, monthly feedback on the measles and rubella surveillance performance, and the monthly routine immunization newsletters. While there may be some differences in the target audience of these feedback bulletins, the national immunization and disease surveillance program staff remain at the primary targets. Every year, the WHO and UNICEF Regional offices jointly organize a meeting of national immunization program managers, to share programmatic information and experiences, monitor performance against regional and global targets and goals and discuss scientific updates. These annual sub-regional level meetings are also attended by global and regional partners. The 2019 annual national immunization program managers' meeting for 20 countries in the Eastern and southern African subregion was held in Asmara, Eritrea from 18 - 20 March 2019. The participants included immunization program managers, data managers, other national program team members, as well as national level partners from the 20 countries. A survey questionnaire was administered to the participants representing the national program and in-country partners across the 20 countries. The questionnaire focused on the programmatic feedback provided to countries from the WHO regional and sub-regional levels. The data was entered and analyzed using MS Excel.

Results

The questionnaire was distributed to 91 persons, and responses were received from 76 participants. One questionnaire was discarded because of incompleteness. Participants from all 20 countries in the subregion provided responses to the survey questions, with at least 2 respondents from each country in the subregion except Mozambique, which had only one response submitted. The 41 participants from various in-county partners were from WHO, UNICEF, John Snow Inc. (JSI), Clinton Health Access Initiative (CHAI), PATH and Aspen Management Partnership for Health (AMP Health). A third of the respondents had 10 years or more of experience with the immunization work at the national level. On average, the respondents receive 1.8 e-mailed feedback bulletins at least monthly. Twenty-three (31%) respondents receive 3 or more written feedback bulletins per month (Table 1). The 15 national immunization program managers or directors who responded to the survey indicated that they receive on average 1.8 feedback bulletins over the course of a month. On the other hand, 9 of the 18 national immunization program officers responsible for immunization data management (or monitoring and evaluation) received no more than one feedback bulletin per month.

The majority (72%) of the respondents receive the feedback bulletins quite regularly, while 18 get them irregularly. On a scale of 1 - 5 (from lowest to highest), 47 of 54 (87%) participants rated the relevance of the bulletins they receive at 4 - 5, while 42 (91%) of 46 respondents stated that the feedback bulletins were detailed enough in their content and rated them 4 - 5. With regards to how the feedback bulletins are received at the country level, only 19% responded that the results are discussed within the national immunization program, and 14% stated that action points are generated based on the feedback received (Table 2). In the future, 49 (65%) would like to see more detailed feedback and content on routine immunization coverage performance, 47 (63%) on data quality, while 31 (41%) would like to see more information on VPD outbreaks in the subregion. With regards to the frequency of feedback, 59 (79%) respondents want to receive more frequent feedback on routine immunisation performance, while 33 (44%) wanted more feedback on surveillance of rotavirus and pediatric bacterial meningitis (surveillance of diseases targeted by the newer vaccines), 48 (64%) on measles and rubella elimination, 38 (51%) on polio eradication and 12 (16%) on maternal and neonatal tetanus elimination.

Table 1: characteristics of respondents and feedback bulletins received

	Ministries of Health	In-country partner agencies
Number of respondents	34	41
Average years of experience at national level	6.8 years	9.8 years
Average number of feedback bulletins received at least monthly	1.5	2.2

Table 2: use of feedback bulletin for program action at country level

	Results in feedback bulletins discussed at national level	National level generates action points based on feedback received	Feedback bulletins shared with decision makers	Technical support from WHO aligned with performance issues as indicated in the feedback bulletins
Never	13 (19%)	9 (14%)	7 (12%)	1 (2%)
Sometimes /rarely	37 (55%)	35 (56%)	38 (67%)	39 (65%)
At least once a month	17 (25%)	19 (30%)	12 (21%)	20 (33%)
Total responses	**67 (100%)**	**63 (100%)**	**57 (100%)**	**60 (100%)**

Discussion

A major objective of providing written feedback to national officers, tabulating and mapping performance across multiple countries, is to allow immunization program managers at subnational and national levels to see their work within the bigger context of the Regional and global goals. In this regard, it is critical that they get accurate, timely, relevant feedback that also provides programmatic guidance and is followed up with the appropriate technical assistance. Currently, all of the immunization program feedback bulletins from the WHO African regional and sub-regional levels that are provided to the national level are shared by e-mail, and none of these bulletins are posted online, which limits the audience of the bulletins. The participants in this survey are the technical leaders and partners for immunization and VPD control work in their respective countries. Given that most of the respondents have been responsible for immunization activities for a number of years, it is expected that they are already familiar with the feedback processes and products. The majority of the respondents rated the feedback bulletins they receive as relevant and detailed enough. Despite this, our study has highlighted needs for improvement in the distribution and utilization of the feedback bulletins. Even among the EPI program managers and the EPI program data managers, the access to these feedback bulletins was quite limited. Only a third of the total respondents receive three or more feedback bulletins a month. The primary objective of the feedback is to monitor performance across multiple countries, with a view to initiate discussions and action as necessary. However, only 17 (23%) responded that such discussions happen regularly at country level. Only 21% of the participants responded that these bulletins are brought to the attention of higher-level decision makers, limiting the advocacy value of the bulletins.

Periodically, countries are supported to do immunization program and/or surveillance reviews, and other similar in-depth program assessment activities to identify their strengths and weaknesses, and address gaps that hinder the attainment of program objectives. However, such exercises are resource intensive, conducted once every 3 - 5 years and cannot replace the frequent provision of program feedback. In many countries, the national immunization program and the surveillance / disease control program are in separate divisions within ministries of health. In such cases, the responsibility for VPD surveillance exists in a program outside of the immunization program. It is expected that these two programs work closely in terms of planning interventions, data sharing and impact monitoring among others. However, multiple national program reviews have identified gaps in information sharing and use in such contexts [15]. In the past two decades, countries have introduced new and under-utilized vaccines, and recently introduced a life-course approach to immunization beyond infancy. With this comes increased complexity of vaccination schedules, increased expectations with regards to monitoring data quality, as well as the need for continuous capacity building to refine technical and managerial skills at all levels [1, 16]. Within such a rapidly evolving and dynamic context, the provision of high quality program feedback is critical to improve overall program management capacity and data quality. Robust monitoring and accountability frameworks are a critical part of improving immunization programs [17]. In addition, the generation of feedback helps improve the immunization monitoring system itself by identifying and highlighting issues related to the monitoring process and data quality [18].

With the adoption of Demographic Health Information Systems (DHIS2), countries are preparing to move into web-based real-time data entry and data management platforms that provide the functionality of generating automated dashboards as well as alerts and reports. However, the linkage of data outputs with programmatic guidance will continue to be relevant and will not replace the need for high quality program feedback [19]. This is the first such study to attempt to provide an insight into the perceptions towards, the distribution and utilization of programmatic feedback within the regional immunization programs. However, this study is limited in scope to the 20 countries and specifically to the participants of the annual immunization program managers' meeting for the East and southern Africa subregion. The meeting participants representing the national ministries of health were mostly from the respective national immunization programs and not necessarily technical staff from the national disease surveillance and/or disease control units responsible for handling VPD surveillance. The study did not also attempt to delve into the contents and format of each feedback bulletin.

Conclusion

Written feedback is a critical element for strengthening public health programs. The written feedback provided by the WHO on the immunization and vaccine preventable disease efforts in the subregion can be improved through the use of updated distribution lists, the additional use of instant messaging platforms for distribution, as well as online posting of program feedback bulletins for wider and longer periods of availability. In addition, bulletins should be better integrated and regularly shared with the inclusion of programmatic guidance to better guide countries towards the RSPI targets. National programs should create regular platforms to review performance widely across the immunization and surveillance programs, and explore ways of utilizing the feedback to improve data quality and overall program performance.

What is known about this topic

- Monitoring and use of data for action is one of the five pillars of the "Reaching Every District" approach;
- The provision of timely, high quality and actionable feedback is an essential component of strengthening health systems;
- The WHO Regional and Sub-regional levels share various emailed program feedback bulletins covering immunization and vaccine preventable disease control initiatives regularly.

What this study adds

- The various feedback bulletins from the WHO regional and sub-regional levels are not reaching all the key program staff at country level;
- All the national immunization programs are not regularly discussing the feedback results and generating action points based on the findings;
- There is a need to explore different approaches to widely sharing the feedback, and making it more useful and actionable for countries.

Competing interests

The authors declare no competing interests.

Authors' contributions

All have contributed to this work. All authors have read and agreed to the final manuscript.

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Research

Descriptive study of measles vaccination second dose reporting and barriers to improving coverage in six districts in Malawi

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Abstract

Introduction: Malawi's National Immunization Program introduced a second routine dose of measles containing vaccine (MCV2) in 2015 but found coverage lagging. We assessed data quality and gaps in service delivery.

Methods: investigators used a modified data quality audit in 6 low performing districts accompanied by questionnaires for health facilities (HF) and households with children with >1 vaccination.

Results: MCV2 doses administered according to source were: 733 in registers, 2364 in reports, 1655 in district reports, 2761 in the electronic database. There was 77% agreement regarding status for MCV2 between the register and the home-based record (HBR). Drop-out differences were found between HF according to the practice of waiting for a minimum number of children to open an MCV vial, canceling sessions due to stock-out and requesting payment for a home-based record. Eighty one percent (81%) of children whose caregivers knew 2 doses were needed had received MCV2 vs fifty eight (58%) of children whose caregivers didn't know. Sixty two (62%) of children who were charged for HBR received MCV2 vs 78% reporting no charge.

Conclusion: the drop-out between the first and second doses of MCV was high and inconsistent with elimination goals. The quality of administrative data in these 6 districts was found to be poor. This investigation found that session cancelation, charging for HBR and lack of caregiver knowledge affected completion of the vaccination series. The authors recommend program improvements in these areas to increase uptake of MCV2 and improved reporting practices at all levels of the system.

Introduction

Measles is a highly contagious disease that prior to widespread vaccination killed an estimate of 2.6 million globally every year [1]. With the introduction of an effective measles vaccine and routine coverage levels over 80%, elimination is considered feasible and a strategic plan to achieve that goal has been developed by the Measles and Rubella Initiative (MRI). In the 2012-2020 plan, MRI calls for countries to "achieve and maintain high levels of population immunity by providing high vaccination coverage with two doses of measles- and rubella-containing vaccines" and sets a target of 95% coverage with a first and second dose of measles-containing vaccine (MCV1 and MCV2) in each district and every country. In 2011, countries in the African Region of WHO adopted the goal to eliminate measles by 2020 [2]. Vaccination against measles started as a routine program in Malawi in 1980 with one dose given at 9 months of age. Coverage as a percent of children under one year of age vaccinated steadily increased reaching 89% in 2017 [3]. Malawi also conducted 7 national Supplementary measles immunization activities (SIAs) from 2000 to 2017 targeting age ranges defined by the epidemiology of the disease at the time. As a result of routine vaccination and SIAs, the reported number of cases of measles steeply declined from 1989 through 2009 [3]. A large measles outbreak in 2010 as well as a WHO recommendation [4] led the Ministry of Health, National Immunization Program to adopt a second routine dose of measles containing vaccine (MCV2) into the schedule at 15 months of age [5]. The program introduced MCV2 progressively in all districts from July through December 2015. An MCV2 post introduction evaluation (PIE) conducted in October 2016 found that MCV2 coverage for the period January - June 2016 was 57% [6], lagging behind MCV1 coverage and insufficient to reach measles elimination goals [2]. This is consistent with coverage levels of several other countries in the African region as documented by Masresha et al. [7]. However, the PIE was unable to determine if the low coverage was due to poor reporting or to service delivery challenges, leading the Ministry of Health to conduct an additional investigation in February 2017. The objectives of this descriptive investigation were to: a) determine if records of MCV1 and MCV2 doses administered in health facility immunization registers agree with the numbers reported to national level; b) determine if record of MCV2 in the health facility immunization register agrees with the home-based record; c) identify non-data gaps in service delivery that might contribute to non-completion of vaccination among children who began the series.

Methods

Six of the country's 29 districts were chosen based on low MCV2 coverage for the period January - June 2016 as reported through the administrative reporting system plus additional districts chosen to provide an urban/rural mix. Within each district, a simple random sample of 3 health facilities (HF) was chosen. Using a modified data quality audit methodology [8], the number of doses of tracer vaccinations (MCV1 and pentavalent (diphtheria, pertussis, tetanus, hemophilus influenzea type B, hepatitis B) vaccine administered to children less than 12 months and more than 12 months of age, and MCV2) was collected from immunization registers, tally sheets and monthly reports at the facility and districts level; and from electronic databases for those facilities at the district and national levels for the months of February, October and December 2016 using standardized tools. A standardized questionnaire covering vaccination practice was administered to Health Surveillance Aids (HSA) in each HF.

To identify children who had begun their primary vaccination series, a simple random sample of 2 communities per HF was chosen by the interviewers using the facility immunization register. All children: a) from those communities; b) born between December 1, 2014 and August 30, 2015 and c) who received at least one vaccination between January 1 and October 31, 2015 were listed and 6 systematically selected for household visits. If there were less than 6 children from a chosen community, a neighboring community was selected based on local knowledge of geography. Households were visited and care givers of children identified from the register were interviewed using a standardized questionnaire and the information in the home-based vaccination record was copied. For purposes of comparing HF, drop-out between MCV1 and MCV2 was calculated from household questionnaires and HF divided into higher and lower drop-out in relation to the mean rate. One HF for which household questionnaires were not completed was excluded from this analysis. Data were collected using tablets preloaded with questionnaires in ODK and analyzed using MSExcel and EpiInfo.

Results

Information was successfully collected at the national level, in all 6 districts and 18 health facilities. After deduplication, there were 189 child records from the immunization registers of 17/18 health facilities and from 38 communities. The immunization register was not useable for child identification in the 18th HF. The health facilities interviewed were 2 hospitals, 12 health centers, 2 dispensaries, 1 clinic and 1 health post. Of the 189 children sought from the register, there was 1 death, 1 refusal and 24 who were not located. Of the 163 interviews, four children no longer lived in the location in the register resulting in 159 completed household questionnaires. The age of the children included in the sample provided a range from 17 through 26 months of age at the time of the survey. There were 6 to 14 household questionnaires per health facility.

Data quality

Immunization registers were available in all health facilities visited. Tally sheets were present and being used in 1/18 HF. Completed monthly reports were found for all 3 months in 17 HF, in the 18th HF 2 completed forms were located. Monthly report forms with printed space for MCV2 were available in 17/18 HF. 7/18 HF reported stockouts of reporting forms for the monthly report and or vaccination cards in 2016 ranging from 1 to 6 months with an average of 3 months. The number of doses recorded administered were collected from HF. As can be seen in Table 1, a total of 1872 doses of MCV1 administered were found in immunization registers and 4550 found in monthly reports. For MCV2, a total of 733 doses administered were found in immunization registers and 2364 found in monthly reports. A total of 4550 doses MCV1 administered were found in health facility monthly reports located at the district level and 3109 found in monthly reports prepared by the district with 10 exactly agreeing. A total of 2362 doses MCV2 administered were found in HF monthly reports located at the district and 1655 found in monthly reports prepared by the district level with 8 exact matches. A total of 3109 doses MCV1 were found in the monthly reports for the health facilities prepared by the district and 3487 in the electronic database at the national level for the 18 health facilities. For MCV2, a total of 1655 doses administered were reported per monthly reports and 2761 per the electronic database. The differences between total numbers of doses administered by source is illustrated in Figure 1. There was 76% and 77% agreement regarding vaccination status for MCV1 and MCV2 respectively between the register and the home-based record (HBR) without taking dates into consideration (Table 2). More children were vaccinated per HBR (128 vs. 97 MCV1; 78 vs. 70 MCV2) than per the immunization register.

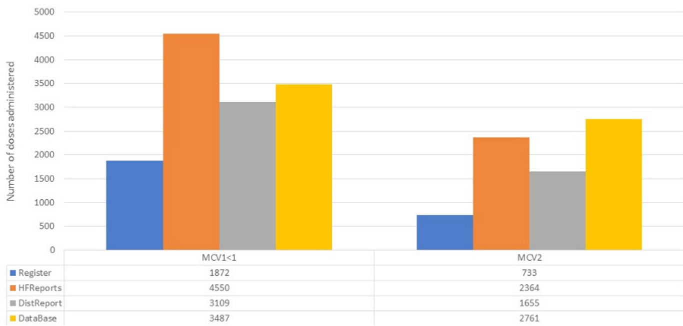

Figure 1: total doses MCV1 < 1 and MCV2 administered by source, 18 health facilities

Table 1: doses of Measles containing vaccine (MCV) administered by Health Facility and by information source, February, October and December 2016

HF #	HF level				District level				National			
	MCV1 <1		MCV2		MCV1 <1		MCV2		MCV1 <1		MCV2	
	Register	*Monthly reports*	*Register*	*Monthly report*	*Monthly report from HF*	*Monthly report of District*	*Monthly report from HF*	*Monthly report of District*	*District Monthly report*	*Electronic database*	*District Monthly report*	*Electronic database*
1	155	816	38	1	816	564	1	2	564	578	2	283
2	29	62	35	46	62	77	46	46	77	99	46	117
3	40	75	24	1	75	69	1	19	69	60	19	51
4	452	1709	0	1180	1709	546	1180	480	546	1470	480	1180
5	144	382	0	148	382	382	148	148	382	321	148	258
6	98	100	81	170	100	100	170	170	100	89	170	170
7	261	325	121	195	325	315	195	194	315	94	194	96
8	79	120	0	40	120	120	40	40	120	100	40	40
9	70	102	18	26	102	74	26	26	74	63	26	26
10	270	276	158	148	276	276	148	148	276	198	148	148
11	72	185	61	150	185	187	150	150	187	131	150	150
12	50	62	41	60	62	62	60	39	62	70	39	66
13	29	109	35	71	109	109	71	72	109	50	72	72
14	29	59	28	32	59	59	32	34	59	47	34	34
15	19	13	8	12	13	13	12	5	13	13	5	5
16	30	107	32	38	107	107	38	34	107	64	34	29
17	14	23	22	26	23	24	26	28	24	17	28	16
18	31	25	31	20	25	25	20	20	25	23	20	20
Total	1872	4550	733	2364	4550	3109	2364	1655	3109	3487	1655	2761

HF4: one monthly report not found at the HF level

Table 2: vaccination status by source of information: home-based record and immunization register

	MCV1			MCV2		
From Home-based record	**From immunization register**			**From immunization register**		
	Yes	**No**	**Total**	**Yes**	**No**	**Total**
Yes	96	32	128	58	20	78
No	1	11	12	12	50	62
Total	97	43	140	70	70	140

Table 3: selected reported service delivery behavior for Health Facilities with less than and greater than average drop-out (DO) rate			
		% of HF	
		<30% DO (n=9)	**≥30% DO (n=8)**
Number sessions/month	Static	8.7	11.6
	Outreach	4.6	3.1
Vaccinate every session	Static	100	100
	Outreach	100	100
Offer MCV every session	Static	100	87.5
	Outreach	100	100
No min children to open MCV Vial		78	100
Canceled at least one session due to stockout		22	62.5
Prioritize for MCV if stock is low		11	0
Request payment for Vax card		11	62.5
Request payment for session		0	0

Table 4: vaccination coverage by source and selected care-giver responses by vaccination status, MCV2 (card + history)					
	MCV1 (n=159)		**MCV2 (n=159)**		
	Number	**%**	**Number**	**%**	
Card	123	77	90	57	
History	8	5	8	5	
Total vaccinated	131	82	98	62	
		MCV2 (card + history)			
		Yes	**No**	**% Vaccinated**	
Is your child completely vaccinated?	Yes	99	40	71	
	No	5	10	33	
	don't know	2	3	40	
How many doses does a child need?	1	23	18	56	
	2	56	13	81	
	don't know	26	18	59	
MSD pre-printed on card	Yes	27	13	68	
	No	71	35	67	
Paid for home-based record	Yes	63	38	62	
	No	35	10	78	
Stay with other adult	Yes	66	34	66	
	No	40	19	68	
Due for MCV1 before MCV2 intro		48	24	67	
Due for MCV1 after MCV2 intro		47	27	64	

Factors affecting MCV2 coverage

The 17 HF with household questionnaires were compared for factors that might influence drop-out (Table 3). Health facilities with less than average drop-out rates planned an average of 8.7 static and 4.6 outreach under-2 well child clinics per month and offered MCV at all sessions. Seventy eight (78%) reported that they had no minimum number of children required to be present to open a vial of measles vaccine. Twenty-two percent reported that they had canceled at least one vaccination session due to stock-out of vaccine. This question was not specific to measles vaccine. Eleven percent stated that they prioritized who would receive measles vaccine if stocks were low. Eleven percent reported that they requested payment for the home-based record, none requested payment for services. The 8 health facilities with greater than average drop-out planned an average of 11.6 static and 3.1 outreach under-2 well child clinics per month, MCV was offered at 87.5% of static and 100% of outreach sessions. All reported that they had no minimum number of children to open a vial of measles vaccine. Sixty-two percent had canceled at least one vaccination session due to stock-out of vaccine. This question was not specific to measles vaccine. Zero percent stated that they prioritized who would receive measles vaccine if stocks were low. Sixty-two percent reported that they requested payment for the home-based record, none requested payment for services.

Among the children included in the household survey, 9 MCV1 vaccinations were misrepresented as MCV2 (in the absence of a first dose, older than one year at the time of vaccination). These were corrected to MCV1. 146/159 children (91%) had a home-based vaccination record present at the time of the survey, 143 of these were the government-issued passport and 3 a vaccination card or other record. Vaccination status was estimated from the home-based record and parental recall. 150/159 (94%) of children had received MCV1 and 106/159 (67%) MCV2 based on the home-based record or care-giver recall - a drop-out rate of 29% (Table 4). Sixty-two percent of respondents thought that the child had received all of his/her vaccinations, 71% of whom had received MCV2. Ninety-eight percent of respondents had heard of measles vaccination. Forty-three percent knew that a child needed 2 doses of MCV. Of those that said a child needed 2 doses, 81% had received MCV2. Of the 53% (85/159) who thought the child needed one dose or said that they did not know 58% had received MVC2. New HBR were printed for the introduction of MCV2 but not all children were in possession of the new cards. Sixty-eight percent of those that had the new cards with MCV2 pre-printed had received that dose. Sixty-seven percent of those with the HBR without MCV2 had received that dose. Of those who reported that they paid for the HBR, 62% had received MCV2. Seventy-eight percent who reported they had not paid for HBR had received MCV2 (Table 4). Eighty-nine percent of caregivers said that the health care worker (HCW) was the most trusted source of information regarding vaccination and 79% that they knew when to return for a vaccination because the HCW had told them during the previous clinic visit.

Discussion

We confirmed that drop-out between the first and second doses of MCV is a problem in the 6 districts included the study. Drop-out ranged from 21% to 61% depending on the data source used, all higher than levels needed to achieve the measles elimination goal endorsed by the national, regional and global levels. This study determined that records of MCV1 and MCV2 doses administered were inconsistent from HBR to HF registers to HF monthly reports, through the district level reports to the national database. This lack of consistency undermines the confidence of program managers at all levels. The figures available at district and national levels were 1.7 - 2.4 times higher than those found in immunization registries, masking the probable low coverage in the HF and the high drop-out rates limiting the use of the data for planning or evaluation. The immunization register at the HF is a key tool in identifying children who have missed doses for follow-up and, in the absence of tally sheets, is the only source of information for the monthly reports [9]. In one of these HF, the immunization register was not name-based, making defaulter tracking impossible. In the other 17, immunization registers missed 25% of the MCV1 doses and 26% of the MCV2 doses found in HBR.

This investigation was not designed to provide a coverage estimate for the districts included. Based on the design, which was intended to determine the quality of reported information and identify potential factors contributing to high drop-out between MCV1 and MCV2, only children who had initiated the vaccination series and were identifiable from the immunization registry were included. A variable number of households were interviewed by HF further limiting interpretation of the responses. Therefore, results of the household component of the investigation are not representative of the HF nor the districts but have provided hypotheses for high drop-out which can be further tested.

While not representative, this investigation found that drop-out was higher than average in HF that more frequently reported cancellation of at least one vaccination session due to stock-out and who reported they charged for HBR. The household questionnaires also identified care giver reports of paying for the HBR as potentially resulting in less MCV2 coverage. The HBR is an essential tool for reminding care givers of vaccination history and facilitating screening for vaccinations due during immunization sessions or curative care [9, 10]. The Malawi national policy is consistent with WHO recommendations and common practice [11]. However, this investigation demonstrates that the policy is not universally followed and may have a negative impact on completion of the vaccination series. Efforts must be undertaken to assure the respect of national policy and provision of HBR free of charge.

Caregiver knowledge of the need for a second routine dose of measles vaccine was another factor identified as potentially affecting MCV2 coverage with 81% of those who knew receiving MCV2 vs 58% of those who thought one dose was needed or replied that they did not know. While interpretation of this observation is further limited by directionality (mothers of children who received 2 doses are more likely to know about the need for 2 doses), HCW are the most trusted source of information regarding immunization in general and the next appointment in particular. HCW must increase communication about the need for a second dose of MCV.

Conclusion

In summary, we found that the drop-out rate between the first and second doses of MCV was high and inconsistent with measles elimination goals. We also found that the quality of administrative data in these 6 districts was poor and greater attention needs to be paid at all levels to improve the collection and use of data. Additionally, this investigation found that session cancelation, charging for HBR and lack of caregiver knowledge are potential factors affecting completion of the vaccination series. These hypotheses may be tested through additional studies. Authors recommend undertaking program improvements that focus on these areas to increase uptake of MCV2 and improve reporting practices at all levels of the system are logical and recommended. Following this investigation, the immunization program began implementation of missed opportunity for vaccination [12] and second year of life [13] strategies in 3 districts.

What is known about this topic

- Coverage with a second routine dose of measles containing vaccine lags behind coverage with the first dose in many countries, including Malawi;
- Health worker behavior does not always follow national policies.

What this study adds

- Addressing the challenge of low coverage and high drop-out between measles doses is complicated by poor data quality;
- Despite national policy on providing home-based-records free of charge, some HF continue to charge which seems to have an effect on completing MCV2;
- Frequent cancelation of sessions due to stock-out may have an effect on drop-out rates.

Competing interests

The authors declare no competing interests.

Authors' contributions

Geoffrey Chirwa, acting director of the National Immunization Program at the time of the PIE and investigation, conceptualized the investigation and oversaw all logistical operations, while taking on the function of national supervisor. Mr. Chirwa contributed significantly to commenting on the drafts of the paper. Karen Wilkins was co-principal investigator on the investigation, secured financing and was principal writer of the manuscript. David Mercer provided key contributions to the manuscript drafts and oriented the data analysis. All authors have read and agreed to the final manuscript.

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PanAfrican Medical Journal

Research

The use of WhatsApp group messaging in the coordination of measles supplemental immunization activity in Cross Rivers State, Nigeria, 2018

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Abstract

Introduction: Cross Rivers State, in southern Nigeria, conducted measles Supplemental Immunization Activities (SIAs) in 2 phases from 2 -15 March, 2018. The SIAs coordination was led by the State technical coordination committee. A total of 90 supervisors from the national and subnational levels, including consultants were deployed to support the SIAs. The instant messaging service - WhatsApp was utilized to help in the communication and coordination among the State and field teams.

Methods: we reviewed the chat logs from the WhatsApp group exchanges made between 28 February 2018 and 31 March 2018. Thematic content analysis was done.

Results: a total of 653 WhatsApp messages were posted among the 55 group members during the study period, including text messages and media content. Eleven percent of the posts related to monitoring processes and data sharing, while posts related to vaccine logistics and waste management made up about 6% of the total. Overall coordination and deployment was covered in 6% of the posts. Forty percent of the media content showed vaccination service delivery and SIAs launching events or monitoring meetings in various areas. The coordination team used WhatsApp to send reminders to the field staff about data sharing, vaccine and waste management, as well as feedback on coverage and completeness of data sharing. The WhatsApp group discussions did not include most of the logistical and hesitancy challenges documented in the State SIAs technical report.

Conclusion: we recommend focusing group discussions on instant messaging platforms so that they can be used for problem solving and sharing best practices, integrating it with other supervisory processes and tools, as well as providing feedback based on processed data from the field.

Introduction

Nigeria has been implementing measles control strategies since 2005 and has adopted the African Regional measles elimination goal [1-3]. The strategies for attaining measles elimination include strengthening routine immunization coverage, conducting periodic Supplemental Immunization Activities (SIAs) and enhancing surveillance with lab confirmation [1]. SIAs provide an opportunity to give measles vaccine to young children that may not have received their doses in the routine immunization service. This is particularly useful in areas where routine immunization service coverage is limited. Nigeria has had annual Measles Containing Vaccine first dose (MCV1) coverage levels of less than 50% at national level [4]. With a large birth cohort and low routine immunization coverage, the number of unprotected young children accumulates rapidly posing risks of measles outbreaks. For this reason, Nigeria has been conducting periodic measles SIAs every two years in the last 12 years [2, 3]. However, SIAs play a critical role to reduce measles incidence if they can attain high coverage across all districts and if they can reach populations that are not reached through routine services. This requires early planning, the timely availability of resources, government ownership and high-level leadership, as well as intensive technical and logistical preparations, community demand generation and very good coordination [5, 6].

In 2017, The National Primary Health Care Development Agency (NPHCDA) of the government of Nigeria decided to implement the scheduled nationwide measles SIAs in a phased manner, starting with the States in northern Nigeria from October to December 2017, and covering the southern states in the first quarter of 2018, to allow for the optimal use of human and logistics resources [7]. Cross Rivers State (CRS) is a coastal state in the southern part of Nigeria. The State has 18 Local Government Areas (LGAs) further partitioned into 196 wards [8]. The projected total population of the State for the year 2018 is 4,727,230. The target population for the measles SIAs in Cross Rivers State was 714,109 children aged 9 - 59 months. The measles SIAs in CRS was carried out from 2 - 15 March, 2018. However, it was implemented in a staggered manner to maximize the available resources for the campaign. Nine LGAs were reached as part of the first phase implemented from 2nd - 7th March, 2018 while the remaining 9 LGAs were reached from 10th - 15th March, 2018 [8]. The SIAs implementation lasted for six days and two days were added to allow mop-up vaccination across all wards and LGAs.

The coordination of the SIAs in Cross Rivers State (CRS) was done by the State technical coordination committee, comprising of various officers in the State Primary Health Care Development Agency (SPHCDA), the NPHCDA, as well as partner agencies (eg., WHO, UNICEF and the African Field Epidemiology Network - AFENET). The first minute meeting of the State coordination body took place on 2nd January 2018. A total of 90 supervisors from the LGA, State and National level, as well as external consultants (recruited through the various technical support agencies) were deployed across the State to supervise, monitor and assist the implementation of the SIAs. The consultants were on board until 31st March 2018. In the weeks preceding the launch of the SIAs, and during the course of the first phase SIAs, the coordination was done from an operations room set up at the State Primary Health Care Development Agency (SPHCDA) in Calabar. The coordination of the second phase of the SIAs was done from a base in Ogoja town [8]. As part of the deliverables in the measles SIAs in Cross Rivers State, the consultants and other supervisors were requested to document their supervisory findings by filling in a questionnaire loaded on their smartphones or tablets using the Open Data Kit (ODK) software [9]. The supervisory information was supposed to be captured and submitted in real time along with time signatures and geo-coordinates [10].

At the same time, in order to address the immediate needs for regular communication and coordination of the state level officers and consultants, the State coordination team decided to set up a WhatsApp Messenger group. WhatsApp was selected because it is already widely used in Nigeria by smartphone users, is free and is considered to work well under poor network conditions. Smartphones are widely used in Nigeria. The number of smartphone users in Nigeria in 2017 was estimated to be 25 - 40 million [11]. Mobile instant messaging services offer real-time communication features. These services allow users to share text, audio, image and video messages across a range of mobile and non-mobile devices. Mobile tools have been used to facilitate supervision, program support and data sharing in the context of polio eradication activities and other disease control activities [12-14]. WhatsApp is one of many smartphone applications which are currently widely used for calls and instant messaging. The application allows many people to come together as part of a messaging group. WhatsApp group communication allows for one-to-many communication, making information generated by one member immediately available to all within the group. The role of instant messaging services like WhatsApp in health worker supervision and team building has been documented in Kenya [15]. In Mozambique, WhatsApp was used as a supplementary tool for mentoring provincial and district health teams during a campaign to distribute bed nets [16]. The authors have observed WhatsApp being used as a communication tool during immunization interventions in many countries in the African Region. In Nigeria, the national measles SIAs technical coordination body has also been using WhatsApp as a communication tool in the SIAs in the northern part of the country. However, despite the increasing use of such mobile instant messaging tools like WhatsApp, there is limited knowledge available on the ways in which these tools can be deployed to best support supplemental immunization activities. This manuscript attempts to look into the experience of using WhatsApp as a coordination tool in the context of the implementation of measles SIAs in Cross Rivers State (CRS) in Nigeria.

Methods

The State level coordination team in Cross Rivers State decided to establish a WhatsApp group for communication purposes and it was set up on 28 February 2018. The group remains live up to April 2019. The group was administered by the CRS immunization program officer for monitoring and evaluation and a consultant supporting the State coordination of the SIAs. The members of the WhatsApp group included national and State level immunization program officers and team members, national and state level partner agency members, monitors and supervisors, as well as external consultants recruited for the SIAs by the technical agencies, all of whom were involved in the support of the SIAs operations, including logistics, communications and monitoring activities. The chat logs from the WhatsApp group exchanges were exported into MS-WORD on 16 April 2019 and reviewed. Decision was made to classify and analyze the data from 28 February 2018 (date of establishment of the group) to 31 March 2018, which was the last workday for the majority of supervisors, who were recruited as consultants. The researchers conducted the content analysis using a thematic coding system, developed after going through the posts and identifying the major programmatic areas addressed in the forum. Two researchers individually went through the chat log manually and assigned each posted message to a thematic category, based on the content of each posting. The coding assignments by the two researchers were compared and any differences in categorization was re-discussed to arrive at a consensus. Data entry and analysis was done in MS Excel. Our study did not review the supervisory information submitted using the Open Data Kit (ODK) platform.

Results

The SIAs in Cross Rivers State were conducted between 2 - 15th March 2018. The WhatsApp group had 55 members by 31 March 2018. Members were being added into the group up to 15th March 2018. A total of 653 WhatsApp messages were exchanged among the group members during the 32 day period under study, from 28 February 2018 to 31 March 2018 (Figure 1). Five media messages could not be retrieved from the chat log. Out of the remaining 648 messages, there were 448 text messages (69%) and 200 media postings (31%), some of which included extensive captions. Out of the 200 media contents posted on the forum, 196 (98%) were images while 4 were audio or video clips. The majority of the messages (91%) shared over the period under study were exchanged from 28 February to 19th March (starting the first day the group was set up and going through to 4 days after the end of phase 2 of the SIAs in the State). The highest number of messages exchanged per day was on 13 March 2018, with 59 messages exchanged.

The thematic categorization of the group messages indicate that the largest number of messages (34%) are social exchanges among the group members including acknowledgement of prior messages, greetings, good wishes and others. There were a total of 71 posts (11%) related to monitoring processes and data sharing, while posts related to vaccine logistics and waste management made up about 6% of the total. Message postings related to technical guidance, program coordination and deployment comprised of another 6%. Posts about vaccination service delivery/vaccination post/vaccinated children as well as posts portraying best practices from the field (especially the involvement of local leaders, partners and stakeholders) each comprised about 10% of the total (Table 1). The most common type of media postings (24%) showed vaccination posts, vaccinated children and/or SIAs service delivery, while 16% of the media postings portrayed photos from SIAs launching events in various LGAs, as well as photos of observer visits from partner agencies and review meetings chaired by local authorities.

The chat log includes postings containing guidance from the State/ National level on vaccine logistics and waste management provided to the field staff. These included instructions to account for vaccine utilized, information about waste management and designated incineration sites. Some typical posts in this category are:

"Please State Technical Facilitators, LGA teams for both 1st and 2nd phase, be reminded of the vaccine accountability for measles vaccine: vaccine received, additional doses received, empty vials, unused vials returned (all physically counted), number of children immunized, wastage rate, remarks, etc. Documentation with the State Logistics Working Group has commenced. Thank you" Partner agency staff member.

"Please ensure filled safety boxes are moved from facility level to LGA by the Ward Focal Person. Waste management should be in the agenda for daily review meetings." SPHCDA staff member.

"Vaccines for the second phase will arrive in the State latest today. All LGAs implementing can come for their vaccines and devices from tomorrow." State cold chain officer.

Another theme that features frequently in the exchanges and discussions was monitoring and data sharing. These included reminders to the field staff to send in daily coverage statistics, supervisory data collected on the ODK platform, as well as feedback on coverage data and completeness of data sharing. The most common challenges raised by supervisors and coordinators in the field included challenges related to uploading ODK data packets and daily data transfer to the State level.

"Please remember to use your ODK implementation checklist. You are expected to upload at least 3 per day from different teams/locations/ wards" Partner agency staff member.

"I have a little challenge, after filling the ODK and trying to send the final list, I noticed that (some variable fields are blank) and trying to correct it was a problem" Consultant 1 supervising implementation.

"Good morning all & welcome to day 5. The state is at 63% as at day 4. Thank God for (LGA 1, LGA 2, LGA 3 & LGA 4) for submitting day 4 data. Five other LGAs were unable to submit as at 11 pm yesterday." Consultant 2 supervising implementation.

There were also text messages from the State level highlighting the deliverables expected from the field staff, as well as instructions on team deployment and movement and technical guidance and clarifications on technical issues.

"Each agency/national monitor on the field should remember to properly document his/her activities, achievements, etc… along with SWOT analysis following outlined report format." Partner agency staff member.

"Sunday plan is a special plan that has list of churches with eligible children. This must include the team to visit the church, time of visit; same applicable to schools. Check your developed plans - these were included." LGA Technical Officer.

Some of the best practices that were identified and communicated from the field included the involvement of heads of LGAs in chairing evening review meetings, resolving non-compliance on an individual level and in schools, the engagement of local authorities/partners/stakeholders in official SIAs launching events and mobilizing communities through traditional community leaders , teachers, etc.

"This (LGA name) Head of LGA´s exemplary leadership vividly translates into positive outcome as indicated by both quantitative and qualitative measles vaccination campaign results from that LGA." Partner agency staff member.

"Attempting to convince an adamant mother to allow her 2 children to be vaccinated. Her decision of refusal was her past experience in another campaign when her child developed some AEFI and the health workers did not allay her concerns ….. And yes, we finally immunized all 2 children after the lengthy dialogue" Consultant 3 supervising implementation.

"(Name of LGA) is starting mop-up this morning. We are determined to comb all settlements and wards to ensure we have no missed children" Consultant 4 supervising implementation.

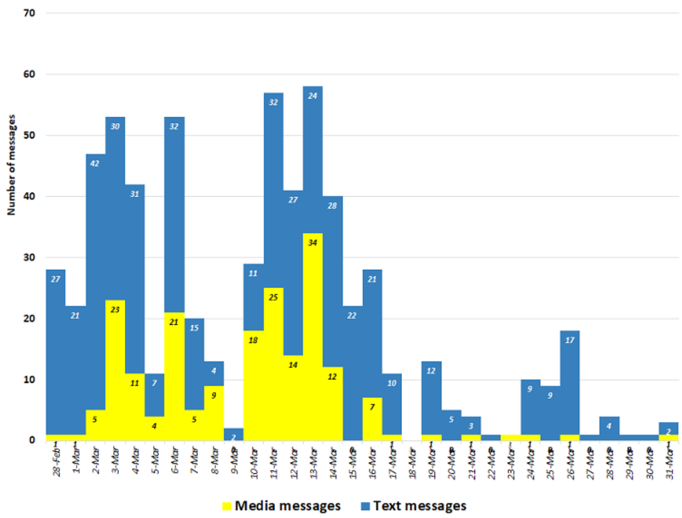

Figure 1: number of text and media messages exchanged in the Cross Rivers SIAs coordination State WhatsApp group 28 February - 31 March 2018

Table 1: thematic categorization of text and media messages exchanged in the Cross Rivers State WhatsApp group, 28 February 2018 - 31 March 2018

Thematic content of WhatsApp posts	Number of text messages	Number of media messages	Total number (%) of messages
Administrative content (adding group members, members leaving group, deleted messages)	67	0	6 (10%)
Acknowledgement to prior messages, greetings, good wishes, encouragements and condolences…	219	2	221 (34%)
Posts containing technical guidance, overall program coordination and staff deployment, program review exercises	30	11	41 (6%)
Posts discussing or showing vaccination service delivery / vaccination post/ vaccinated children	2	61	63 (10%)
Posts about vaccine logistics	16	1	17 (3%)
Posts on waste management	9	9	18 (3%)
Posts related to monitoring and supervisory processes	16	25	41 (6%)
Posts dealing with coverage data request, data sharing and feedback on received data/ coverage	28	2	30 (5%)
Sharing best practices from the field – involvement of local leaders, partners and other stakeholders	15	48	63 (10%)
Sharing best practices from the field - resolving problems/ reaching the unreached/ community mobilization	7	31	38 (6%)
General information from the field	18	0	18 (3%)
Posts not related to the SIAs or the group dynamics	21	10	31 (5%)
TOTAL MESSAGES	448	200	648 (100%)

Discussion

The information contained in the WhatsApp chat-log is highly unstructured as it contains text-messages. As the primary objective of the WhatsApp group was to share information for better coordination of the SIAs, the group communication on the forum was focused on this objective in the time period up until the end of the SIAs. On 16th March (the day after the end of the phase 2 SIAs), the first post containing unrelated subject matter was shared on the forum. One third (34%) of the posts in this WhatsApp group included civilities and encouragements exchanged between group members, which is an essential ingredient to foster team spirit as the group works towards the same goal. Overall, a total of 200 (31%) posts had media content, most of which were images showing service delivery, the conduct of meetings or SIAs launching events sent for informational purposes and occasionally captioned to showcase best practices. Around 17% of the messages were related to monitoring systems and data sharing, as well as to vaccine logistics and waste management. These messages mostly originated from the State level, and were providing reminders, specific instructions and clarifications to the field staff in order to ensure the smooth and safe conduct of the SIAs, as well as better monitoring of implementation.

The SIAs technical report for Cross Rivers State, which was compiled at the end of the exercise, identifies the following challenges; delays in the release of funds for social mobilization and SIAs logistic inputs, delayed procurement and inadequate supply of AEFI kits and cotton wool, poor road infrastructure and telecommunication network affecting staff movement and daily submission of SIAs data, late arrival of communication and mobilization materials to the State level, population non-compliance due to rumors following the monkey-pox outbreak, and the lengthy data collection tool loaded on the ODK platform for use by supervisors [8]. Most of these challenges are amendable to solutions including better coordination and alternative logistical arrangements, which require smooth communication across various levels. However, some of the challenges dealing with delayed and inadequate distribution of various materials did not feature at all in the WhatsApp group exchanges we reviewed. The problem of non-compliance and the challenges with the ODK tool were mentioned very few times in the WhatsApp group exchanges. Obviously, WhatsApp was not the only communication means that was available to the State coordination and field team. More pressing issues related to logistics as well as specific challenges are likely to have been dealt with through phone calls and face to face discussions. This may explain why some of the challenges reported in the technical report were not documented across the social media platform.

In addition, the field supervisors and consultants were expected to capture and share supervisory data using the ODK platform as a formal supervisory tool. Since data sharing is expected to be in real time, this should avail more detailed and quantified information for the State and national coordination team. We have noted that none of the posts on the WhatsApp group from the State coordination team referred to the results of analysis of ODK supervision findings at any time, nor explicitly linked guidance to the supervisory findings. WHO guidelines recommend that a provincial/ district level coordination team be in place at least 9 months before the SIAs with clear roles and tasks designated to specific members/subcommittees [6]. The State level coordination structure in CRS had its first minute meeting 8 weeks before the SIAs. The WhatsApp group was set up 3 days before the official start of the SIAs and so it was not possible to see its use in facilitating the precampaign preparedness. Countries have used WhatsApp for coordination in the context of immunization service delivery, but its use has not been analyzed or documented. In Mozambique, during a bednet distribution campaign, WhatsApp group messaging was used for coordination, and the experience among multiple groups with a total of 511 members was documented. It was noted that the use of WhatsApp was critical for implementation support to subnational level teams [16]. Other studies have documented the use of instant messaging for disease surveillance and program supervision [17, 18].

During the measles SIAs in Cross Rivers State, the administrative coverage was 103.4%. There were no severe cases of adverse events following immunization recorded during the SIAs [8]. The post-campaign coverage survey showed 88.5% coverage in the State, with 19.4% of the children having been vaccinated for the first time ever [19]. The results of this study show that instant messaging platforms are useful tools to facilitate the exchange of information and coordination among groups of people, and especially within a SIAs context. We have observed that the major part of the exchange within this WhatsApp group was more of information sharing than problem solving in nature. However, the State coordination team has used WhatsApp messaging to pass specific guidance and reminders to the supervisors in the field on key aspects of SIAs implementation, like monitoring processes and vaccine logistics.

Limitations

Our analysis looks at only one WhatsApp group's experience and does not represent other areas, groups or use cases. The study is descriptive and does not compare the use of WhatsApp with any other means of communication. We did not compare the findings with the outcome of the supervision done at the same time using the ODK platform. The WhatsApp group was set up three days before the SIAs implementation started and so we did not have the opportunity to see the potential uses of such communication platforms in a pre-campaign preparations setting. Moreover we looked at archived messages 1 year after the end of the SIAs, and a small proportion of the postings were lost. We cannot rule out the possibility of supervisors exercising reservations with regards to exposing logistics gaps in a group chat forum since their superiors were on the forum as well.

Conclusion

With the increasing penetration of smartphone use and internet services, we think that instant messaging platforms like WhatsApp provide a very convenient means for one-to-many communication and can be used as supplementary tools in the coordination of public health interventions like SIAs. However, the use of such platforms can be better focused to respond to the program needs, if clear rules are set out governing the group communication; the objectives and life span of the group, as well as the inclusion and exclusion criteria are clearly mapped out from the outset. Adequate linkage needs to be made with other supervisory processes and tools (eg., integrated supervision data). Moreover, the platform can be better managed for problem solving and sharing best practices, especially if the central coordination team harvests critical information and interprets important lessons from the posts, generates program action, and provides feedback to the group. The sharing of maps, charts and other graphics related to the SIAs logistics or monitoring outputs helps the field team better visualize and capture information.

What is known about this topic

- Instant messaging services are widely used applications;
- Coordination is an important role in the success of SIAs and smooth communication is a key part of coordination of public health interventions like SIAs.

What this study adds

- WhatsApp messaging can serve as an important supplementary tool for better SIAs coordination;
- Careful management of a WhatsApp group communication platform along with clear protocols for use can make it into a more useful tool for SIAs coordination, problem solving and sharing best practices.

Competing interests

The authors declare no competing interests.

Authors' contributions

All authors contributed to this work. All authors have read and agreed to the final manuscript.

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Research

Progress towards measles elimination in Eritrea: 2003 - 2018

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Abstract

Introduction: the Expanded Program on Immunisation (EPI) has been operational in Eritrea since 1980. Eritrea has endorsed the resolution of the Regional Committee of the World Health Organisation African region, committing to a measles elimination goal for 2020 in the African Region. The country is implementing the recommended strategies.

Methods: we reviewed administrative coverage and WHO UNICEF coverage estimates for Diphtheria-Pertussis-Tetanus (DPT) and measles routine vaccination, as well as for measles supplemental immunization activities. We reviewed national surveillance performance and analyzed the epidemiological trends of measles as reported in the case-based surveillance database.

Results: Eritrea has maintained more than 90% coverage with the first dose of measles vaccine at national level since 2001 and 88% MCV2 coverage from 2015 - 2017 according to the WHO-UNICEF coverage estimates. Since 2011, the country has not met the surveillance performance target of at least 80% districts reporting suspected measles cases with blood specimen. Measles incidence was between 16.8 - 24.7 cases per million population in the period 2015 - 2018. The mean and median age of confirmed measles cases was more than 10 years in 8 of the 14 years covered by the analysis. In 2017, Eritrea reported 1,199 cases of measles which differs significantly from the 185 suspected cases in the case based surveillance database for the same year. Eritrea has maintained high coverage for MCV1 and MCV2 and made progress towards measles elimination. However, the country has gaps in surveillance performance which may mask the true incidence of measles.

Conclusion: in order to attain elimination of measles, Eritrea needs to implement measures to improve surveillance quality, to conduct regular risk assessment and implement targeted measures to close immunity gaps. In addition, setting up a national committee for the verification of measles elimination will help the country document progress and also to highlight and advocate for addressing issues related to data quality and performance gaps.

Introduction

Eritrea has a projected total population of 3,905,066 in 2018 including an estimated 117,152 surviving infants. Children less than 5 years of age are estimated to make up 15% of the total population. The country is divided into six administrative regions known as Zobas: Gash Barka, Anseba, Debub, Maekel, Debubawi Keih Bahri and Semanawi Keih Bahri Zobas (Zones), which in turn are divided into 58 subzobas (sub-zones) [1]. The 2018 report of the UN Inter-Agency Group for Child Mortality Estimation indicates that, in Eritrea, under-five mortality rate was reduced from 151 per 1,000 live births in 1990 to 43 per 1,000 live births in 2017. Infant mortality rate was also reduced from 93 per 1,000 live births in 1990 to 32 per 1,000 live births in 2017 [2]. The second national Health Sector

Strategic Development Plan of Eritrea for 2017 - 2021 (HSSDP-II) further aims to reduce under-five and infant mortality rates to 32 and 25 per 1,000 live births respectively [3].

The Expanded Program on Immunisation (EPI) has been operational in Eritrea since 1980. Currently, the EPI program is housed as a unit within the Department of Public Health and is responsible to the director of family and community health division. EPI service delivery is integrated with other maternal and child health services and it is delivered as a package in all health facilities. By 2017, the ministry of health was providing healthcare service through 349 health facilities, in three-tier structure - namely primary care level, secondary care level and tertiary care level. A total of 295 (85%) health facilities provide routine immunization services 6 days per week in the country. In addition, immunization service is provided at 450 outreach sites across the country [1]. The HSSDP-II prioritizes, among others, the delivery of accessible and equitable immunization service for children below 5 years of age using the reaching every district approach [3]. As of 2019, the national EPI schedule includes antigens against 11 vaccine preventable diseases. These include a dose of BCG vaccine provided at birth, three doses of pentavalent vaccine (DPT/HiB/hepatitis B) and pneumococcal vaccine (PCV13) at 6, 10 and 14 weeks of age, four doses of oral polio vaccine (at birth, at 6, 10 and 14 weeks), Injectable Polio Vaccine (IPV) at 14 weeks of age, 2 doses of measles-rubella vaccine at 9 months and 18 months of age, and 2 doses of rotavirus vaccines at 6 and 10 weeks of life. Every woman of childbearing age (15 - 45 years) is expected to receive 5 doses of tetanus toxoid and diphtheria (Td) vaccine as per the WHO recommendations [4].

In 2011, the WHO African Region adopted a regional measles elimination goal for 2020, comprised of the following targets: 1) ≥ 95% coverage with the first dose of measles-containing vaccine (MCV1) at national and district levels; 2) ≥ 95% coverage in all districts during measles supplemental immunization activities (SIAs); 3) confirmed measles incidence < 1 per million population in all countries; 4) attaining high quality measles surveillance - to investigate ≥ 2 cases of non-measles febrile rash illness (NMFRI) per 100,000 population annually, and to obtain a blood specimen from ≥ 1 suspected measles case in ≥ 80% of districts annually [5]. The regional measles elimination goal is reflected as one of the objectives of the regional immunisation strategic plan 2014 - 2020 [6]. In line with the Regional goals, the Eritrean national comprehensive Multi-year plan for immunization (2017 - 2021) aims to achieve > 95% vaccination coverage with the first dose of measles-rubella vaccine (MR1) and 90% with the second dose of MR by 2021 [1]. This manuscript aims to describe the performance of Eritrea in the implementation of measles elimination strategies, the epidemiology of measles in the country and the overall progress towards measles elimination as at end of 2018.

Methods

Routine immunization: the antigens provided to eligible persons as part of the routine immunization service are recorded and reported by health facilities to the sub-zobas, and the zobas, and onward to the National Immunization Programme. Sub-national and national coverage is calculated against the respective denominator targets and the national level coverage is reported annually to WHO and UNICEF. WHO and UNICEF use coverage data from administrative reporting and from surveys to generate coverage estimates for each antigen provided through the routine immunization services [7]. We analyzed the administrative measles vaccination service data, coverage information from surveys and the annual WHO-UNICEF measles vaccination coverage estimates for Eritrea for the years 1993 - 2017.

Supplemental immunization: Eritrea has been conducting preventive measles supplemental immunization activities (SIAs) periodically since 2003. At the end of each SIAs, technical reports are compiled, and often coverage surveys are done to corroborate administrative coverage levels. We reviewed the various technical reports and coverage survey results following the measles SIAs conducted in Eritrea between 2003 and 2018 [8].

Measles surveillance and disease incidence: Eritrea established measles case-based surveillance, with the support of a national serological laboratory for the confirmation of measles cases starting in 2005. Measles surveillance protocols as well as the methods and tools used by the measles serological laboratory network are standardized across the WHO African Region [9]. We analyzed the surveillance database for the years 2005 to 2018. We reviewed the epidemiological pattern of measles cases confirmed by laboratory testing, epidemiological linkage or clinical criteria. Measles IgM negative specimens are tested for rubella IgM as part of the standard protocol. We reviewed the number of lab confirmed rubella cases reported in the same period.

Measles surveillance performance is monitored using standard performance indicators. The two principal performance indicators are: non-measles febrile rash illness rate (target of at least 2 per 100,000 population) and the proportion of districts that have investigated at least one suspected case of measles with blood specimen per year (target at least 80% of districts per year). The incidence of confirmed measles is calculated as a rate per million, by dividing the total number of confirmed measles cases (confirmed by laboratory, epidemiological linkage and clinical criteria) by the total population [9]. In addition to the analysis of data from the case-based measles surveillance database, we reviewed the official number of measles cases reported by the country annually to WHO and UNICEF through the Joint Reporting Form (JRF) [10].

Results

Routine immunization: national coverage with the first and third doses of Diphtheria-Pertussis-Tetanus containing vaccine (DPT1 and DPT3) sharply increased from 49% and 32% respectively in 1993 to 97% and 93% in 1999 according to the WHO UNICEF coverage estimates. During the same period, the first dose of measles vaccine (MCV1) coverage improved from 34% to 88%. Coverage for all antigens dropped by about 10 percentage points in 2000 but recovered by 2002. From 2003 until 2017, vaccination coverage with the primary antigens has been maintained at above 90% (Table 1).

Table 1: DPT1, DPT3 and measles first and second dose vaccination coverage according to the WHO UNICEF coverage estimates, Eritrea, 1993 - 2017

	DPT1	DPT3	MCV1	MCV2
1993	49%	32%	34%	
1994	61%	49%	51%	
1995	68%	58%	58%	
1996	75%	66%	66%	
1997	83%	75%	73%	
1998	90%	86%	79%	
1999	97%	93%	88%	
2000	88%	81%	76%	
2001	91%	86%	84%	
2002	94%	90%	83%	
2003	97%	93%	92%	
2004	99%	98%	96%	
2005	99%	96%	95%	
2006	97%	94%	95%	
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2010	98%	95%	97%	
2011	97%	94%	98%	
2012	97%	94%	98%	
2013	97%	94%	94%	
2014	97%	94%	90%	
2015	98%	95%	97%	88%
2016	97%	95%	99%	88%
2017	97%	95%	99%	88%

Eritrea introduced the second dose of measles vaccine (MCV2) in the routine immunization schedule in July 2012, providing it to children starting at 18 months of age. However, the country started reporting MCV2 coverage to the WHO and UNICEF in 2015. The WHO-UNICEF estimates of MCV2 coverage for 2015 - 2017 have been consistently 88%, with the drop-out rate between the first and second doses of measles vaccine staying at 9 - 11% (Table 1, Figure 1). Eritrea introduced rubella vaccine into the routine immunization schedule in December 2018, following a nationwide measles -rubella catch-up SIAs.

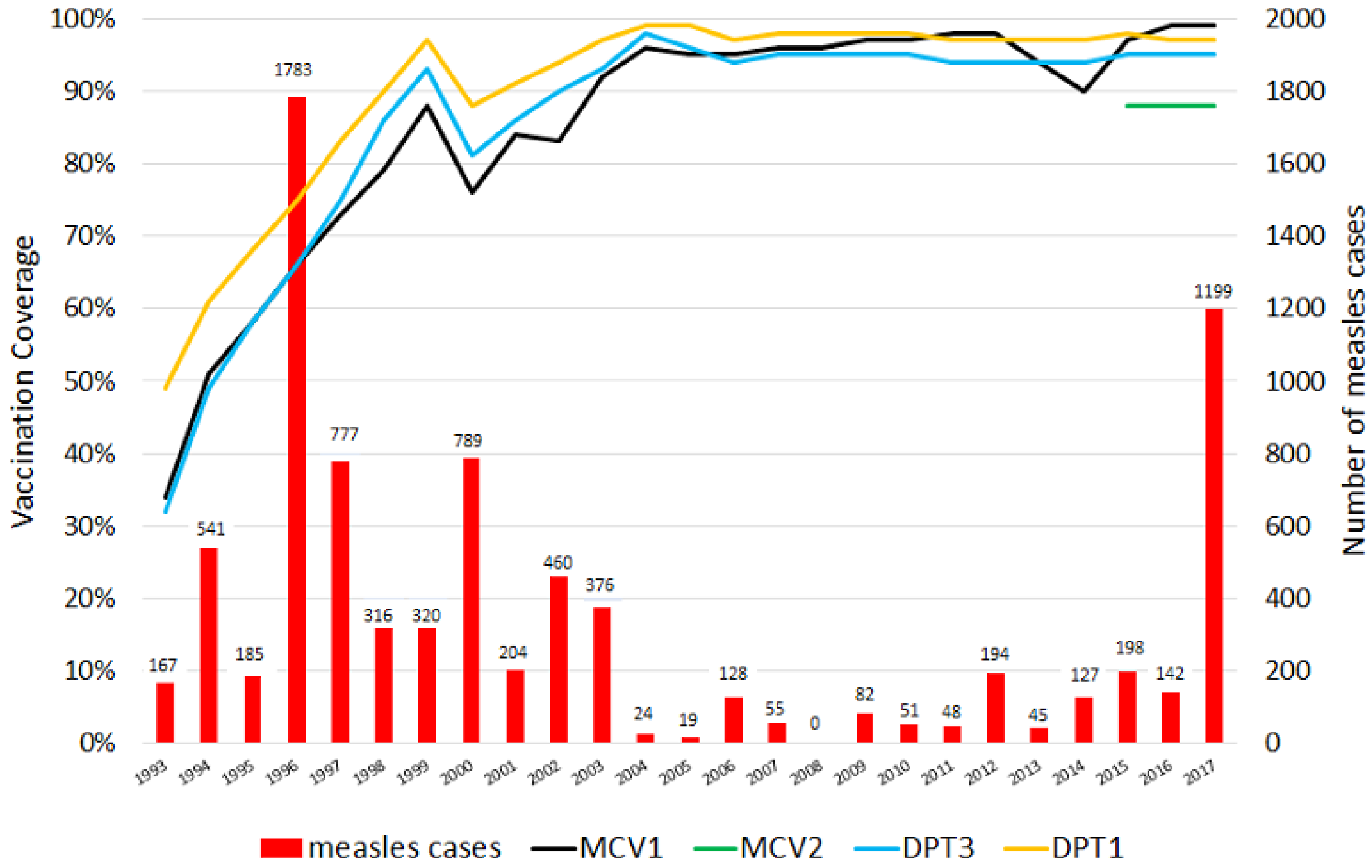

Figure 1. Officially reported measles cases, and WHO UNICEF coverage estimates. Eritrea. 1993 - 2017.

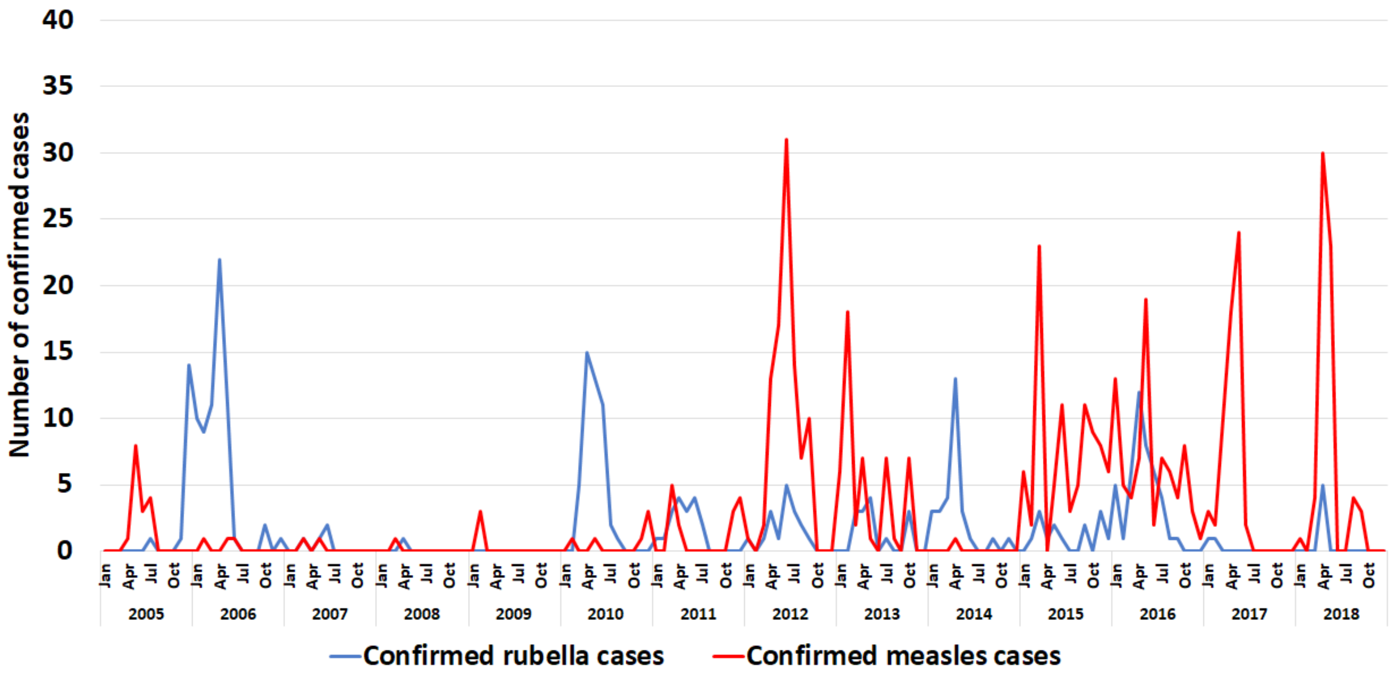

Figure 2. Monthly trends of reporting of confirmed measles and rubella in Eritrea. 2005 - 2018.

The Demographic Health Survey (DHS) done in Eritrea in 2002 indicated BCG coverage of 91.4%, DPT3 coverage of 82.8% and MCV1 coverage of 84.2% [11]. The National EPI coverage survey done in 2017 indicated that 98.9% had received BCG, while 97.3% received the third dose of pentavalent vaccine and 96.8% were vaccinated with the first dose of measles vaccine. Coverage with the second dose of measles vaccine (MCV2) was 86.7% among 24 - 35 months old children. According to the 2017 survey, MCV1 coverage by province ranged from 92.1% in Gash Barka to 99.2% in Maekel and MCV2 coverage ranged between 66.5% in Debubawi Keih Bahri and 92.7% in Maekel [12].

Table 2: measles supplemental immunization activities (SIAs) coverage in Eritrea, 2003 - 2018

Year	Age group of children targeted	Number of children vaccinated	Administrative coverage at national level (% of target)	% districts with administrative coverage ≥ 95%	Coverage survey result
2003	9 months - 14 years	1,047,862	82%		Not Done
2006	6 - 59 months	387,479	95%		Not Done
2009	9 - 59 months	285,285	82%		Not Done
2012	6 - 47 months	277,928	75%	16.0%	95.6%
2015	9 - 59 months	350,765	80.1%	36.2%	Not Done
2018	9 months - 14 years	1,276,364	84%	0.0%	97.8%

SIAs: Eritrea conducted the first preventive SIAs against measles in 2003, targeting children from 9 months to 14 years of age and reaching a total of 1,047,862 children (82% of the target). In subsequent years, the country conducted measles follow-up SIAs every 3 years and a wide age range measles-rubella (MR) catch-up SIAs in 2018. Administrative coverage at national level was less than 85% in all SIAs except in 2006. However, coverage surveys conducted after the 2012 and 2018 SIAs both indicated coverage of more than 95% at national level (Table 2) [8, 13]. During the MR catch-up SIAs of 2018, the administrative coverage ranged from 73% in Anseba to 95% in Gash Barka (Table 3). Post-campaign survey results showed > 95% coverage in all Zobas. Only 5.4% children aged 9 - 59 months of age had no prior measles vaccination prior to the MR SIAs in 2018, according to the survey report.

Measles and rubella surveillance performance: the national level target of 2 non-measles febrile rash illness cases per 100,000 population (NMFRI) has been met since 2010 but the target was missed in 2007 - 2009. However, since 2011, Eritrea has not attained 80% target for districts reporting suspected measles cases with blood specimen (Table 4). The national serological laboratory for the confirmation of suspected measles and rubella cases has recently been accredited since 2010, though with varied performance. Training was done in October 2018. There is no sentinel surveillance system in place to investigate and report congenital rubella syndrome (CRS) cases and no retrospective review has been done to date.

Table 3: measles-rubella supplemental immunization activities (SIAs) administrative and survey coverage at Zoba level, Eritrea, 2018

Zoba	Target Population	Vaccinated children	Administrative coverage	Survey coverage
Maekel	223,020	179,046	80.30%	99.40%
Gash Barka	396,981	376,699	94.90%	97.80%
Anseba	224,056	163,163	72.80%	99.60%
Debub	368,055	301,595	81.90%	95.30%
Semenawi Keih Bahri	191,306	154,047	80.50%	99.70%
Debubawi Keih Bahri	36,070	32,200	89.30%	99.60%
National	1,439,488	1,206,750	83.80%	97.80%

Measles and rubella incidence: between 2005 and 2018, Eritrea reported a total of 2,112 suspected measles cases through the case-based surveillance system, of which 529 were confirmed by laboratory, epidemiological linkage or clinical compatibility. On average, annually, 150 suspected measles cases were reported through the case-based surveillance system. There were 278 laboratory confirmed rubella cases in the same period (Table 5). The incidence of confirmed measles in Eritrea ranged from 0.3 per million in 2008 and 2014 to 24.7 per million population in 2015. The country reported measles incidence levels of less than 1 measles case per million in 2007, 2008, 2009 and 2014. The incidence of confirmed measles was more than 10 per million in 7 out of the 14 years analyzed, including from 2015 - 2018. The peak period of measles occurrence in Eritrea is between January and May in most years. Similar peaks are seen in the occurrence of lab confirmed rubella cases in the first half of the year (Figure 2).

More than half (60.5%) of the confirmed measles cases reported between 2005 and 2018 are more than 15 years of age. This high proportion was also evident from 2015 - 2018, with children more than 15 years of age comprising of more than 40% of all confirmed measles cases in 2015, 2016 and 2018. Both the mean and median age of confirmed measles cases were more than 10 years in 8 of the 14 years covered by our analysis. All of the years with documented incidence of more than 1 per million (except 2006) had mean age of measles cases of more than 10 years.

Vaccination status was not documented in the records of 162 of the 529 confirmed measles cases. Of the remaining confirmed cases whose status was documented, the proportion of cases with no history of measles vaccination ranges between 51% and 89% in the years 2015 - 2018 (Table 5). The comparison of the number of confirmed measles cases in the case-based surveillance database and in the official annual country report to WHO and UNICEF through the Joint Reporting Form (JRF) showed differences. In 2006, 2007 and 2015, the officially reported figure is closer to the number of suspected cases in the case-based surveillance database. However, the comparison shows significant difference in the other years. Especially in 2017, a total of 1,199 measles cases were officially reported to WHO and UNICEF, while the case based surveillance database contained 185 suspected cases of which only 65 were confirmed. There is no detailed epidemiological data or investigation report available to explain this spike in 2017 (Table 6). Eritrea does not yet have any documented measles or rubella viral strains.

Table 4: measles case-based surveillance performance, Eritrea, 2005 - 2018 (Source: Measles case-based surveillance system)

Year	Total suspected measles cases	Suspected measles cases that were investigated	Non-measles febrile rash illness (NMFRI) rate – [Target: ≥ 2 cases per 100,000 population]	% districts investigating suspected cases per year [Target: ≥ 80% districts]
2005	159	155	4.2	100%
2006	125	125	3.9	100%
2007	52	52	1.6	100%
2008	61	59	1.8	100%
2009	45	45	1.2	30%
2010	168	168	4.6	83%
2011	145	145	3.6	75%
2012	243	243	4	66%
2013	139	139	2.3	41%
2014	103	102	2.6	36%
2015	195	195	2.9	59%
2016	334	334	6.8	60%
2017	185	183	3.4	36%
2018	155	154	2.1	53%

Table 5: measles incidence and age patterns by year 2005 – 2018, Eritrea (Source: Measles case-based surveillance system)

Year	Number of suspected measles cases	Number of confirmed rubella cases	Number of confirmed measles cases	Incidence of confirmed measles per 1,000,000 population	Mean age (in years) of confirmed measles cases	Median age (in years) of confirmed measles cases	% of measles cases unvaccinated
2005	159	16	32	10.6	13	7	100%
2006	125	67	9	3	7	6	0%
2007	52	4	2	0.6	4.5	4.5	0%
2008	61	1	1	0.3	0	0	0%
2009	45	0	3	0.9	22.3	25	100%
2010	168	47	6	1.7	18.5	22	75%
2011	145	18	14	3.9	18.9	18	100%
2012	244	17	95	24	23.8	25	88%
2013	139	15	50	13.1	23.6	21	91%
2014	105	32	1	0.3	3	3	0%
2015	195	14	104	24.7	25.5	27	89%
2016	334	44	81	16.8	20.9	22	81%
2017	185	2	62	16.8	10.7	9	51%
2018	155	5	69	17.7	13.7	12	63%

Table 6: comparison of the reported measles cases through the case-based surveillance system and the aggregate annual official reporting to WHO and UNICEF through the joint reporting form 2005 - 2018

Year	Measles case reports		
	Total suspected measles cases in the national measles case-based surveillance database	Confirmed measles cases in the national measles case-based surveillance database	Measles cases reported officially to WHO and UNICEF through the JRF
2005	159	32	19
2006	125	9	128
2007	52	2	55
2008	61	1	0
2009	45	3	82
2010	168	6	51
2011	145	14	48
2012	243	95	194
2013	139	50	45
2014	103	1	127
2015	195	104	198
2016	334	81	142
2017	185	62	1199
2018	155	69	70

Discussion

Eritrea has made significant progress towards measles elimination. The country has managed to sustain very high coverage with MCV1 for more than 10 years and an equally high coverage with the second dose of measles vaccine since it started reporting MCV2 coverage. The dropout rate between these two doses is less than 11% at national level in the three years of reporting. However, coverage is not homogeneous across all Zobas especially for MCV2 coverage. In order to achieve and sustain measles elimination, Eritrea will need to reach at least 95% coverage with both MCV1 and MCV2.

The fact that Eritrea has had low routine immunization and SIAs administrative coverage, but significantly high coverage by surveys indicates that the official population figures may be overestimated. These denominator figures are generated as projections. Eritrea has never done any census. The wide age-range MR SIAs of 2018 has attained ≥ 95% coverage by survey across all provinces, and it will likely take care of any immunity gaps among the targeted population of children 9 months to 15 years of age. The expected impact of the MR SIAs on measles and rubella incidence among the targeted cohort of children under 15 years of age will need to be documented through a sensitive surveillance system [14].

The total number of measles cases reported has markedly declined following the SIAs in 2003. Incidence of confirmed measles has been low until 2012. In the years 2013 - 2018, measles incidence rate was between 10 and 20 per million population despite the high coverage attained for many years. The country has had a large proportion of school age children and adults among measles cases in the past decade, with mean age of confirmed measles being higher than 10 years of age. It is evident that measles incidence is driven by susceptible in the adolescent and adult age group. This epidemiological shift to older age groups can be explained on the low population density and the relatively high measles vaccination coverage over the last two decades [15].

Measles surveillance is integrated with active surveillance for acute flaccid paralysis in Eritrea. However, there are gaps in case-based surveillance performance for measles, with the country failing to attain the target for district reporting since 2011. Information on the vaccination status of cases was missing in 30% of the 529 confirmed cases from 2005 - 2018. These performance gaps will need to be addressed through further investigation to identify the specific non-reporting districts and the factors leading to the weak performance. In addition, there is a need to investigate and document all outbreaks of measles in order to identify the specific populations that may be at risk and take the necessary measures. This will help to better understand the epidemiological factors and populations at risk in Eritrea.

With the gaps documented in surveillance performance, the information on incidence from the surveillance system will need to be interpreted cautiously. The analysis has shown that the surveillance system was not able to launch a detailed investigation and documentation on the febrile rash illness cases which occurred in 2017 as reported to WHO through the joint reporting format. In addition, the discrepancy in the number of measles cases reported in various years through the case-based surveillance system and the annual summary reports to WHO and UNICEF indicates the need for regular harmonization of data, and for aggressive efforts to investigate all suspected cases and take timely programmatic action to limit measles outbreaks spread as much as possible.

The national EPI policy emphasizes that immunization service provision will be done as an integral part of the primary health care services including prevention and control of childhood diseases, growth monitoring, information, education and communication, nutritional advice, ante-natal, post-natal care and family planning. It also states that provision of insecticide treated bednets, vitamin A supplementation and de-worming shall be supplied through routine immunization and campaign settings, with a view to reduce missed opportunities. Eritrea is eligible for Global Alliance for Vaccines and Immunization (GAVI) support. Starting from 2016 the government has started co-financing 20% of the total costs on traditional vaccines, including measles vaccine [4].

The sustained high immunization coverage in Eritrea is a function of the strength of the immunization program. A national immunization program review done in 2016 identified programmatic strengths that included the delivery of integrated services offered 6 days a week, very good caretaker awareness of the benefits of immunization and high demand for services. However, it was also noted that lack of transportation may pose a risk of delaying vaccine availability to the population, and to reaching out to hard to reach populations [16, 17]. The country has conducted very good programmatic preparation and roll out of MCV2 which has also contributed very well to the sustained high coverage of MCV2 [17, 18]. Following the introduction of MCV2, an evaluation done in April 2015 found out that staff knowledge was satisfactory, monitoring of service data was being done systematically, cold chain capacity was adequate, supervisory support to the health facility level was being provided regularly and that the community awareness of the vaccine schedule was good. However, the evaluation identified the need for more active monitoring of adverse events following immunisation [18].

It has been documented that having a cadre of community health workers, immunization services tailored to community needs, health system and community partnership, and a regular review of health worker performance are key drivers of improvement in district level immunization program coverage in the African context [19]. The HSSDP II plans to expand and improve the work of community health workers guided by an integrated comprehensive community strategy. In the area of maternal and child health, there are plans to scale up community involvement on microplanning at district level to address population groups in less accessible geographical areas [3]. These activities will have a strong impact on the progress towards sustainable measles elimination in Eritrea.

The World Health Organisation has developed a framework for the verification of measles elimination which has set the criteria for defining measles elimination and the processes for verifying measles elimination in a country. The framework requires that countries establish the necessary independent structures responsible for compiling the programmatic and epidemiological information necessary to assess progress and document, measles elimination [20]. This includes the establishment of National Verification Committees (NVC) with the primary responsibility for guiding countries in the preparation of their documentation of progress towards the achieve¬ment of measles elimination and the Regional Verification Commission (RVC), which validates and verifies elimination in each country and eventually in the Region [21]. As of April 2019, Eritrea has not yet established an NVC or started the documentation of progress towards measles elimination.

Limitations: this study has limitations. First, there may be inaccuracies in administrative coverage monitoring. Surveys have been shown to provide higher coverage than reported data due to inaccuracies of denominators used for coverage monitoring. Secondly, the study did not look at the measles laboratory performance indicators or the quality of serological specimens. Thirdly, the weaknesses in surveillance performance and the gaps in the investigation of cases and outbreaks may conceal the true incidence and epidemiological pattern of measles in the country.

Conclusion

In order to further advance towards the measles elimination goal, we recommend that Eritrea strengthen its surveillance system, investigate and fully document outbreaks of measles, ensure that all districts report and investigate suspected cases, conduct regular risk assessment to identify and address immunity gaps. The triangulation of data from coverage monitoring, surveillance and risk assessment exercises helps to target tailored interventions within the routine immunization service delivery platform or through the Periodic Intensification of Routine Immunization (PIRI) model [22]. With the current levels of coverage in the childhood population, the country can extend its inter-SIAs interval to 4 - 5 years, without risking a rapid accumulation of young children susceptible to measles infection. Depending on the findings from risk assessment exercises and disease surveillance, SIAs may be tailored to target susceptible adolescent and adult populations in specific areas, in addition to young cohorts. Eritrea should set up a national verification committee to document the progress with measles elimination. This will serve as an opportunity to raise the profile of measles elimination in the national health agenda, and to advocate for rubella/congenital rubella syndrome (CRS) control in the country. As a way of monitoring the impact of the introduction of rubella vaccine, the country should consider doing a retrospective review of CRS in a few tertiary care centers and initiate sentinel CRS surveillance on a prospective basis.

What is known about this topic

- Eritrea has managed to reduce under five and infant mortality significantly in the past 25 years;
- Eritrea has been implementing measles elimination strategies since 2003;
- Eritrea introduced measles vaccine MCV2 in 2012.

What this study adds

- Eritrea has maintained high MCV1 and MCV2 coverage, with drop-out rates of less than 11% between the two doses;
- Measles surveillance performance gaps persist, and there is a discrepancy in the number of reported measles cases between the case-based surveillance data and aggregate reporting;
- The mean and median age of measles cases in Eritrea has been mostly above 10 years in the past 15 years.

Competing interests

The authors declare no competing interests.

Authors' contributions

All authors have contributed to this work. All authors have read and agreed to the final manuscript.

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Research

The impact of a prolonged ebola outbreak on measles elimination activities in Guinea, Liberia and Sierra Leone, 2014-2015

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Abstract

Introduction: Guinea, Sierra Leone and Liberia have attained significant reduction in measles incidence between 2004 and 2013. The Ebola outbreak in 2014-2015 in West Africa caused significant disruption of the health service delivery in the three worst affected countries. The magnitude of the impact on the immunization program has not been well documented.

Methods: we reviewed national routine immunization administrative coverage data as well as measles surveillance performance and measles epidemiology in the years before, during and after the EVD outbreak in Guinea, Liberia, Sierra Leone.

Results: both Liberia and Guinea experienced a sharp decline of more than 25% in the monthly number of children vaccinated against measles in 2014 and 2015 as compared to the previous years, while there was no reported decline in Sierra Leone. Guinea and Liberia experienced a decline in measles surveillance activity and performance indicators in 2014 and 2015. During this period, there was an increase in measles incidence and a decline in the mean age of measles cases reported in Liberia and Sierra Leone. Guinea started reporting high measles incidence in 2016. All three countries organized measles supplemental immunization activities by June 2015. Liberia achieved 99% administrative coverage, while Guinea and Sierra Leone attained 90.6% and 97.2% coverage respectively. There were no severe adverse events reported during these mass vaccination activities. The disruptive effect of the Ebola outbreak on immunization services was especially evident in Guinea and Liberia. Our review of the reported administrative vaccination coverage at national level does not show significant decline in measles first dose vaccination coverage in Sierra Leone as compared to other reports. This may be due to inaccuracies in coverage monitoring and data quality problems. The increases in measles transmission and incidence in these three countries can be explained by the rapid accumulation of susceptible children. Despite the organization of mass vaccination activities, measles incidence through 2017 has remained higher than the pre-Ebola period in all three countries.

Conclusion: the Ebola outbreak in West Africa significantly affected measles vaccination coverage rates in two of the three worst affected countries, and led to persistent gaps in coverage, along with high measles incidence that was documented until two years after the end of the Ebola outbreak. Liberia and Sierra Leone have demonstrated coverage improvements after the end of the Ebola outbreak.

Introduction

In 2011, Member States of the WHO African Region established a goal to achieve measles elimination by 2020 [1]. The strategies to achieve elimination include increasing access and measles vaccination coverage with routine immunization services in all districts; achieving high coverage during all measles Supplemental Immunisation Activities (SIAs), as well as outbreak response immunization activities, improving the quality of measles surveillance and rapidly investigating measles outbreaks in all countries. The Member States adopted a goal comprised of the following targets: (i) ≥ 95% coverage with the first dose of measles-containing vaccine (MCV1) at national and district levels; (ii) ≥ 95% coverage in all districts during measles SIAs; and (iii) confirmed measles incidence < 1 per million population in all countries. (iv) Conducting high quality measles surveillance defined as ≥ 2 cases of non-measles febrile rash illness (NMFRI) per 100,000 population annually and collecting a blood specimen from ≥ 1 suspected measles case in ≥ 80% of districts annually [1]. The measles elimination goal is also an objective of the African Regional Immunization Strategic Plan 2014 – 2020 [2]. By the end of 2017, the African Region of the WHO attained 86% reduction in the estimated mortality from measles as compared to estimated measles mortality for 2000 [3].

Guinea and Sierra Leone began implementing measles control strategies in 2003 when both countries implemented their initial national measles supplemental immunization activities (SIAs) targeting children aged 9 months to 14 years of age, while Liberia had its initial measles SIAs in 2004. All three countries established case-based surveillance for measles supported by serological testing of suspected cases by the end of 2004. Since then, these three countries have made considerable progress controlling measles. They reported officially to the WHO a total of 96,910 measles cases in the 10 years period from 1994 to 2003, while this number declined sharply to a total of 6,937 over the 10 years period between 2004 and 2013 [4]. The Ebola virus disease (EVD) outbreak in 2014-2015 in West Africa was the largest Ebola epidemic ever documented. Between December 2013 and April 10, 2016, a total of 28,616 suspected, probable, and confirmed cases of Ebola virus and 11,310 deaths were reported, of which all but 36 cases were from the three countries. The peak period of Ebola case reporting was in the second half of 2014 in Liberia, while Sierra Leone continued to report many cases in the first quarter of 2015, and transmission continued until the third quarter of 2015 in Guinea. The Ebola outbreaks in Liberia, Sierra Leone, and Guinea ended in May, November, and December 2015 respectively [5, 6]. During the period of intense Ebola transmission in the three countries, many health facilities were closed, and others operated at lower capacity than usual, because of shortage of staff and disruption of medical logistics supplies. In addition, health service utilization declined significantly due to fear of acquiring Ebola infection at health facility settings, the shifting of health resources towards the Ebola response, and due to the death of health care staff [7].

Routine immunization services, previously scheduled SIAs and the introductions of new vaccines, as well as supervisory visits and program reviews were cancelled or postponed as health systems were overwhelmed by the scale of the Ebola outbreak and the magnitude and duration of response efforts [7, 8]. Studies have also documented the decline in maternal and child health services in Guinea, as well as curative services in Sierra Leone [9-11] Others have modelled the expected increase in deaths from diseases such as malaria, as a result of significant reduction in the availability of treatment services in health facilities [12]. Measles has been previously recognized as an important communicable disease to anticipate during disasters and humanitarian crises that result in population displacements and in the disruption of health systems [13]. Takahashi et al have modelled the increased susceptibility to measles resulting from the Ebola epidemic in West Africa [14], while others have highlighted the programmatic difficulties in maintaining routine vaccination services [15]. Measles outbreaks have been documented in the three countries during and after the Ebola epidemic [16, 17]. Suk et al reported on 284 cases of measles from January 23, 2015–April 4, 2015 in Lola prefecture in Guinea, with the average and median age of patients being 2.8 years and 2.0 years of age, and with 95% cases not having been vaccinated [17].

With the prolonged disruption of immunization and health services, the risk for outbreaks of vaccine preventable diseases was recognized and WHO issued specific guidance to immunization programs in the region affected by Ebola in March 2015 [18]. The recommendation proposed that intensified routine vaccination activities and/or vaccination campaigns should be conducted, subject to certain conditions, when a risk assessment indicates that risk of vaccine-preventable disease outbreaks (i.e. measles, etc.) outweighs the risk of increased Ebola virus transmission. This manuscript examines the immunization program and surveillance data from Guinea, Liberia and Sierra Leone, and quantifies the impact of the EVD outbreak on service delivery, surveillance performance and measles disease burden in the three countries.

Methods

We conducted a review of secondary data available with the WHO Regional office for Africa. The datasets we reviewed included national routine immunization administrative coverage data as well as measles surveillance performance and measles epidemiology data in the years before, during and after the EVD outbreak in Guinea, Liberia, Sierra Leone. These datasets are shared with the WHO by Member States regularly, for purposes of monitoring of trends and performance, as well as for assistance with analysis and feedback. Analysis of data was done using MS Excel and Epi Info software.

Routine immunization coverage: in these countries, vaccination coverage is determined by recording the number of children who receive each vaccine antigen on paper reporting forms in every service delivery point in the health system. Data on children vaccinated is aggregated and entered into a database at the district level for onward transmission and compilation at the national level. The national level shares the compiled country data with the WHO as a monthly report detailing the monthly number of children vaccinated by antigen and by district. We reviewed the routine immunization coverage administrative data to analyze the monthly number of children who received measles vaccine for the years 2012 – 2017. WHO and the United Nations Children's Fund (UNICEF) estimate vaccine coverage for each country and each antigen by conducting a country-by-country review of administrative data, data from surveys and other sources. These estimates are published annually on the WHO website, and are updated as additional data becomes available [19]. We reviewed the WHO UNICEF national coverage estimates for DPT3, yellow fever and the first dose of measles vaccine for the three countries over the years 2012 – 2017.

Coverage in Supplemental Immunization Activities: the Measles and Rubella Initiative and the Global Alliance for Vaccines and Immunization support countries to conduct periodic measles SIAs to increase population immunity against measles. At the end of the SIAs, countries submit technical reports to the WHO, detailing administrative coverage results and lessons learned. In most cases, post-campaign coverage surveys are implemented immediately after the end of the SIAs and survey reports are shared. We reviewed national SIAs technical reports and post-campaign coverage survey reports available with the WHO Regional Office for Africa to assess coverage levels [20].

Case based surveillance performance and epidemiological trends: we examined data from the case-based measles surveillance system in all three countries for the period 2012 - 2017. The measles case definition used to report suspected cases in the case-based surveillance system is: fever and generalized maculopapular rash plus one of the following clinical symptoms: cough, runny nose, or red eyes. For each suspected measles case, an investigation form was completed, a blood specimen was collected and sent to the national laboratory for measles specific immunoglobulin M (IgM) antibody testing. Suspected measles cases were confirmed by laboratory when there is serological confirmation of recent measles virus infection (measles IgM positive). In the case of lab confirmed measles outbreaks, cases may also be confirmed by epidemiological linkage. A clinically compatible case of measles is a suspected measles case that does not have a blood specimen taken for serologic confirmation and is not linked to any measles outbreak [21]. Surveillance performance was monitored using standard performance indicators. The two principal performance indicators are the non-measles febrile rash illness rate (target of at least 2 per 100 000 population) and the proportion of districts that have investigated at least one suspected case of measles with blood specimen per year (target at least 80% of districts per year). The incidence of confirmed measles was calculated as a rate per million, by dividing the total number of confirmed measles cases (confirmed by laboratory, epidemiological linkage and clinical criteria) by the total population [21].

Results

MCV1 coverage Liberia

According to the administrative coverage data, an average of 9332 children get vaccinated with MCV1 for the period January 2012 – Dec 2017 in Liberia. However, between August and November 2014, the number of children vaccinated with MCV1 declined, ranging between 3196 and 4494, which is more than 2 standard deviations from the period average of 9332 (SD = 2371). Compared to the monthly mean for 2012 (prior to the ebola outbreak), the mean monthly number of children vaccinated with MCV1 declined by 30% in 2014 and by a further 25% during 2015. By the end of 2017, the monthly mean number of children vaccinated with the first dose of measles vaccine showed a 13% increase compared to 2012 (Table 1). This decline was also reflected in the data from the WHO UNICEF estimates for national coverage with MCV1 in Liberia, where the 2-year mean MCV1 coverage in 2014 and 2015 (corresponding to the Ebola outbreak period) was 16% lower than the mean for the previous 2-year period (2012 – 2013). By the post-Ebola period of 2016-2017 Liberia's MCV1 coverage was 84% as compared to the average of 77% for the years 2012-13 corresponding to the two year pre-ebola period (Table 2)

Table 1: monthly mean of children vaccinated with MCV1 by year, and relative change compared to the mean for 2012

Monthly mean number of children receiving MCV-1 nationally						
	Guinea		**Liberia**		**Sierra Leone**	
Year	**Mean**	**Change against 2012 levels**	**Mean**	**Change against 2012 levels**	**Mean**	**Change against 2012 levels**
2012	34882	—	10084	—	16998	—
2013	34231	-2%	9483	-6%	18657	10%
2014	23403	-33%	7100	-30%	17139	1%
2015	25669	-26%	7583	-25%	17459	3%
2016	31885	-9%	10390	3%	20772	22%
2017	34394	-1%	11353	13%	19369	14%

Table 2: WHO UNICEF estimates of annual coverage for DPT3, yellow fever vaccine and MCV1, by country

		DPT3	**YFV**	**MCV1**	**2 year mean MCV1 coverage**
Guinea	2012	53%	51%	51%	45%
	2013	44%	39%	39%	
	2014	34%	28%	28%	38%
	2015	45%	43%	48%	
	2016	45%	43%	48%	48%
	2017	45%	43%	48%	
Liberia	2012	80%	78%	80%	77%
	2013	76%	73%	74%	
	2014	50%	54%	58%	61%
	2015	52%	56%	64%	
	2016	79%	73%	80%	84%
	2017	86%	84%	87%	
Sierra Leone	2012	91%	80%	86%	86%
	2013	92%	80%	85%	
	2014	83%	78%	80%	79%
	2015	86%	80%	78%	
	2016	84%	85%	85%	83%
	2017	90%	85%	80%	

Guinea

In Guinea, the administrative coverage data shows that the mean monthly number of children who received MCV1 in the period January 2012 – Dec 2017 is 30744 (Standard deviation = 9557). This monthly average declined by 33% in 2014 and by 26% in Guinea in 2015 and remained 1% below the 2012 level by the end of 2017. In the last four months of 2014 and in December 2015, the number of vaccinated children ranged between 1195 and 4513, which is 2 standard deviations below the monthly mean of 30744 (SD = 9557) for the entire period. The WHO UNICEF national coverage estimates also show that the 2-year mean MCV1 coverage in 2014 and 2015 (corresponding to the Ebola outbreak period) was 7% lower than the mean for the previous 2-year period (2012 – 2013) in Guinea. After the end of the Ebola outbreak, the MCV1 coverage estimates in Guinea was higher (48% average for 2016-2017) as compared to 2012 - 2013 (45% coverage). On the other hand, the coverage estimates for DPT3 and YF vaccination coverage showed a decline (Table 2).

Sierra Leone

The national immunization program in Sierra Leone reached an average of 18399 (Standard deviation = 2431) children with MCV1 monthly between January 2012 and December 2017, according to the routine immunization administrative coverage data. This data shows that none of the monthly records of vaccinated children showed a decline below 2 standard deviations from the monthly mean at any time (Figure 1). On the other hand, compared to the reported data in 2012, the mean monthly number vaccinated in 2014 - 2015 increased slightly by 1-3%, and had a 14% increase by the end of 2017 as compared to 2012 (Table 1). The MCV1 coverage estimate in Sierra Leone showed a 3% decline from an average of 86% for 2012 – 2013 to 83% in 2016 – 2017 (Table 2).

Supplemental Immunization Activities (SIAs) in the Ebola period

Liberia:

Confronted with the deleterious effect of the Ebola outbreak on the health system, Liberia postponed a measles SIA scheduled for November 2014. In January 2015, after more than 6 months of disruption in health care delivery service including routine vaccination and a corresponding decline in the number of children receiving vaccination, the risk for measles outbreaks increased with reports of measles outbreaks in some areas. As a result, Liberia organized Periodic Intensification of Routine Immunization (PIRI) activities to selectively reach unvaccinated children aged 9 – 59 months vaccinating 109,069 children across 13 of the 15 counties. In 2 of the 13 counties, the intervention was limited to providing vaccination only to unvaccinated infants 9 – 11 months of age. The postponed nation-wide measles SIA was conducted in May 2015 and was integrated with the administration of oral polio vaccination, deworming and Vitamin A supplementation). The campaign targeted 596,545 children aged 6 - 59 months of age and achieved 99% administrative coverage. The post-campaign coverage survey showed that national coverage was 90.4%, while subnational coverage ranged from 99.2% in Grand Gedeh County to 72.4% in Grand Bassa County.

Guinea: in the face of intensifying measles transmission and outbreaks, Guinea organized outbreak response vaccination campaigns in 2 phases between February and April 2015, and vaccinated 1,259,690 children 6 months to 10 years of age in 263 centres de sante across 15 of 21 provinces attaining administrative coverage of 90.6% at national level. This activity was integrated with Vitamin A supplementation and Mebendazole administration to children under 5 years of age. Another measles follow-up SIAs was organized in February 2016 and reached 2,412,923 children 9 – 59 months of age in 38 districts across 8 provinces, attaining 102.7% administrative coverage. Post-campaign coverage survey results indicated coverage of 92.7% (95% CI: 92.1% - 93.2%).

Sierra Leone: Sierra Leone organized a nation-wide measles SIA in June 2015 vaccinating 1,205,865 children from 9 – 59 months of age and achieving 97.2% administrative coverage. The SIA was integrated with OPV administration for children less than 5 years of age, as well as the identification of children who had missed certain vaccines and provision of other antigens to eligible infants. Following the occurrence of continued outbreaks involving children over 5 years of age, Sierra Leone conducted a wide age range nationwide measles immunization in May 2016 which reached 2,795,686 children aged 6 months to 14 years and achieving 100% administrative coverage. The post-campaign coverage survey results was 97.7% at national level (95% CI: 97.2% - 98%). The survey reported that 20.2% of the children vaccinated in the campaign received measles vaccination for the first time.

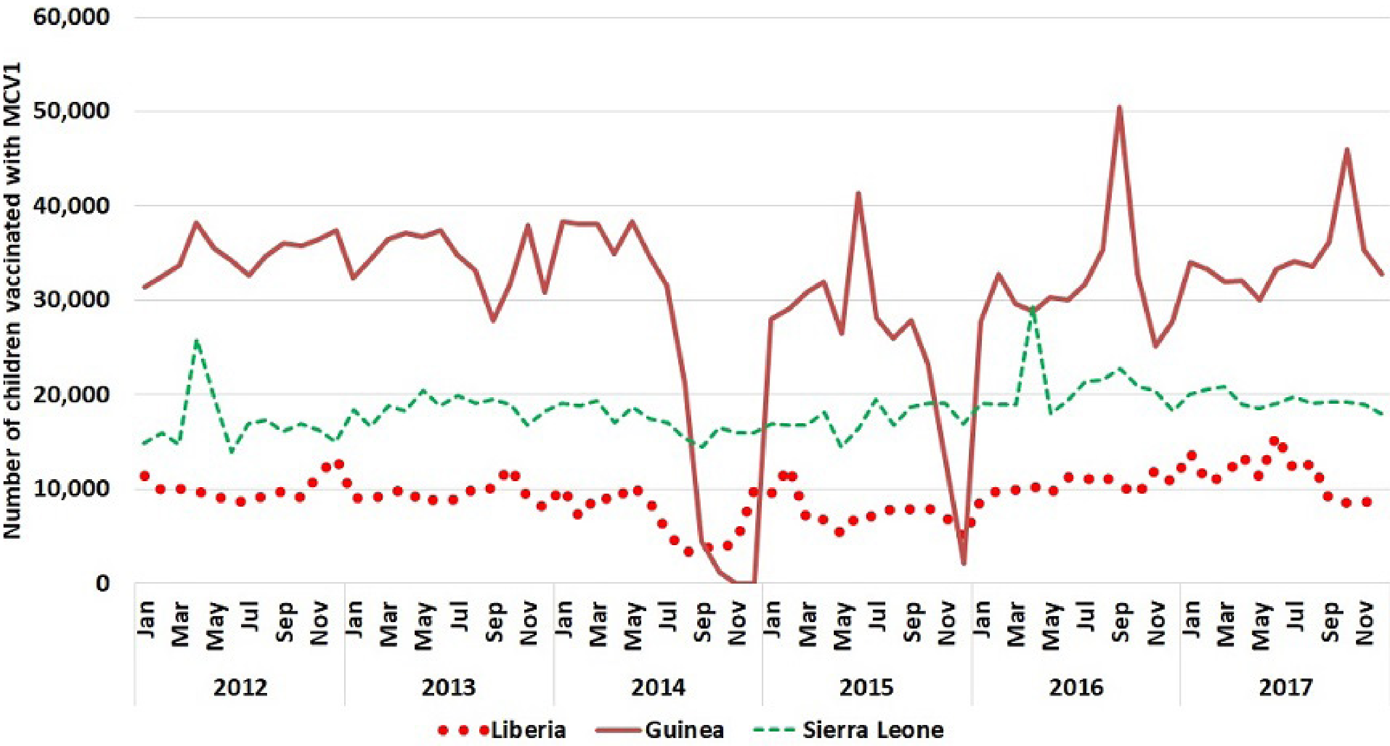

Figure 1: monthly number of children vaccinated with MCV1 by country - January 2012 - December 2017

Table 3: measles surveillance performance, measles incidence and age patterns by country, 2012 - 2017

	Year	% districts reporting (target ≥ 80%)	NMFRI rate per 100,000 population (target ≥ 2:100,000)	# of suspected measles cases	Blood specimens collected	# confirmed measles	Measles incidence/ million population	% confirmed measles aged < 5 years	Mean (median) age of confirmed measles cases
Guinea	2012	95%	1.0	140	140	7	0.6	43%	4.5 (5) years
	2013	97%	0.9	163	163	39	3.3	74%	3.5 (2) years
	2014	97%	0.4	266	266	35	2.9	83%	3.1 (2) years
	2015	39%	0.2	48	48	29	2.7	61%	4.2 (3) years
	2016	97%	2.7	636	628	128	11.5	65%	4 (3) years
	2017	100%	6.1	1268	1268	583	52.5	70%	4.2 (3) years
Liberia	2012	88%	1.0	42	41	4	0.1	67%	12.6 (7) years
	2013	44%	0.5	20	20	0	0.0		
	2014	6%	0.1	3	3	0	0.0		
	2015	13%	1.1	479	12	436	108.5	60%	5.3 (3) years
	2016	31%	1.1	449	269	400	97.4	43%	9.4 (5) years
	2017	88%	0.4	409	328	96	23.4	27%	8.9 (7 years)
Sierra Leone	2012	93%	1.2	123	123	42	0.6	56%	5.8 (4) years
	2013	93%	0.6	59	59	13	2.1	62%	4.4 (4) years
	2014	93%	1.7	150	150	44	6.9	68%	4.2 (2.5) years
	2015	93%	1.9	266	266	128	18.0	61%	6 (4) years
	2016	87%	2.9	414	414	195	26.7	46%	7.4 (5) years
	2017	93%	6.2	536	536	76	10.4	22%	7.8 (7) years

Case based measles surveillance:

Liberia

In Liberia, the proportion of districts reporting suspected cases with blood specimens decreased from 88% in 2012 to 44% in 2013 and to 6% in 2014. The non-measles febrile rash illness rate (NMFRI rate) for 2014 and 2015 also declined by 20% in Liberia as compared to the 2-year averages for 2012 and 2013. Liberia missed the NMFRI target of 2 per 100,000 in all 6 years from 2012-2017. Liberia achieved the district reporting target only in 2017 (Table 3). In Liberia, there were no confirmed measles cases reported through the case based surveillance system in 2013-14, but measles incidence rose to 108.5 per million in 2015. The mean (5.3 years) and median ages (3 years) of cases was lowest in 2015 as compared to the other years.

Guinea

Guinea experienced a decline in the proportion of districts reporting suspected measles cases from 95% in 2012 to 39% in 2015. in addition, Guinea had a significant reduction in the non-measles febrile rash illness rate (NMFRI rate) for 2014 and 2015 (declined by 68% as compared to the 2-year averages for 2012 and 2013). In 2016 and 2017, Guinea attained the targets for both principal performance indicators (Table 3). In 2014, 84% of the confirmed measles cases were less than 5 years of age while the mean age of confirmed cases (3.1 years) was the lowest during the period. In Guinea, the incidence of measles increased from 2.7 per million in 2015 to 11.5 per million in 2016.

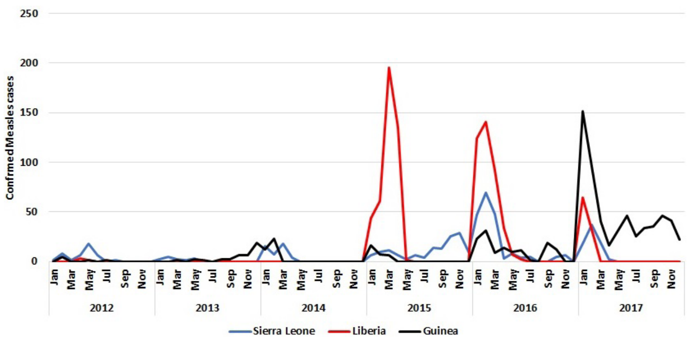

Figure 2: monthly trends of confirmed measles cases by country January 2012 - December 2017

Sierra Leone

The proportion of districts collecting blood specimens from suspected measles cases did not show a decline in Sierra Leone in the years of the Ebola outbreak. Sierra Leone did not meet the target of 2 per 100,000 NMFRI rate in 2012 – 2015. the country managed to attain the targets for both principal performance indicators in 2016 and 2017. The incidence of measles increased from 6.9 per million in 2014 to 18 per million in 2015 in Sierra Leone. The proportion of confirmed measles cases less than 5 years of age was greatest in 2014 (68%) as compared to the other years, and mean (4.2 years) and median ages (2.5 years) were the lowest during the period. Confirmed measles incidence increased markedly in all three countries around the time of the Ebola outbreak and remained high in 2016 and 2017. The monthly trend of reported measles indicates that all three countries had increased case reporting in the first 4 months of the calendar year (Figure 2).

Discussion

Guinea, Liberia and Sierra Leone experienced protracted civil conflict in the last 20 years. These countries have low developmental indices and very low scores for most of the health system matrices [22]. These factors contributed to the unprecedented scale and duration of the EVD outbreak in west Africa. The resulting disruption of routine health care delivery systems was severe and had multiple social-behavioral, logistical, and economic dimensions [7, 8]. Nationwide health emergencies put already fragile health systems under stress. As health services are disrupted, vaccination services fail to reach children resulting in an accumulation of infants and young children who are not protected against measles, diphtheria and other vaccine preventable diseases. At the same time, the health system's capacity to detect, notify and confirm reported cases declines sharply complicating efforts to do meaningful and complete epidemiological analysis of the situation [8, 15, 23]. Because of the highly infectious nature of measles, large and explosive measles outbreaks often occur early in the course of conflicts, natural disasters or other political crises that cause a disruption of health systems [13, 24].

The disruptive effect of the Ebola outbreak on immunization services was especially evident in Guinea and Liberia. From the administrative coverage data during the peak of the EVD transmission, Guinea experienced an extreme decline in the number of children vaccinated by routine services with MCV1, especially in the second half of 2014. Administrative coverage followed a similar dynamic in Liberia, while Sierra Leone experienced a smaller reduction in the number of children vaccinated in the 2014-2015 period. This is also reflected in the WHO- UNICEF coverage estimates, where Sierra Leone had smaller Ebola related decreases in coverage; however MCV1 coverage levels had not returned to pre-Ebola levels in 2017 [19]. Nonetheless, Elston et al. have reported a more than 50% decline in the monthly mean number of children receiving all recommended childhood vaccinations in the second half of 2014 as compared to January–June 2014 in Koinadugu district in Sierra Leone [7]. Similar declines were reported by the government of Sierra Leone in the proceedings of the Regional workshop on building resilient health systems in April 2016 [8]. Our review of the reported administrative vaccination coverage at national level does not show significant decline in measles first dose vaccination coverage in Sierra Leone. This may be due to differences in coverage changes across districts, or as a result of relatively high coverage maintained with one dose measles vaccination as compared to other antigens, or to the gaps in the completion of the primary series of antigens as reported by Elston et al. This discrepancy could be attributable to inaccuracies in administrative immunization coverage reporting. The combined Ebola-related drop in routine immunization coverage against existing sub-optimal coverage reflected in the WHO-UNICEF estimates, suggests that increases in measles transmission and incidence were probable in these three countries due to insufficient population immunity and a rapid accumulation of susceptible children. An increase in the incidence of confirmed measles was identified in each of the three countries starting in the 2015-2016 period. Despite the organization of mass vaccination campaign and outbreak response vaccination activities, confirmed measles incidence through 2017 has remained higher than the pre-Ebola period in all three countries. These results emphasize the lasting effects of persistent weakness in the provision of immunization service from the time of the Ebola outbreak and improved performance of surveillance in the post-Ebola period.

In addition, the age of measles cases was comparatively lower in the period 2014 – 2015, also suggesting a disruption in vaccination services that may have left young children unvaccinated which is likely a result of a rapid accumulation of unvaccinated susceptible children occurring at the peak of the EVD outbreak and in the months immediately after the end of the outbreak, when efforts to rebuild the health systems were still in the early stages. This indicates the prolonged impact of acute and severe health system failure that resulted in lingering insufficiency in population immunity to measles and other VPDs. The disruption of essential health services during the EVD outbreak was also documented in the area of maternal and child health services in Guinea, with declines in the number of institutional deliveries and frequency of antenatal visits and in the declines in the number of hospital admissions and surgical procedures in Sierra Leone [9-11]. The Ebola-related decline in measles surveillance performance was also more pronounced in Guinea and Liberia. The decline in surveillance quality, decline in health-care seeking, as well as the inability to collect and ship specimens for testing combined to underestimate actual incidence levels. As measles surveillance was re-established, case detection and confirmation improved at the same time that measles transmission intensified. The guidance from WHO on immunization during the Ebola outbreak recommended intensified routine vaccination activities and/or vaccination campaigns if programmatic assessment shows a risk of vaccine-preventable disease outbreaks [18]. The guidance specifically suggested that countries with intense and widespread transmission of Ebola virus implement crowd control, triage, infection prevention and control measures when conducting vaccination activities, as well as observing safe injection and waste disposal practices.

All three countries organized measles campaigns within the Ebola period due to outbreaks and surveillance data that confirmed measles transmission and heightened risks. Vaccine hesitancy was reported in various districts of all three countries due to the fear of acquiring Ebola infection via injection. Intensified community engagement and dialogue with traditional and religious leaders was employed to gain acceptance of the campaigns. Liberia and Guinea reported challenges in conducting the campaigns due to insufficient number of health staff to act as supervisors. Special provisions were made in all 3 countries to assure injection safety during the campaigns. Only trained and qualified health workers were engaged to administer the vaccine. Vaccination teams were supplied with auto-disable syringes for injection, safety boxes for the disposal of sharps, as well as hand sanitizers, gloves and aprons to observe recommended infection prevention and control procedures. There were no reports of ebola contamination or transmission resulting from injection practices during the supplemental immunization activities and no severe cases of adverse event following immunization were reported. The measles SIAs in early 2015 in all three countries were the first large-scale immunization interventions conducted during an ongoing Ebola outbreak. The experience of organizing measles SIAs during an Ebola outbreak and achieving high coverage, indicates that mass vaccination campaigns can be effectively undertaken in such conditions with appropriate planning and precautions to assure safe injection practices to prevent Ebola transmission.

In addition, when rebuilding damaged health systems, immunization remains a cost-effective first-line priority intervention and should be re-established with a view to provide timely and complete protection to the most vulnerable segments of the population against vaccine preventable diseases [25]. The coverage improvements documented in

Liberia and Sierra Leone in 2016 – 2017 demonstrate that focusing on immunization in the agenda to rebuild health systems can be effective. This analysis is subject to limitations. First, the completeness and reporting of administrative immunization coverage data was negatively affected by the ebola outbreak and may report a greater drop in numbers than actually occurred in health facilities. Second, where surveillance performance decreased, the ability of the health system to detect and confirm suspected cases was adversely impacted potentially resulting in under reporting of the measles cases and actual measles incidence.

Conclusion

The immunization service delivery was affected early in the course of the Ebola outbreak in the three worst affected countries in West Africa, and led to persistent gaps measles immunization coverage and high measles incidence that was documented until two years after the end of the Ebola outbreak. All three countries implemented measles outbreak response and supplemental immunization activities with the necessary precautions. The reporting and investigation of measles cases improved in the immediate post-Ebola period, while Liberia and Sierra Leone have demonstrated coverage improvements after the end of the Ebola outbreak, attesting to the high level programmatic attention paid to immunization in the health system rebuilding efforts.

What is known about this topic

- Guinea, Liberia and Sierra Leone had weak health systems before the EVD outbreak, which was further impacted negatively with the EVD outbreak;
- The EVD outbreak in 2014 – 2015 significantly disrupted health services in the country's worst affected, including childhood immunization services;
- Periodic supplemental immunisation activities (SIAs) are essential in order to close immunity gaps created through suboptimal routine immunisation coverage and as a result of disruption of health service delivery.

What this study adds

- This study quantifies the degree of disruption of the immunization services during and after the EVD outbreak in West Africa;
- Disease surveillance systems were disrupted at the same time as immunisation service delivery, and were not able to provide sensitive and timely indication of the immunity gaps and the increasing transmission of measles in the EVD affected countries;
- The measles SIAs were the first major immunisation interventions implemented in the three countries affected by the EVD outbreak, and were conducted with appropriate caution to avert the occurrence of AEFIs, and respecting the infection prevention and control measures in place to limit the spread of EVD.

Competing interests

The authors declare no competing interests.

Authors' contributions

All authors have read and agreed to the final version of this manuscript.

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PanAfrican Medical Journal

Letters to the Editors

Impact on refusal rates of house visits by Red Cross volunteers in Benin

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Guest editors: Robert Davis, James Goodson, Raoul Kamadjeu

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To the editors of the Pan African Medical Journal

The Republic of Benin, and its partners, pursue a two-pronged approach to measles vaccination, both through routine immunization from public and private health facilities, and through periodic mass campaigns, typically targeting 9- to 59-month-olds. During the mass campaigns, social mobilization is done both through conventional mass media approaches (TV, radio, newspapers) and, in selected areas, through house to house social mobilization by Benin Red Cross volunteers.

In Benin, measles control had seen good levels of incidence reduction since the catch-up and follow-up campaigns of 2001, 2003, 2005, 2008, 2011 and 2014. The World Health Organization recommends that countries already engaged in accelerated measles control extend their activities to the problems of rubella and congenital rubella syndrome. It is within this framework that Benin undertook in 2019 a mass campaign against measles and rubella, with the objective of protecting all children from 9 months to 14 years of age against both diseases, with post-campaign introduction of the Measles-Rubella (MR) vaccine into the routine immunization schedule.

There were 5,142,466 children targeted by this campaign. In addition to vaccines, 1.8 million children aged 9 months to 5 years of age were targeted for vitamin A supplementation. The major funders of this campaign were the government of Benin, the GAVI Alliance, the UN Childrens Fund (UNICEF), the World Health Organization, and the American Red Cross.

In its role as an auxiliary to the public authorities, Benin Red Cross (BRC) has in recent years committed itself to social mobilization during measles campaigns, targeting in 2019 the high risk communities in Cotonou (the economic capital of Benin) and communities in Abomey-Calavi, Allada, Djougou, Kpomassé, Porto-Novo, Semé-Podji, So-Ava, Tchaourou, Toffo, and Zé. Starting before the 2019 campaign, which lasted from 6 through 11 March, Red Cross volunteers did house to house social mobilization from 2 through 11 March in the areas listed in the table.

It should be noted that the key to success in convincing the refusals was the strong collaboration of the Benin Red Cross with health actors and local elected representatives in the communities. The latter spared no effort to reassure their community of the relevance of vaccination. This mixing between health actors, politico-administrative authorities and Red Cross actors was due to the daily participation of the BRC in daily wrap-up meetings within the Ministry of Health where joint actions were decided according to the refusals notified (Table 1).

Source: Social Mobilization in the Framework of the National Measles/ Rubella Vaccination Campaign for Children aged 9 Months to 14 Years, with Vitamin A Supplementation for Children aged 9 Months to 5 Years" (Unpublished report, Benin Red Cross, 2019, in French). NB: in the commune of Djougou, there was one ethnic group which, for religious reasons, was categorically opposed to vaccination despite the intervention of health actors and local elected officials. In Tchaourou, the other outlier, the EPI worker in the locality assured us that the cases of refusals were mastered by the end of the campaign with the help of opinion leaders."

Reasons for initial refusals

When caregivers were asked to explain why they did not initially intend to vaccinate their children, the reasons most often cited by initial refusers were (in descending order) fear of side effects, distance to the vaccination site, mother´s other activities, family problem or maternal illness, ignorance of hours and location of sites, illness of the child, inconvenient clinic hours, absence of the child, and long waiting times at the sites. Taken as a whole, 87 percent of the initial 862 refusers became accepters after revisits by Red Cross volunteers, sometimes accompanied by community leaders. This underlines the difference between "soft refusers" and "hard refusers."

Table 1: initial refusers and acceptors among Benin caregivers, 2019 measles/rubella campaign

Region	Total households visited	Total children in the age range	Total initial refusers	Total final refusers
Abomey-Calavi	22,508	51,172	67	0
Allada	16,982	40,517	357	1
Cotonou	90,769	190,999	450	25
Djougou	21,390	55,641	4	4
Kpomassé	10,436	22,754	28	0
Porto-Novo	43,092	95,392	84	24
Semé-Podji	35,259	83202	26	0
So-Ava	11,619	31,862	112	0
Tchaourou	21,033	51,661	49	49
Toffo	15,123	32,888	16	0
Zé	14,514	33,555	26	9
Totals	299,725	689,643	862	111

Conclusion

In Benin, as elsewhere, the historic decline in morbidity and mortality from measles and other childhood diseases has been associated with vaccine hesitancy among a minority of parents [1]. Such reluctance can, at least in some contexts, be overcome by interpersonal communication with trusted members of the community, such as Red Cross volunteers.

Competing interests

The authors declare no competing interests.

Authors' contributions

All authors have read and agreed to the final manuscript.

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Case series

Seroprevalence of rubella in pregnant women in Southern Morocco

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Abstract

Rubella is a generally benign but dangerous viral infection in early pregnancy, due to the teratogenic potential of the virus. Indeed, it causes spontaneous abortions, in-utero fetal death, premature labor and congenital malformations known as congenital rubella syndrome. The purpose of this study is to determine the immune status of rubella in pregnant women in southern Morocco. A prospective, multicentre study was conducted in 2017 for the detection of rubella IgG and IgM antibodies in 380 pregnant women aged 17 to 46 years, using the Architect i1000 chemiluminescent microparticle immunoassay. Eigthy for percent (84.7%) of women were seropositive. Ten percent of multiparous women remained seronegative despite recommendations for vaccination after delivery. Preventive measures against congenital rubella need to be strengthened, and vaccination is needed in non-immunized women. Vaccination awareness campaigns, especially among non-immunized multiparous women, remain essential.

Introduction

Rubella is an acute viral disease, basically one of children. Its clinical course is generally favorable in almost all cases when it affects the child in the postnatal period. It is, however, a real public health problem because of the teratogenicity of the virus. When a woman contracts the disease during pregnancy, the consequences can be dramatic for the fetus, especially when the infection takes place in the first trimester, sometimes leading to spontaneous abortion, fetal death, or the birth of a child with congenital malformations known as Congenital rubella syndrome (CRS). Vaccination or, better, early natural infection are the only ways to prevent this important disease [1]. In Morocco, the epidemiology of rubella remains poorly understood, since it is not a reportable disease. This study has for its objectives the determination of the rubella immunity status of pregnant women in southern Morocco and the effort to establish a link between rubella seroprevalence and the socio-demographic factors studied.

Methods

This is a cross-sectional, multicentre study, both descriptive and analytic, done in 2017 at the Bacteriology and Virology Laboratory of the Avicenna Military Hospital, Marrakech. The study includes 380 pregnant women, either hospitalized or consulting at one of three hospitals: the Hassan II Hospital, Agadir, the Avicenna Military Hospital, Marrakech, and the Ourzazate Provincial Hospital Center, and one of the three Ouarzazate regional health centers. The nature of the study was carefully explained to the study population and oral consent was obtained from each participant. A questionnaire was filled for each woman covering age, socio-demographic factors, gestational age, previous obstetrician-gynecological (OB-GYN) care and vaccinations received. IgG and IgM studies were done with ARCHITECT i1000 (Abbott Diagnostics), closed systems immunoanalysis, based on chemiluminescent microparticle immunoassay. For IgM, a result counts as positive (reactive) if the sample value is > 1 and negative (non-reactive) with a value < 1. For IgG, a result was considered positive if the IgG value was ≥ 10.0 IU/ml, negative if the value was between 0 and 4.9, and ambiguous if between 5.0 and 9.9 IU/ml. In our study, ambiguous values were considered negative. Data entry was done using Excel©, and statistical analysis used SPSS, ver. 19 for Windows. The study of association between rubella sero-immunity and socio-demographic characteristics was based on chi^2 and Fisher's exact test for qualitative variables. Values were considered statistically significant at the level of $p < 0.05$.

Results

The mean age of the patients was 28, ranging from 17 to 46 years. The age range 25-34 was most represented, accounting for 50.8 percent of the cases (Figure 1). Of the women studied, 41 percent were in their third trimester, the remainder divided between first and second trimesters. Of the patients, 69.5 percent were multiparous, 15 percent had had a miscarriage and 4.5 percent had a history of in-utero fetal death. Women of a middle social and educational status were, respectively, 84 and 74 percent of the study population. Among the 380 women studied, 84.7 percent were IgG positive, while all the women were IgM negative (there was no current risk of rubella infection). The age range 25 through 34 was the most likely to have immunity, with seropositivity of 40.5 percent and seronegativity of 10.3 percent (Figure 2). Some 51.5 percent of the immune women lived in urban areas, and 30.5 percent in rural areas. Ten percent (10.3%) of the multiparous women remained seronegative for rubella during their previous pregnancies (Figure 3). There was no statistically significant relationship between rubella immunity and all of the factors cited ($p < 0.05$).

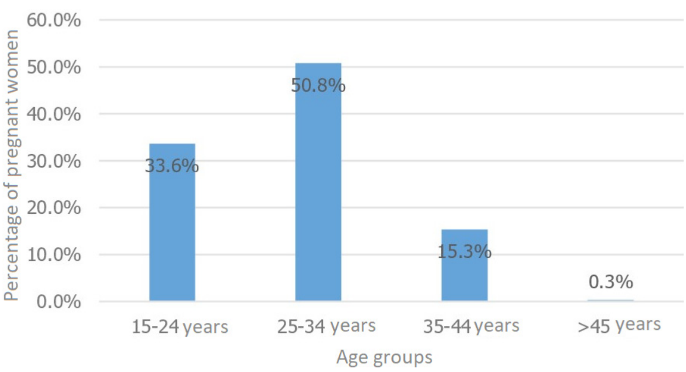

Figure 1: distribution of patients by age range

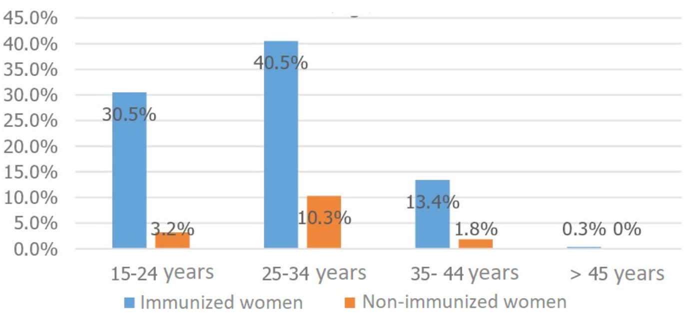

Figure 2: distribution of immunized and non-immunized women by age range

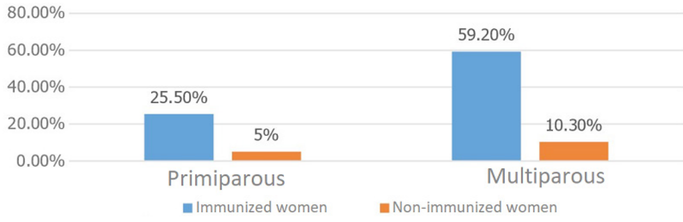

Figure 3: immune status of pregnant women by parity

Discussion

Rubella is generally a benign viral infection, but can cause spontaneous abortion, fetal death or the birth of a child with congenital malformations when the pregnant woman is exposed to the virus during the first trimester of pregnancy. In case of infection before 12 weeks, the frequency of fetal infection is 90 percent and the risk of major fetal anomalies is very high (on the order of 90 percent) [1].

In Morocco, the epidemiology of rubella remains poorly understood, since it is not a reportable disease. Studies, very limited and done at the national level (Rabat, Meknès), examined IgG antibody seroprevalence among pregnant women. There have been susceptibility reports of 11.3 percent [2] and 9.8 percent [3]. In this study, 84.7 percent of women were seropositive for rubella immunity (antibody value > 10IU/ml). This immunity rate is comparable to those reported at the national level. Other studies in numerous countries have reported seroprevalence from 58 percent to 98 percent [4-11] (Table 1). The significant difference in rubella immune status in different countries can be explained by the date of rubella vaccine introduction, of any mass vaccination campaigns, and of sensitization of the population. According to the results of this study, there is no significant relation between the IgG seropositivity and the various factors studied, notably age, rural/urban origin, parity, and socio-economic and educational levels.

Table 1: national and international comparison of rubella seroprevalence

Study	Year	Seropositivity
Our study	2017	84.7%
Meknes (Morocco) [2]	2015	88.7%
Rabat (Morocco) [3]	2009-2011	90.2%
Tunisia [4]	2010	79.7%
Canada [5]	2008-2011	85%
Namibia [6]	2010	85%
China [7]	2010-2012	58.4%
Brazil [8]	2007-2012	97.2%
Spain [9]	2008-2013	94.1%
Norway [10]	2010-2011	94.4%
Togo [11]	2013	85%

Analysis of the qualitative rubella serology results shows that none of the women were IgM positive, and that there had not been any recent infection during the period of the study. Specific IgM can be detected not only in the case of a recent primary infection, but also in the case of a reinfection (a highly exceptional situation), or because of non-specific polyclonal stimulations of the immune system, as well as a cross reaction with rheumatoid factors in the case of systemic disease. Because of these different situations during which IgM is detectable, recourse to complementary tests like IgG avidity is indispensable to confirm or deny a diagnosis of recent infection. The use of this technique rests on the fact that the avidity matures with the time before the start of the infection. Thus, a weak rubella IgG avidity shows a recent infection, while a high avidity permits the exclusion of a recent primary infection [12].

The global coverage of rubella vaccination is on the rise, having gone from 21 percent in 2000 to 40 percent in 2012, then to 47 percent in 2016 [13]. Nonetheless, the Moroccan vaccination program does not take women of child bearing age into consideration. The decline in incidence of the number of CRS cases in Morocco would be possible only if the virus circulation were interrupted by mass vaccination of women of child bearing age, and of school age girls, along with routine vaccination of children with Measles-Rubella (MR) or Measles, Mumps and Rubella (MMR). In our study, 10 percent of the multiparous women were seronegative for rubella in their previous pregnancies, though they should have been immunized [14]. The World Health Organization recommends that every seronegative pregnant woman, or one whose immune status is unknown, should be vaccinated post-partum before hospital discharge in order to achieve a seroprevalence of 100 percent [2]. The non-vaccination of seronegative women is explained by the lack of communication between patients and health personnel about knowing one´s immune status before marriage, and the importance of post-partum vaccination.

Conclusion

Congenital rubella is a serious condition which should be eradicated, since there is a live attenuated vaccine against the disease. Every women of reproductive age needs to be immunized. Premarital rubella serodiagnosis is recommended, since interpretation of the serology becomes more complicated if done during pregnancy. Despite implementation of rubella vaccination in the national vaccination program, seronegativity remains high when compared to the eradication objectives of the Ministry of Public Health. Vaccine sensitization campaigns, especially among unvaccinated multiparous women, remain indispensable to achievement of the objectives.

What is known about this topic

- The epidemiology of rubella remains poorly understood, since it is not a reportable disease;
- Vaccination or early natural infection are the only effective ways to prevent this disease.

What this study adds

- The rate of sero-negativity remains high when compared to the eradication objectives of the Ministry of Public Health;
- Vaccination sensitization campaigns for non-immunized women are indispensable for control of congenital rubella syndrome.

Competing interests

The authors declare no competing interests.

Authors' contributions

Hanane Zahir: conception of the protocol, gathering and analysis of data, development of concluions, bibliographic research, editing of the article, final approval of the version for publication. Lamiae Arsalane: conception and refinement of the protocol, analysis and interpretation of the data, critical revision of the content and final approval of the version for publication. Ghita Elghouat: data collection and statistical analysis, contribution to editing of the article and final approval of the version for publication. Hanane Mouhib: analysis and collection of data, contribution to the editing of the article, and final approval of the version for publication. Youssef Elkamouni: analysis and interpretation of data, critical revision of the content and final approval of the version for publication. Said Zouhair: conception of the study, validation of the work methodology, analysis and interpretation of data, critical revision of content, and final approval of the version for publication. All authors read and agreed to the final manuscript.

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Supplement article

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Research

Assessing the incremental costs and savings of introducing electronic immunization registries and stock management systems: evidence from the better immunization data initiative in Tanzania and Zambia

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Abstract

Introduction: poor data quality and use have been identified as key challenges that negatively impact immunization programs in low- and middle-income countries (LMICs). In addition, many LMICs have a shortage of health personnel, and staff available have demanding workloads across several health programs. In order to address these challenges, the Better Immunization Data (BID) Initiative introduced a comprehensive suite of interventions, including an electronic immunization registry aimed at improving the quality, reliability, and use of immunization data in Arusha Region, Tanzania, and Southern Province of Zambia. The objective of this study was to assess the incremental costs of implementing the BID interventions in immunization programs in these two countries.

Methods: we conducted a micro-costing study to estimate the economic costs of service delivery and logistics for the immunization programs with and without the BID interventions in a sample of health facilities and district program offices in each country. Structured questionnaires were used to interview immunization program staff at baseline and post-intervention to assess annual resource utilization and costs. Cost outcomes were reported as annual cost per facility, cost per district and changes in resource costs due to the BID interventions (i.e., costs associated with health worker time, start-up costs, etc.). Sub-group analyses were conducted by health facility to assess variation in costs by volume served and location (rural versus urban). One-way sensitivity analyses were conducted to identify influential parameters. Costs were reported in 2017 US dollars.

Results: in Tanzania, the average annual reduction in resource costs was estimated at US$10,236 (95% confidence interval: $7,606-$14,123) per health facility, while the average annual reduction in resource costs per district was estimated at $6,542. In Zambia, reductions in resource costs were modest at an estimated annual average of $628 (95% confidence interval: $209-$1,467) per health facility and $236 per district. Resource cost reductions were mainly attributable to reductions in time required for immunization service delivery and reporting. One-way sensitivity analyses identified key cost drivers, all related to reductions in health worker time.

Conclusion: the introduction of electronic immunization registries and stock management systems through the BID Initiative was estimated to result in potential time savings in both countries. Health worker time was the area most impacted by the interventions, suggesting that time savings gained could be utilized for patient care. Information generated through this work provides evidence to inform stakeholder decision-

making for scale-up of the BID interventions in Tanzania and Zambia and to inform other Low-to-Middle-Income Countries (LMICs) interested in similar interventions.

Introduction

Immunization has proved to be the most cost-effective public health intervention through reducing childhood mortality and morbidity attributable to vaccine-preventable diseases. Despite immunization being such an effective public health tool, not all children are being reached with the lifesaving vaccines they need [1]. One key challenge faced by immunization programs, especially in the sub-Saharan African region, is the stagnation of coverage rates [2]; coverage rates for the third dose of diphtheria, tetanus and pertussis-containing vaccine have plateaued in the 70% percentile since 2010 [3]. In addition, drop out rates between the first and second dose of measles containing vaccine can be high and this has implications for the ability of countries to achieve disease elimination.

Several factors have been identified as inhibiting immunization program performance improvement, including the poor quality of data and the poor use of existing data [2, 4-7]. Data quality challenges include inconsistencies and inaccuracies in reported data, which impact key program metrics such as target populations and coverage rates. Poor use of data includes failure to use existing data to inform planning, which can result in low product stock or stockouts and delays in transmission of data to program managers. In addition, programs have challenges tracking which children have received which vaccines and hence during campaigns, vaccines are given to all children in the target age group because there is no data to inform the program about which children are fully vaccinated through routine immunization. Embedded in these data challenges are data formats that make it difficult for health workers to easily identify and track children who are due for vaccinations or track children who move from one area to another, which hinders the provision of optimal services to intended recipients. In addition, low- and middle-income countries are plagued by a shortage of health care workers, who lack the infrastructure to effectively and efficiently manage their programs [8].

Given these challenges with immunization program data, there is a global effort to strengthen country immunization systems by supporting the collection of better-quality data and better use of these data to inform program decision-making. One such effort is through the Better Immunization Data (BID) Initiative [9], led by the Ministry of Health, Community Development, Gender, Elderly and Children in Tanzania and the Ministry of Health in Zambia, in partnership with PATH and funded by the Bill & Melinda Gates Foundation. The initiative is designed to shed light on the challenges surrounding data collection, quality, and use and has identified solutions to improving immunization program data - and potentially applying them to other health areas. The BID initiative worked with the governments of Tanzania and Zambia to develop data quality and use solutions, which include a package of interventions that contains an electronic immunization registry with supply chain information, which enables automatic report generation; data use campaigns; online peer support networks and targeted supportive supervision for health workers. These interventions were implemented at the health facility and district levels. Several research studies were conducted to evaluate the impact of the BID initiative, including monitoring and evaluation of the impact of the BID interventions and costing studies. This article focuses on the findings from the costing studies.

Very few studies have evaluated the costs of interventions aimed at improving data quality and use in other countries that have implemented similar interventions. Hence, we sought to provide some evidence on these costs using data from Tanzania and Zambia. Our objective was to estimate the economic costs of immunization program logistics and service delivery before and after the implementation of the BID interventions, and use these data to estimate the incremental costs or savings attributable to the interventions. The findings from this study are intended to inform the scale-up of such interventions within the two countries and across other countries in the region.

Methods

Overview of the baseline system and the BID initiative interventions implemented

Table 1 provides an overview of the immunization registry before and after implementation of the BID interventions. At baseline, health facilities in Arusha Region, Tanzania, and Southern Province, Zambia, were using paper immunization registers, tally sheets and vaccine stock ledgers. Child health cards were used to document vaccines given and these cards were kept by caregivers. Monthly immunization reports were compiled manually using paper report templates. Through BID, tablets were provided to health facilities, which contain software for an electronic immunization registry that include functionality for immunization registration, tallying, stock management and reporting. Tablets were provided to all health facilities in Southern Province. Initially, the tablets were provided only to high-volume facilities in Arusha Region, while low-volume facilities implemented a simplified paper system that helped to streamline data entry and reporting. However, by the end of the project, low-volume facilities had adopted the electronic system, due to challenges of the simplified paper version. The electronic registry is integrated with data use interventions, including an online peer network platform (WhatsApp) and provision of data use job aids to health workers. District staff also provided targeted supportive supervision for health workers. A barcode/quick response code was added to child health cards so that health workers can scan the barcode to retrieve the vaccination record for any given child from the registry. The electronic registration system also automatically generates the monthly reports on the standard immunization reporting metrics.

Facility- and district-level costing

We conducted a micro-costing study [10] to estimate the annual economic costs of resources used for immunization logistics and service delivery before and after implementation of the BID initiative in Arusha Region in Tanzania and Southern Province in Zambia. The study focused on the health facilities and districts in which the BID interventions were implemented and hence did not include regions/provinces or the national level.

We developed primary data collection tools to identify resources used for transporting and storing vaccines, staff time for logistics and service delivery, office equipment and communications, and printing and office supplies. Similar questionnaires were used to collect data on the resources used at district level, focusing on activities related to the logistics and management of health facilities. The tools used in the two countries were similar, but adaptations were made to reflect country-specific characteristics of each immunization system.

We collected data from a sample of health facilities in each district and a sample of districts in each region/province. We included 4 of the 7 districts in Arusha Region and 6 of the 13 districts in Southern Province. Health facility sample sizes are shown in Table 1. Baseline and post-intervention data were collected from the same sample of facilities and districts, which we selected using a purposive sampling approach based on key characteristics expected to affect the costs of providing immunization services. These parameters included average number of monthly immunizations dichotomized into low (< 50 children) and high volume (≥ 50 children), location (rural versus urban) and distance from the district immunization office. BID staff administered the questionnaires through in-person interviews at each facility.

At the time of post-intervention data collection, the facilities in Tanzania had been using the electronic immunization registry for an average of 8 months (range 4 to 11 months); in Zambia, the average was 3.5 months (range 1 to 8 months). In addition, at the time of post-intervention data collection, health facilities in both countries were still using the paper-based system as back-up because policy decisions had not yet been made to eliminate the paper system and solely rely on the electronic system. Therefore, we asked health workers to assess the change in resource use under a scenario in which only the electronic system was in use.

Types of costs included in the costing study

We collected immunization service delivery costs across five main categories: (1) human resources; (2) cold chain equipment; (3) communications, printing and office supplies; (4) facility office equipment

Table 1: sample size for the health facility analysis and overview of the immunization registry system before and with the BID interventions				
	Arusha Region, Tanzania		Southern Province, Zambia	
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
	n	n	n	n
Health facilities				
Total number of health facilities in the region/province	253	253	253	253
Health facilities sampled for costing study[a]	43	34	52	46
Overview of the immunization registry system				
Immunization registration	Relied on paper immunization registry	Electronic registration using a tablet	Relied on paper immunization registry	Electronic registration using a tablet
Immunization stock management	Paper-based immunization stock management system	Electronic management of vaccine stock using tablets and bar codes	Paper-based immunization stock management system	Electronic management of vaccine stock using tablets and quick response codes
Reporting	Paper reports submitted in person at the district	Reports automatically generated and submitted electronically	Paper reports submitted in person at the district	Reports automatically generated and submitted electronically
[a] Fewer facilities were available to participate in interviews at post-intervention compared to baseline. In Tanzania, at the time of the post-intervention assessment some of the facilities were still using the paper system and so there was no difference from baseline; hence, we did not collect post-intervention data at these facilities. In Zambia, some facilities had not started using the electronic system at the time of post-intervention data collection, so they were also excluded from the post-intervention data collection. The number of facilities sampled at each time point are reported here				

Table 2: selected unit prices (in 2017 US dollars)		
Resource	**Tanzania**	**Zambia**
Nurse monthly salary	$549	$532
Nurse assistant monthly salary	$426	$486
District immunization officer monthly salary	$1,098	$773
Truck/Pickup	$70,000	$70,000
Refrigerator (average of brands used)	$2,315	$1,323
Tablet (at district level)	$325	$325
Tablet (at health facility level)	$152	$152
Barcode/Quick response code scanner	$175	$175
Printer (at district level)	$600	$600
Scanner (at district level)	$550	$550
Immunization register	$1.24	$0.50
Stock register	$0.91	$0.50
Fuel costs	$0.84	$1.25
Electricity price per kWh	$0.09	$0.03
kWh: kilowatt hour		

and (5) transport. Human resources costs included salaries and per diems for staff working in the immunization program. Staff were asked to self-report the time spent on providing fixed and outreach immunization services, logistics and stock management for the immunization program and data reporting. The costs of cold chain equipment captured the capital costs of refrigerators, freezers, cold boxes, and vaccine carriers used in the immunization program, and the annual costs of electricity or gas to run the cold chain equipment, as relevant. Costs of office equipment and communications included capital costs for computers, tablets, printers, scanners, and other equipment used by the immunization program and communication and printing costs. Finally, transport costs reflected the costs to collect vaccines and immunization supplies from the district and transport them to facilities or to conduct outreach services (hired vehicles, public transportation and capital and fuel costs for vehicles owned and maintained).

Data analysis

For resources shared with other programs, costs were allocated to the immunization program based on the reported percentage spent or use of the immunization program. Capital costs were annualized using different lifespans: 3 years for office equipment; 5 years for vehicles; and 10 years for cold chain equipment. All local cost data were collected in local currencies and converted into 2017 US dollars using average exchange rates for the year [11]. As necessary, we updated prices for inflation using consumer price indices from the World Bank [12]. Unit prices (Table 2) were obtained from various sources, including local data sources, World Health Organization (WHO) Comprehensive Multi-Year Plans [13], online databases [14-17] and BID Initiative project records.

Resource use data were combined with unit costs to calculate economic costs at the district and facility levels. All cost estimates (baseline, post-intervention and incremental) were reported as annual economic costs per facility or district. Our incremental cost estimates relied on the cross-sectional data from the two surveys conducted, one at baseline and one at post-intervention. These surveys were conducted at different time points. However, given that time use was self-reported and subject to recall bias, at post-intervention, along with asking survey respondents to estimate time spent on immunization activities with the BID interventions, we asked them to recall and report how much time they had been spending on these same activities before the implementation of the BID interventions. We used these data to provide an alternative set of estimates for the analysis. In addition, we conducted univariate sensitivity analyses to identify the cost drivers and time use for the interventions.

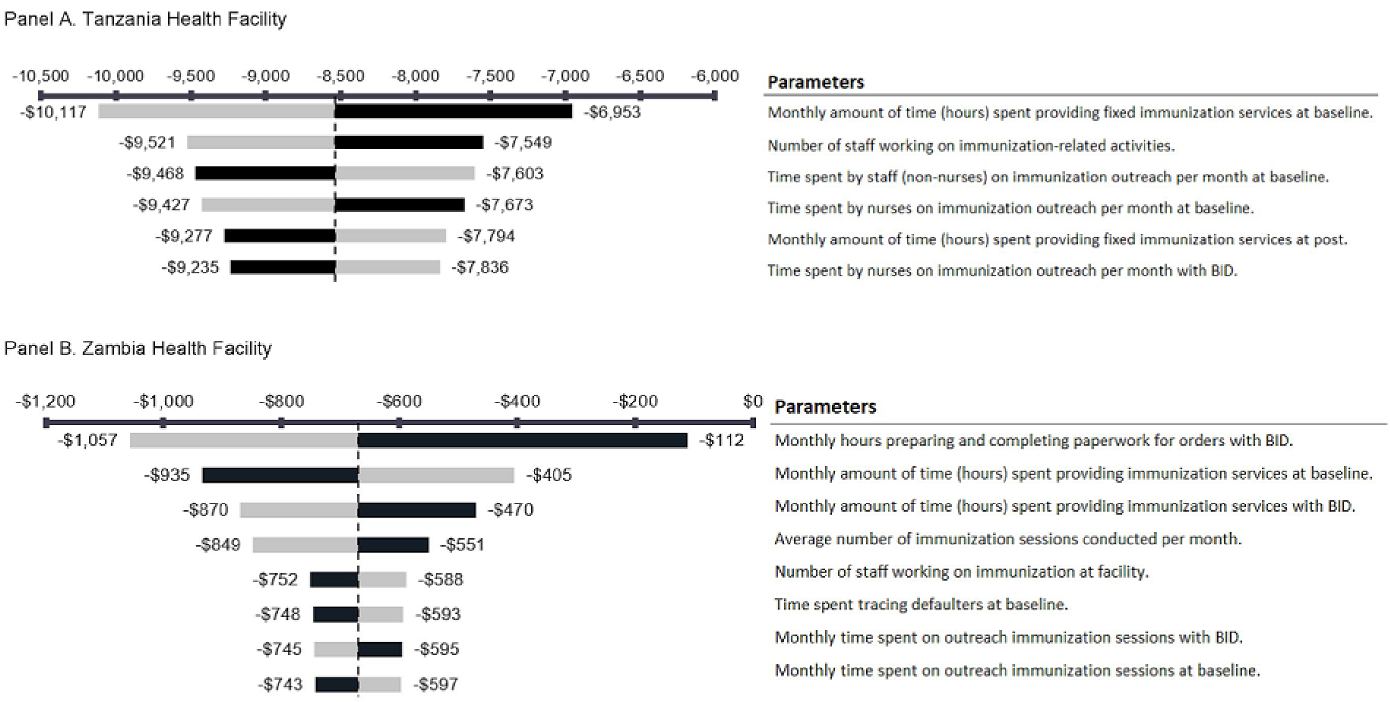
Results

Health facility costs

Table 3 shows the economic cost estimates for the health facilities, comparing the costs of the resources used using the data from the baseline and post-intervention surveys. In Tanzania, we estimated at baseline that the annual average economic costs per health facility totaled US$17,318 (95% confidence interval [CI]: $12, 113–$24, 289]. Post-intervention average facility costs were $7,082 [95% CI: $4, 506–$10, 116], reflecting estimated annual savings of $10,235 per facility each year due to efficiencies generated in the immunization supply chain, service delivery, and time spent on immunization activities at the facility level (Table 3). These savings are attributable to reductions in several areas, including human resources costs because of reductions in time spent on immunization reporting and management activities and emergency trips for vaccine resupply, and elimination of printing costs for paper registers and tally sheets not required for the BID interventions. The one cost category that increased because of the BID interventions was office equipment, because of the provision of tablets and barcode or quick response code readers at each health facility. Capital costs for cold chain equipment remained unchanged from pre- to post-intervention because the interventions had no impact on these costs. Using the time use data for baseline and post-intervention based on responses from only the post-intervention survey, we found that for the health facilities in Arusha Region, Tanzania, the estimated savings in salary and per diem costs were $6,642, lower compared to the $10,245 reported when using the responses from the baseline and post-intervention surveys.

Table 3: average annual cost per facility for the immunization program at baseline and post-intervention (in 2017 US dollars)						
Parameters	Facilities in Arusha Region, Tanzania			Facilities in Southern Province, Zambia		
	Baseline	Post	Incremental	Baseline	Post	Incremental
	mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)
Salaries and per diems	16,468 (11,509, 23,175)	6,223 (3,806, 9,127)	−10,245 (−14,048, −7,703)	4,391 (854, 5,974)	3,663 (2,211, 5,693)	−728 (−291, 1,357)
Cold chain equipment	399 (395, 403)	399 (395, 403)	0 (0, 0)	313 (255, 371)	313 (255, 371)	0 (0, 0)
Transportation	302 (145, 476)	258 (118, 420)	−44 (−28, −56)	534 (341, 739)	520 (337, 715)	−14 (−24, −5)
Office equipment	0 (0, 0)	138 (138, 138)	138 (138, 138)	11 (0, 22)	149 (138, 161)	138 (138, 138)
Printing, Internet, and telephone	148 (63, 235)	63 (49, 78)	−85 (−14, 157)	74 (55, 93)	50 (40, 60)	−24 (−15, −33)
Total per facility	17,318 (12,113, 24,289)	7,082 (4,506, 10,166)	−10,236 (−14,123, −7,606)	5,324 (1,506, 7,209)	4,695 (2,981, 6,999)	−628 (−209, 1,476)
CI: confidence interval						

In Zambia, we estimated similar trends as for Tanzania but Zambia's baseline costs were lower at $5,324 [95% CI: $1,506-$7,209]. Post-intervention costs were estimated at $4,695 for Zambia [95% CI: $2,982-$6,999]; therefore, savings attributable to the BID interventions were smaller (we estimated a savings of approximately $628 per facility each year). This represents a 12% reduction in costs per facility with BID



Footnotes:

The width of the bar shows how the incremental savings changes when each parameter changes.

High-parameter input values are shown using gray bars and low input values are shown using black bars.

Bars on the left show the impact of increasing the parameter value on the incremental savings; the bars on the right show the impact of reducing the parameter value on incremental savings.

Figure 1: univariate sensitivity analysis evaluating influential parameters on incremental savings from introducing electronic immunization registries and stock management systems into Tanzania and Zambia

compared to baseline. Similar to Tanzania, the largest savings would be achieved through reduction in staff time on immunization activities. We also estimated a reduction in annual transport costs of $14 per health facility, resulting from a reduction in emergency trips to the district vaccine store to collect vaccines and transportation for immunization-related outreach activities.

We conducted univariate sensitivity analyses to assess uncertainty and identify influential parameters on changes in resource utilization due to the interventions (Figure 1). Influential parameters were considered any variables with uncertainty ranges wider than 20% of the total incremental change in health facility costs. Across all Tanzanian facilities, time spent on provision of routine and outreach immunization services and total number of staff allocated to the immunization program (stratified by nurses and other staff) appeared to be the largest drivers of the incremental cost per health facility (Figure 1 A). Sensitivity analyses in Zambia derived similar results (Figure 1 B). Incremental costs appeared to be driven by the time spent on paperwork and providing fixed immunization services, as well as the estimated number of immunization sessions per month.

When results were stratified by health facility characteristics -rural versus urban and low volume versus high volume- we found that in Tanzania, there was a smaller variation across health facility categories based on location (results not shown in tables). For example, rural facilities were estimated to save an average of $8,144 [95% CI: $6,812-$9,820] with the introduction of the interventions, compared to $9,423 [95% CI: $5,787-$13,972] savings in urban facilities. The variation was slightly higher based on volume served; we found that low-volume settings were estimated to save approximately $7,683 [95% CI: $5,116-$10,964] per facility compared to $9,367 [95% CI: $7,671-$11,560] in high-volume facilities. In Zambia, the immunization volume categorized as low or high volume resulted in much larger variation between strata, with savings of $275 [95% CI: $205-$298] in low-volume facilities compared to $2,177 [95% CI: $1,408-$3,037] in high-volume facilities. Stratified cost savings were $380 [95% CI: $612 cost savings to $247 increased costs] and $776 [95% CI: $2,218 cost savings to $89 increased costs] in rural and urban facilities, representing 9% and 13% decreases in costs, respectively.

District-level costs

Table 4 shows the results of the baseline and post-intervention costing analysis at the district level. At baseline, the average logistics and service delivery costs in Tanzania were $23,001 per year, excluding the value of vaccines. Human resources accounted for the largest share of costs, at more than 50%. Based on the responses provided by staff at the district level about the impact of the interventions, we found that the interventions did not have any impact on the costs of cold chain or transport. The BID interventions impacted the costs of the following items: communications, printing and office supplies, office equipment and human resources. The interventions resulted in an average increase in communication costs of $167 per district. Equipment costs increased by about $491 per district because a tablet, printer and scanner were provided to each district immunization office. Other equipment costs were not expected to change with the introduction of the interventions. Human resources costs were the most impacted by the interventions, as district office staff reported a significant reduction in time spent on estimating vaccine needs, processing orders and distributing vaccines to health facilities. A few human resources activities saw an increase in time use, such as supervision and support, due to more time being spent with facilities to provide technical support with the electronic registry. On average, a district office in Tanzania estimated that human resources time valued at $7,200 would be saved per year when compared to the system without the interventions. Overall, we estimated that the rollout of the interventions would result in net savings in the amount of $6,542 per year at the average district office in Arusha Region, Tanzania. This represents a 28% reduction in costs after the introduction of the interventions.

The estimated savings in Zambia from the implementation of the interventions were more modest. The new equipment increased district annual costs by $491 and communication costs by $62. Most of the savings were derived from reduced labor time and fewer printing costs for immunization registers, stock ledgers and tally sheets. We estimated that time valued at $789 would be saved per year by staff at each district office. Overall, the rollout of the interventions was estimated to result in annual net savings of $236 for the average district office in Southern Province.

Table 4: average annual cost per district for the immunization program at baseline and post-intervention (in 2017 US dollars)

Parameters	Districts in Arusha Region, Tanzania			Districts in Southern Province, Zambia		
	Baseline	Post	Incremental	Baseline	Post	Incremental
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Salaries and per diems	$13,655 ($7,121, $21,061)	$6,456 ($2,452, $10,362)	−$7,200 (−$10,699, −$2,807)	$3,693 ($1,082, $6,23)	$2,904 ($1,043, $6,559)	$−789 (−$2,116, $276)
Cold chain equipment	$2,258 ($1,046, $3,847)	$2,258 ($1,046, $3,847)	$0 ($0)	$855 ($470, $1,364)	$855 ($470, $1,364)	$0 ($0)
Printing, Internet, and telephone	$269 ($110, $503)	$436 ($298, $688)	$167 ($118, $222)	$1,188 ($59, $2,416)	$1,250 ($200, $2,365)	$62 (−$51, $141)
Office equipment	$68 ($63, $70)	$559 ($554, $561)	$491 ($491, $491)	$19 ($7, $39)	$510 ($498, $530)	$491 ($491, $491)
Transport costs	$6,751 ($2,499, $11,607)	$6,751 ($2,599, $11,607)	$0 ($0, $0)	$11,823 ($2,524, $16,609)	$$11,823 ($2,524, $16,609)	$0 ($0)
Total per district	$23,001 ($11,064, $35,718)	$16,459 ($8,891, $25,695)	−$6,542 (−$10,023, −$2,173)	$17,578 ($6,595, $23,724)	$17,341 ($7,280, $22,178)	−$236 ($1,456, $800)

Discussion

This study aimed at estimating the cost implications of introducing electronic immunization registries and stock management systems in Arusha Region, Tanzania, and Southern Province, Zambia. In both countries, we found that electronic systems may result in savings compared to paper immunization and stock registers. Savings were mostly attributable to reduction in health workers' time spent on immunization activities, such as administrative tasks and reporting. Efficiencies gained due to electronic registration and reporting were, as expected, higher in absolute terms in high-volume facilities compared to low-volume facilities.

To our knowledge, this study is the first to estimate the savings to be realized using electronic immunization registries and stock management systems in resource-limited settings. Few studies published in the literature evaluated interventions similar to those introduced through the BID Initiative [18-24], most of which were based in high-income countries. Due to the vast differences in financial resources, immunization programming, and health care delivery systems, these findings provide little opportunity for comparison or use in decision-making for immunization programs in sub-Saharan Africa. In terms of benefits, the US-based studies identified increases in administrative efficiency such as the reduction in reporting burden. We found similar efficiencies from reductions in time spent on daily registration during immunization sessions and on monthly reporting. The dearth of studies in low- and middle-income countries highlights a lack of evidence on the costs and benefits of electronic immunization registries and relevant immunization interventions in these countries.

While not having a direct financial implication for health ministry budgets, the reduction in health worker time represents an important finding and suggests that human resources could be freed up at health facilities so that staff could spend more time on patient care rather than administrative tasks. Also, given the competing time demands of health workers who work across different programs, the benefits of the time savings could be spread to other programs. At the district level, the time saved from the automatic generation of monthly reports is expected to allow district immunization officers to divert energy to other activities, such as supervision.

We found that the estimated savings were much larger for districts and health facilities in Arusha Region, Tanzania, than those in Southern Province, Zambia. While there could be other reasons for these differences, we suspect that the shorter evaluation time in Zambia (between the deployment of the BID initiative interventions and the collection of the post-intervention costing data) may partially explain these findings. In fact, we hypothesize that staff were still adjusting to the new system in Zambia and hence had not gleaned the full benefits of the new system.

Our study has several limitations. First, the cost estimates are not representative, as a purposive sampling approach was used and samples were relatively small. To address this limitation, we conducted sensitivity analyses and varied input values over low and high ranges to assess how the cost implications would differ under varying assumptions. Second, the time between rollout of the interventions and post-intervention data collection was short, especially in Zambia. This choice was driven by the project timelines and the broader delays experienced during rollout of the interventions. Therefore, estimates reported here are likely to capture learning costs and thus underestimate savings from the BID interventions. A longer-term evaluation of the BID initiative may be warranted to provide more accurate estimates of its cost implications. Third, all time use data included in this analysis were self-reported and thus may have been under- or overestimated. Also, at the time of post-intervention data collection, countries were continuing to use both their paper-based system and the electronic system, making it difficult to assess system changes. This is because the relevant ministries of health had not yet made the decision to solely rely on the electronic system. As a consequence, we relied on staff's assessment of what their time use would be if they were using only the electronic system. Fourth, due to the lack of data or complexity in assessing them, the study did not include all benefits that could result from the BID interventions, further underestimating its benefits. For example, potential benefits in terms of a decrease in the number of stockouts and wastage, better forecasting, more timely immunizations and higher coverage, and improved decision-making could not be taken into account because of the shortness of time between deployment and evaluation. In addition, our ability to capture the costs of the immunization program relied on the availability and quality of the data. Finally, in this study we did not include the upfront costs of implementing the BID interventions, such as the system development costs or the costs of rolling out the BID interventions to facilities and districts and the costs of maintaining the system. These costs will be reported in a separate analysis.

Conclusion

The introduction of electronic immunization registries and stock management systems through the BID initiative was estimated to be cost saving in Tanzania and Zambia. These savings were primarily due to time efficiencies and associated staff cost savings. Information generated through this work provides evidence for key stakeholders in Tanzania and Zambia to inform decision-making for the scale-up of the BID interventions in these countries and to inform decisions in other countries that may be interested in similar interventions.

What is known about this topic

- Poor data quality and low data use are key challenges that negatively impact immunization programs in low- and middle-income countries;
- Electronic immunization registries (EIRs) together with related data use interventions can be a solution for these challenges.

What this study adds

- Evidence on the incremental costs of implementing EIRs and data use interventions in immunization programs in Tanzania and Zambia;
- The study found that the interventions introduced resulted in savings in health worker time.

Competing interests

The authors declare no competing interests.

Authors' contributions

Mercy Mvundura (MM) and Laura Di Giorgio (LDG) were responsible for the conception and design of the work; Robert Kindoli (RK) and Chipo Zulu (CZ) were involved in the acquisition of data for the work; MM, LDG and Elisabeth Vodicka (EV) were responsible for data analysis; MM and EV were responsible for drafting the manuscript; all authors (MM, LDG, EV, RK and CZ) reviewed and provided important feedback on the various iterations of the manuscript and all authors provided approval of the final version submitted to this journal.

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PanAfrican Medical Journal

Research

Impact on child vaccination completion rates of short message services (SMS) reminders in developing countries

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Guest editors: Robert Davis, James Goodson, Raoul Kamadjeu

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Abstract

Introduction: the Expanded Programme on Immunization has, since its inception, struggled to achieve high completion rates for child immunizations. The introduction of 2YL (second year of life) immunizations presents the programme with fresh challenges to assuring high completion rates.

Methods: using the same procedures as those employed in the 2017 article on SMS reminders, of which this is an update, I searched the NLM database for all recent articles from developing countries on SMS reminders for reduction of vaccination dropout rates. I summarized these and earlier articles in tabular form.

Results: the freshly reviewed articles are confirmatory of earlier studies which show an improvement in vaccination completion rates when SMS reminders are sent to mothers and other caregivers.

Conclusion: all of the studies reviewed were based on pilot projects. It is time, and past time, to go to scale with SMS reminders, perhaps stand alone, or as part of a larger system of electronic immunization registers. There may be potential for use of WhatsApp in dropout reduction, thus far documented only in other public health applications.

Introduction

When the Expanded Programme on Immunization was created in 1974, there were six diseases targeted for infant vaccination. Vaccinations began at birth and were completed with measles vaccine, which was typically given from 9 months of age. In the current century, most vaccination programmes vaccinate against a dozen or more childhood diseases, and many have gone over to a second year of life (2YL) delivery platform, including a second dose of measles containing vaccine given from 15 or 18 months of life. Although, by 2017, there were 167 countries implementing MCV2 in the second year of life, dropouts between the first and the second dose remained a problem (Table 1). Since measles vaccination at 9 months confers only about 85 percent protection, the failure to complete the MCV series is an important obstacle to the measles elimination goal endorsed by all six of the W.H.O. regions. Table 1 shows the heterogeneity of coverage statistics. The Republic of Rwanda already has coverage statistics consistent with interruption of measles transmission. Nigeria has coverage for all doses of all antigens which require improvement. Kenya, Senegal and Zimbabwe all show coverage and dropout figures which would benefit from reminder systems. It is vitally important, both for measles eradication and for protection against other vaccine preventable diseases, that all multi-dose vaccinations be complete and on time. A 2018 Cochrane review [1] examined evidence on reminder and recall systems for assuring completion of vaccinations from both developed and developing countries. The authors concluded that "patient reminder and recall systems, in primary care systems, are likely to be effective at improving the proportion of the target populations who receive immunizations."

Methods

The present article is an update of a 2017 article, published in this journal, on the impact of SMS reminders on child vaccination completion rates, with specific reference to sub-Saharan Africa [2]. We have followed the methodology of Manakongtreecheep, described in his article, and have included studies published since 2017 and articles from outside Africa. The present review complements a systematic review by Mekonnen and colleagues, who found from their meta-analysis that SMS reminders had a significant impact on child vaccination coverage [3]. There are two from Kenya [4, 5], two from Nigeria [6,7] and one each from Zimbabwe [8], Burkina Faso [9], Guatemala [10], China [11], Bangladesh [12], India [13] and Pakistan [14]. Neither the current study, nor the much more comprehensive Cochrane update, has looked at nationwide SMS reminder systems.

Table 1: WHO/UNICEF estimates of vaccination coverage, selected African countries, 2017

Country	DPT 1	MCV1	MCV2
Ethiopia	85	65	N/A
Kenya	93	89	35
Madagascar	80	58	N/A
Mozambique	90	85	45
Nigeria	49	42	N/A
Rwanda	99	95	95
Senegal	97	90	70
South Africa	74	66	60
Uganda	95	80	N/A
Zimbabwe	94	90	78

Source: World Health Organization Vaccine-preventable diseases: Monitoring System, 2018 Global Summary, consulted on 13 May 2019

Results

The five additional studies, summarized in Table 2, have added to our understanding of SMS messaging. The Guatemala study is cautionary: when completion rates are already very high, the marginal benefit from SMS reminders may be less than in underperforming countries.

Table 2: published findings on impact of SMS Messaging on vaccination dropouts, developing countries

Country	Author(s)	Main findings
Kenya	Gibson *et al.*	Vaccination coverage ↑ 4% with SMS, ↑8% with SMS plus conditional cash transfer
Kenya	Haji *et al*.	Dropouts were 4 % among SMS recipients, 17% among controls.
Nigeria	Brown *et al*.	Ibadan mothers willing to record their numbers at clinics for reminder/recall, in preference to home visits and Email reminders.
Nigeria	Eze, Adeleye	Coverage 8.7% higher in the intervention group; SMS reminders cheaper than house visits
Zimbabwe	Bangure *et al*.	Coverage at 14 weeks was 95% in the intervention group and 75% in the non-intervention group, $p<0.001$.
Burkina Faso	Schlumberger *et al.*	At 4 months of age, attendance for children was significantly better for children whose parents were sent SMS messages, $p<0.001$.
Guatemala	Domek *et al.*	"Both intervention and usual care participants had high rates of vaccine and visit completion, with a non- statistically significant higher percentage of children in the intervention completing both visit 2 and visit 3."
China	Chen *et al.*	"An app and text messages can be used by village doctors to improve full vaccination coverage, though no significant increase in coverage was found when assessing the effect of the app on its own."
Bangladesh	Uddin *et al.*	"Difference-in-difference estimates were +29.5% for rural intervention versus control areas and +27.1% for urban areas."
India	Seth *et al.*	"Median coverage at enrolment was 33% in all groups and increased to 41.7%, 40.1% and 50.0% by the end of the study in the control group, the group with mobile phone reminders, and the compliance-linked incentives group, respectively."
Pakistan	Kazi *et al.*	"Only children in the per protocol analyses, who received an SMS reminder for vaccine uptake at 6 weeks visit, showed a statistically significant difference (96.0% vs 86.4%)."

Note: The first six citations are from Manakongtreecheep, *op. cit*.

The China study shows an additive impact of mobile phone app and texting, compared to the impact of the mobile phone app alone. The Indian study summarized in Table 2 shows the compliance linked group achieved higher results than the SMS reminders. This confirms the results of the first Kenyan study, which also showed a positive impact of cash incentives. Both these studies raise issues about long term financial sustainability of cash incentives. The Pakistan study showed a 10 percent difference in coverage, based on the per protocol analysis, confirming the positive results of the studies reviewed in 2017. The Bangladesh study is also confirmatory of the earlier African studies, showing significant coverage improvements associated with SMS reminders.

Discussion

The studies reviewed showed a positive impact on routine vaccination coverage of SMS reminder systems. All were of pilot projects. Further work in this area is important as more countries move to a 2YL (second year of life) approach, with more demanding requirements for sustained high coverage over the first two years of life. Without improved MCV2 coverage, most developing countries (Rwanda is a remarkable exception) will continue to need measles campaigns every two or three years, with all which this implies in terms of demands on human resources at the national and subnational levels. It would be useful for governments and donors in countries with successful SMS projects to go to scale. Countries which have not yet launched SMS projects may wish to do so, especially if they have poor completion rates.

SMS reminders are but one of several approaches to vaccination reminders. The most recent Cochrane review, cited above, lists telephone calls, letters, postcards, text messages, and autodial messages as among reminder/recall methods. However, many of these rely, for example, on efficient postal systems for implementation. Some are labour intensive, whereas health workers in developing countries are often short of time. When part of a larger system including birth registration, SMS reminders have the potential to work without heavy time inputs and wherever mothers or other caregivers have access to mobile telephones. Combining SMS reminders with an electronic immunization register, as in Burkina Faso, places the SMS reminder in a larger, comprehensive health management information system. Such registers, in addition, present economic advantages in terms of savings on printing. Voice reminders, only feasible in places with stable network signals, are an alternative to SMS messaging.

Conclusion

Like its 2017 forerunner, this review covers only pilot projects, since no pilots have been scaled up. For scale-up, both management capacity and costing need careful analysis. The costs of SMS messaging and of other methods need careful assessment. Will reminders using WhatsApp, not yet well documented, emerge as a less expensive reminder method? There may be potential for use of WhatsApp, but the 303 publications listed on WhatsApp in the National Library of Medicine (NLM) database (consulted at end October 2019) cover such topics as clinical medicine and, for developing countries, such activities as bed net use and smoking cessation. So WhatsApp use for immunization remains in posse rather than in esse. As of this writing (2019), SMS messaging is certainly among the best documented and most promising technologies for improving childhood vaccination completion rates.

What is known about this topic

- No pilots review have been scaled up.

What this study adds

- SMS messaging is certainly among the best documented and most promising technologies for improving childhood vaccination completion rates.

Competing interests

The authors declare no competing interests.

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PanAfrican Medical Journal

Research

Temporal trend of measles cases and impact of vaccination on mortality in Jigawa State, Nigeria, 2013-2017: a secondary data analysis

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Guest editors: Robert Davis, James Goodson, Raoul Kamadjeu

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Abstract

Introduction: measles is a highly infectious vaccine-preventable viral disease that mostly affects children less than five years old. Jigawa located in the north-west zone has the highest burden of measles in Nigeria. We reviewed Jigawa State measles surveillance data to identify measles trend and factors associated with mortality.

Methods: we conducted a secondary data analysis of measles specific integrated disease surveillance and response data for Jigawa State from January 2013 to December 2017. We extracted relevant variables and analyzed data using descriptive statistics and logistic regression model ($\alpha = 0.05$). We estimated seasonal variation using an additive time series model.

Results: a total of 6,214 cases were recorded with 1038 (16.7%) confirmed by laboratory investigation. Only 1,185 (19.7%) had at least one dose of measles vaccine. Age specific attack and fatality rates were highest among children under the age of five years (503/100,000 and 1.8% respectively). The trend showed a decrease in number of cases across all the years. Seasonal variation existed with cases peaking in the first quarter. The likelihood of mortality associated with measles was higher among cases who had no vaccination (AOR = 4.7, 95% CI: 2.9-7.5) than those who had at least one dose of measles vaccine.

Conclusion: there was a decrease in the trend of measles cases, however, the vaccination coverage was very low in Jigawa State. Receiving at least one dose of measles vaccine reduces mortality among the cases. Strengthening routine immunization will reduce number of cases and mortality associated with the disease.

Introduction

Measles is a highly infectious vaccine-preventable viral disease characterized by a prodrome of fever, cough, coryza and conjunctivitis, followed by a maculopapular rash. The disease remains one of the leading causes of death among young children, despite the availability of a safe and effective vaccine [1]. In 2017, an estimated 110,000 measles deaths occurred globally, mostly among children under the age of five. Routine measles vaccination for children, combined with mass immunization campaigns, case-based surveillance and standard case management are key public health strategies to reduce global measles deaths [1, 2]. Measles is still common in many developing countries - particularly in parts of Africa and Asia [1]. In these countries, measles case fatality rate is estimated to be 3-5% but may reach 10-30% in cases with complications [3]. Malnutrition, poor case management, complications like pneumonia, age at infection, overcrowding and underlying immune deficiency disorders are associated with the high measles mortality rate [1, 4]. High prevalence of childhood diseases including measles constitute a challenge to mortality reduction agenda in Nigeria where the under-five mortality rate is 120/1,000 live births [5]. The burden of measles is highest in the north-western region of the country with recurrent outbreaks occurring at irregular intervals [6]. Unvaccinated children are at higher risk of the disease and its complication and Nigeria has the highest number of unvaccinated children globally [1, 7]. The WHO African Region adopted a regional measles mortality reduction goal in 2001. The recommended strategies to achieve the program goal included improved case management, achieving and maintaining ≥ 80% coverage with routine measles vaccination of infants, providing a second dose of measles vaccination through supplemental immunization activities (SIAs) and intensified measles case-based surveillance [8]. In 2011, the Member States of the WHO African Region established a goal to achieve measles elimination by 2020 with the following targets: ≥95% coverage with the first dose of measles-containing vaccine (MCV1) at national and district levels, ≥ 95 SIA coverage in every district, and confirmed measles incidence of < 1 per million population in all countries, and attaining the targets for the two principal surveillance performance monitoring indicators which are: ≥ 80% of districts with ≥ 1 suspected measles case with blood specimen reported per year and a non-measles febrile rash illness rate of ≥ 2 per 100,000 population [9]. With the implementation of these recommended strategies, the African Region of the WHO has achieved 85% reduction in estimated measles deaths by the end of 2015 as compared to mortality estimates in 2000 [10]. Accelerated measles control activities started in Nigeria in 2006 with the conduct of the first catch-up measles campaign. Since then, nationwide mass vaccination campaigns were conducted every two years in the country targeting children aged 9-59 months. Consequently, the national measles vaccination coverage increased from 33% in 2006 to 42% in 2017 [5] and a significant decline in measles incidence was observed following the initial measles catch-up campaign, but later the country experienced resurgence [11]. Contribution to high prevalence of measles cases varied widely across the 36 states in Nigeria including the Federal Capital Territory. Jigawa State is among the states with highest burden of measles in Nigeria which can be attributed to the very low measles vaccination coverage of 10.4% [5]. Studies have shown that a 95% measles vaccination coverage is required to interrupt measles transmission [2, 12]. Consequently, this low coverage drives recurrent outbreaks of measles in the state. Thus, analysis of the measles surveillance data might generate information that will help in prevention and control of the disease. We therefore conducted this analysis to determine the magnitude of measles in Jigawa State, identify its trend and determine the factors associated with mortality.

Methods

Study design

This study is a cross-sectional study of Jigawa State measles specific Integrated Disease Surveillance and Response (IDRS) data from 2013 to 2017.

Study setting

Jigawa State is in the north-western part of Nigeria and has twenty-seven local government areas. It lies between latitude 11°N and 13°N and longitude 8°E and 10.15°E and shares common national boundaries with Kano to the west, Katsina to the north, Yobe to the east and Bauchi to the south-east and an international border with Niger republic. It covers an area of 22,410sq.km with a population of 5,624,614 of which 20.0% are children aged 5 years and below (2015 projected figure from 2006 census). There are two seasons in a year, namely; rainy and dry seasons. The rainy season starts from April to October while the dry season covers the period of November to March. Measles transmission occurs throughout the year but peaks in the dry season.

Data source

IDSR weekly epidemiological data for the year 2013 to 2017 were obtained from Epidemiology Unit of Jigawa State Ministry of Health. The base population figures for the estimation of attack rates were obtained through the projection of 2006 census figures for Jigawa state using the 2.9% annual growth rate.

Measles surveillance

Measles surveillance in Jigawa State is based on the IDSR strategy which is a reporting platform for all priority diseases. A suspected case of measles is any person with fever and maculopapular (non-vesicular) generalized rash and cough, coryza or conjunctivitis or any person in whom a clinician suspects measles. For every suspected measles case, a case investigation form was completed, and a blood specimen collected and sent to the national reference laboratory for testing for measles-specific immunoglobulin M (IgM) antibody. The designated local government disease surveillance and notification officer is responsible for the completion of the form and transportation of the specimen. Suspected measles cases are confirmed by laboratory testing, epidemiologic linkage to a confirmed case, or by clinical criteria. A laboratory confirmed case of measles was a suspected case with serological confirmation of measles specific IgM antibody in a person who had not received measles vaccination within 30 days before the specimen collection. Epidemiologically linked case was a suspected case from whom blood specimen was not collected and is linked in person, place and time to a laboratory confirmed case. While a measles associated death is defined as any death from illness in a confirmed case of measles within 1month after the onset of rash. Completed individual case investigation forms and laboratory results were entered into an Excel database. Information flows from the health facilities, through the ward focal persons to the local government disease surveillance and notification officers (DSNOs), to the state DSNO and State Epidemiologist, and then collated by the Nigeria Center for Disease Control (NCDC). Feedback goes through the opposite direction.

Data management

Relevant data variables were sorted, extracted, and cleaned from the IDSR line list. This included age, sex, location, number of cases, date of onset of rash, vaccine doses, laboratory results and outcome. The outcome variable was disease outcome (alive/dead) while the explanatory variables were age, sex, location and vaccination status. Data were analyzed using Microsoft Excel 2016 and Epi-Info7. Frequencies and proportions were used to summarize the data while multivariate analysis was used to examine the relationship between the explanatory variables and disease outcome. The monthly reported cases of measles in a specific year was grouped into 3 months. The data were aggregated in 3-months as 1st quarter (January to March), 2nd quarter (April-June), 3rd quarter (July-September), 4th quarter (November-December) from 2013 to 2017. We decomposed the data and used the estimates of the quarters to describe the time series. This was done by computing the 3-quarter moving average in order to eliminate seasonal variations and irregular variations from the data. The number of cases in a quarter was represented by Yt and the trend line (Tt) was obtained using the seasonal variation method [13]:

$$T_t = \frac{Y_{t-1} + Y_t + Y_{t+1}}{3}$$

In order to obtain the seasonal variation in the data, the multiplicative model was used based on the pattern exhibited by the observed data, and this is given by [13]:

$$\text{Seasonal variation (SV)} = \frac{Y_t}{T_t} * 100$$

The data was deseasonalized to obtain the variation in each quarter of the year as [13]:

$$\text{Quarterly variation } (\text{QV}_\text{i}) = \frac{\sum_{i=1}^{L} SV_i}{L} - \Delta SV\left(\frac{\sum_{i=1}^{n-m} SV}{4}\right)$$

Where ΔSV is the excess of the sum of all the seasonal variations and L is the number of quarters that are present in the seasonality of a given year. Table 1 shows the procedures involved in the estimation of seasonal variation. In Figure 1, the monthly pattern was merged into quarter on yearly basis and smoothed using a time series approach to obtain the trend.

Ethical consideration

Approval to use the surveillance data was sought from and granted by Public Health Department of the Jigawa State Ministry of Health Ministry.

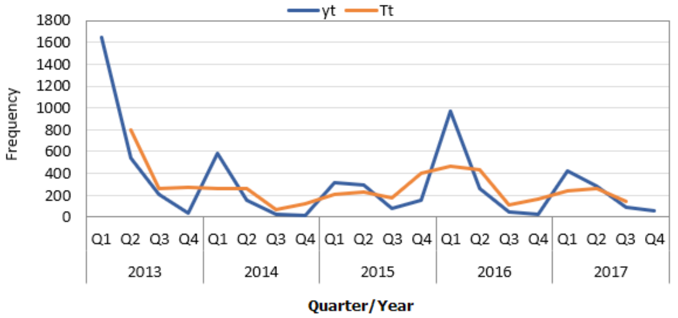

Figure 1: frequency distribution of quarterly reported cases (yt) of measles and the trend line, Jigawa State, Nigeria, 2013-2017

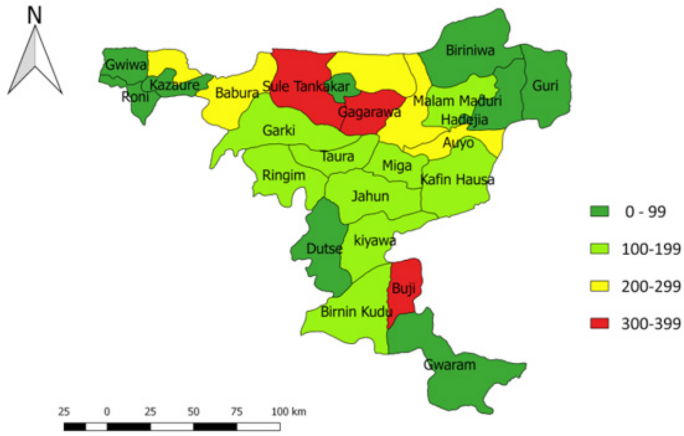

Figure 2: measles attack rate by local government areas in Jigawa State, 2013 to 2017

Table 1: estimation of quarterly trend of measles cases in Jigawa State, 2013-2017

Year	Quarter	Actual (Yt)	3-Qtr Moving Total	Trend (Tt)	Seasonal Variation SV= (Yt/Tt)*100
2013	Q1	1646	-	-	-
	Q2	545	2400	800.00	68.13
	Q3	209	788	262.67	79.57
	Q4	34	826	275.33	12.35
2014	Q1	583	775	258.33	225.68
	Q2	158	770	256.67	61.56
	Q3	29	204	68.00	42.65
	Q4	17	365	121.67	13.97
2015	Q1	319	630	210.00	151.90
	Q2	294	688	229.33	128.20
	Q3	75	529	176.33	42.53
	Q4	160	1209	403.00	39.70
2016	Q1	974	1399	466.33	208.86
	Q2	265	1285	428.33	61.87
	Q3	46	333	111.00	41.44
	Q4	22	490	163.33	13.47
2017	Q1	422	722	240.67	175.35
	Q2	278	785	261.67	106.24
	Q3	85	416	138.67	61.30
	Q4	53	-	-	

Table 2: distribution of measles cases by selected demographic and health characteristics in Jigawa State, 2013-2017

Characteristics	Frequency (n= 6214)	Percentage (%)
Age group		
<5	4556	73.3
5-9	1469	23.6
10-14	132	2.1
15-19	38	0.6
≥20	19	0.3
Sex		
Male	3247	52.3
Female	2967	47.7
Vaccination status		
None	4974	80.0
Had at least one dose	1190	19.2
Unknown	50	0.8
Outcome status		
Alive	5936	95.5
Dead	106	1.7
Unknown	172	2.8

To protect patient confidentiality, personal information was de-identified during extraction and data analysis.

Table 3: age specific attack and case fatality rates of measles cases in Jigawa State, 2013-2017

Age group (Years)	Case (%)	Deaths (%)	ASCFR*	Estimated age group pop†	ASAR#/10,000 pop†
<5	4556 (73.4)	84 (79.3)	1.8	905597	50.3
5-9	1469 (23.6)	21 (19.8)	1.4	802035	18.3
10-14	132 (2.1)	1 (0.9)	0.8	646694	2.00
15-19	38 (0.6)	0	-	597165	0.60
≥20	19 (0.3)	0	-	2676828	0.01
Total	6214 (100)	106 (100)	1.7	5628319	11.0

† population; #age specific attack rate; *age-specific case fatality rate

Results

There were 3,247 (52.3%) males and the most affected age group was 1-5 years (73.3%). Only 1,190 (19.2%) had at least one dose of measles vaccine (Table 2). Buji (284/100,000) local government area had the highest attack rate while Gumel (16/100,000) had the least attack rate reported for the five-year period (Figure 2). The overall case fatality rate (CFR) was 1.7%. The age-specific attack and case fatality rates (50.3/10,000 and 1.8% respectively) were highest among those less than five years (Table 3).

A downward trend of the measles cases was observed throughout the years. There was a slight variation in the cases with only 6.2% of the variation being explained by month (Figure 3). In Table 4, the data show the adjusted seasonal variation to establish the exact variation. The data indicates that the highest cases of measles were observed in the first quarter of the year and this falls consistently through the remaining quarters of the year. The seasonal variation was found to be highest in the first quarter across all the years and fells consistently in the subsequent quarters. The adjusted seasonal variation was 1.8, 0.7, 0.4 and 0.1 for the 1st, 2nd, 3rd and 4th quarter respectively. Compared to those aged 5 years and above, those less than 5 years were more likely to die of measles (AOR= 2.0, 95% CI: 1.1-3.6). Similarly, males were more likely to die compared to their female counterparts (AOR= 1.7, 95% CI: 1.1-2.7). Also, those who were never vaccinated were more likely to die compared to those who had had at least one dose of the measles vaccine (AOR = 4.7, 95% CI: 2.9-7.5) (Table 5).

Table 4: deseasonalization of seasonal variation of measles cases and estimation of quarterly variation in Jigawa State, 2013-2017

Year	**Quarter**					
	1	2	3	4		
2013	-	68.1	79.6	12.4		
2014	225.7	61.6	42.7	14.0		
2015	151.9	128.2	42.5	39.7		
2016	208.9	61.9	41.4	13.5		
2017	175.4	106.2	61.3	-		
Total	761.8	426.0	267.5	79.5		
Average	**190.448**	**85.2**	**53.5**	**19.9**	349.0	12.3
	12.3	12.3	12.3	12.3		
Estimated quarterly variation	**1.8**	**0.7**	**0.4**	**0.1**		

Table 5: factors associated with measles mortality in Jigawa State, 2013-2017

Exposure factors	Dead (%) (n=86)	Alive (%) (n=5959)	OR (95% CI)	AOR (95% CI)
Age				
<5 years	72 (1.6)	4386 (98.4)	1.8 (1.0-3.3)	
≥5 years	14 (0.9)	1573 (99.1)		2.0 (1.1-3.6)*
Sex				
Male	56 (1.8)	3109 (98.2)	1.7 (1.1-2.7)	
Female		2850 (99.0)		1.7 (1.1-2.7)*
Vaccination status	30 (1.0)			
Unvaccinated	62 (2.8)	2160 (97.2)	4.5 (2.8-7.3)	
Vaccinated	24 (0.6)	3799 (99.4)		4.7 (2.9-7.5)*

****Significant at 5.0%***

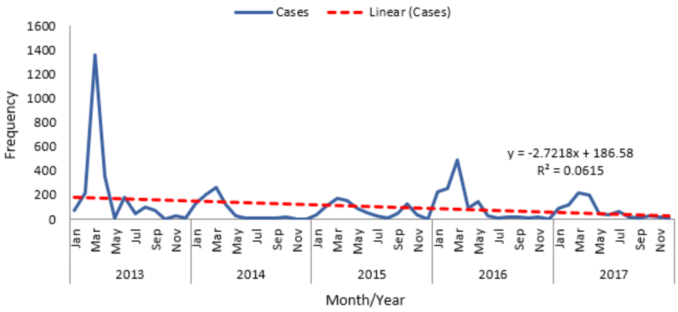

Figure 3: trend of measles cases in Jigawa State, 2013-2017

Discussion

Our study found that the overall CFR found in Jigawa State was lower than the country's CFR of 0.6% [6]. The age-specific fatality rate was higher among children under the age of five years with no mortality recorded in those aged 15 years and above. Likewise, the age-specific attack rate was highest among those under five children and decreased as age advances, with the lowest rate recorded among those twenty years and above. This might be explained by the lifetime immunity conferred by measles. Most of the individuals aged 5 years and above might have been exposed to the antigen either through vaccination or measles infection before that age and have acquired immunity [14]. Sule Tankarkar, Gagarawa, Kaugama, Yankwashi and Buji LGAs had the highest measles attack rates within the five-year period under review. These LGAs are border towns with hard-to-reach settlements and majority of the inhabitants are herds men who are seasonal migrants. This might explain the low immunization coverage in the LGAs. High immunization coverage and low measles attack rate found in Dutse, Kazaure, Hadejia and Gumel LGAs could be attributed to the metropolitan nature of the LGAs and emirates being situated in the area since these traditional institutions play a major role in immunization uptake. The other LGAs with attack rates of less than 100/100,000 are contiguous to these LGAs and have high immunization coverages.

The National Measles Surveillance and Outbreak Response Guidelines specified all suspected measles cases are to be confirmed by laboratory testing and thus underestimates the burden of the disease in the state. However, our study revealed that only 16.7% of all the reported measles cases were tested. This reflects that laboratory confirmation of measles is very low in Jigawa State. Similar findings were reported in Nigeria, Uganda and Ethiopia [6, 15-17]. The finding of low vaccination coverage among cases was consistent with studies in other parts of the WHO Africa region which revealed low vaccination coverage among measles cases [6, 18-20].

Our study revealed high number of measles cases in the state in 2013 following which there was a supplemental immunization activity (SIA), hence the fall in the number of cases in 2014. Ironically, there was another SIA conducted in 2015, however, there was increase in the number of measles cases in 2016. This might be due to vaccine failure or failure to achieve herd immunity. Similar findings were reported in other parts of Nigeria, Kenya and Congo where outbreaks occurred due to suboptimal measles vaccination coverage [19, 21-23]. Our model depicted a decreasing trend over the years which is in line with the goal of measles mortality reduction globally. Similar finding was reported in the country [6]. However, a contrasting finding which shows an upward trend was reported in a study in south-western Nigeria [21]. This might be due to the support given to the northern part of the country by development partners in areas of immunization. In addition, we observed annual seasonality of measles, with an increase in the number of cases in the first quarter. Similar patterns have been reported in separate studies conducted in other parts of Nigeria [6, 18, 21].

Furthermore, our study revealed that age less than five years, male sex and failure to receive measles vaccine were associated with measles mortality. Different reports have shown that majority of measles deaths occur in children under the age of five years [1, 24]. As regards male sex having higher mortality than females, this finding might be attributed to the health care seeking behaviors of mothers in the country as it was reported that mothers tend to seek advice/care for their female children than the male counterparts [5].

Our study had some limitations. The data was not collected primarily for this purpose and was incomplete. Thus, only cases with complete information on at least 3 variables were included in the study. Also, not all suspected measles cases get notified and reported through the surveillance system. This may have under-estimated the number of measles cases and the vaccination coverage reported.

Conclusion

Measles remains a public health concern in Jigawa State. Case-based surveillance provided an insight into understanding the epidemiology of measles infection in Jigawa State. There was poor vaccination coverage among cases and laboratory investigation was low. Compared to those who had received at least one dose of measles vaccine, those who had never been vaccinated were more likely to die. The government of Nigeria through NCDC should strengthen laboratory testing capacity and Jigawa state government should revamp routine immunization and ensure every eligible child is reached during Routine Immunization and Supplemental Immunization Activities to build herd immunity and interrupt measles transmission in Jigawa state.

What is known about this topic

- Measles is a highly contagious vaccine preventable viral disease targeted for elimination by the year 2020;
- Despite decrease in global measles deaths, measles is still common in many developing countries, particularly in Africa and Asia.

What this study adds

- There is a decreasing trend and seasonal variation in measles cases in Jigawa State, Nigeria;
- Measles mortality was associated with age, sex and vaccination status.

Competing interests

The authors declare no competing interests.

Authors' contributions

Conceptualization and designing the study was done by Aisha Sani Faruk. Acquisition of data was done by Samaila Mamuda. Data analysis and interpretation was done by Aisha Sani Faruk and Adebowale Ayo Stephen. Drafting the manuscript was done by Aisha Sani Faruk. Editing the manuscript was done by Adebowale Ayo Stephen, Olawunmi Adeoye and Muhammad Shakir Balogun. Critical revision of the manuscript was done by Lydia Taiwo and Ndadilnasiya Endie Waziri. All authors have read and approved the final version of the manuscript.

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PanAfrican Medical Journal

Review

Global trends in measles publications

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Abstract

Introduction: beginning with the 1960s, this review analyzes trends in publications on measles indexed by the National Library of Medicine from January 1960 to mid-2018. It notes both the growth in numbers of published papers, and the increasing number and proportion of publications, in the current century, of articles on such items as costing, measles elimination, and determinants of coverage.

Methods: a two-person team extracted from the National Library of Medicine (NLM) homepage all citations on measles beginning in 1960 and continuing through mid-2018. These were then classified both by overall number and by subject matter, with tabular summaries of both by decade and by subject matter. The tabular presentation forms the basis for a discussion of the ten most frequently cited subjects, and publication trends, with a special emphasis on the current century.

Results: as in the past, the most often currently published items have been on coverage and its determinants, measles elimination, outbreak reports, SSPE, and SIAs. The putative relationship between vaccination and autism saw a spurt of articles in the 1990s, rapidly declining after the IOM report rejecting the causative hypothesis.

Conclusion: there is a discussion on the sequencing of polio and measles eradication, the former unlikely before 2022, and an examination of likely research priorities as the world moves from measles control to measles eradication. There is a key role for social science in combatting vaccination reticence. The role of technical innovations, such as micropatch vaccination, is discussed.

Introduction

The licensing of the monovalent measles vaccine (now joined by combination vaccines, including MR and MMR) led, in the developing countries, to its inclusion, in the 1960s, in routine immunization programs. The 1974 creation of the Expanded Programme on Immunization extended the reach of measles immunization to the developing world. The growth in program development has been matched by a concomitant growth in published articles on measles (Table 1). We sought, in the present article, to review both major topics of interests to authors, decade by decade, and trends in publishing (Table 2).

Table 1: published citations on measles by decade

	1960-1969	1970-1979	1980-1989	1990-1999	2000-2009	2010 – mid-2018
Number of Articles Published	2434	3629	3907	4894	5455	5762

Source: www.pubmed.gov, retrieved on 1 July 2018

Methods

This paper presents findings on trends in measles publications using decade-by-decade frequency distribution analyses of key topics addressed in the published literature from 1960 to mid-2018. To obtain the frequency analyses presented, articles indexed as measles by the National Library of Medicine database were divided by decade from the 1960s to the 2000s. In order to capture current trends in publication, articles published from January 1st, 2010 to June 30th, 2018 were also examined as a partially-completed decade.

Table 2: top 12 most-published topics of the present decade, with ranking in prior decades

	1960-69	1970-79	1980-89	1990-99	2000-09	2010-18
Rank						
1	Subacute sclerosing panencephalitis, SSPE, 26	Measles epidemiology, 34	Outbreak reports, 41	Vaccination coverage, including determinants, 121	Autism, 166	Vaccination coverage, including determinants, 266
2	Measles epidemiology, 21	SSPE, 21	Measles elimination, 39	Outbreak reports, 82	Vaccination coverage, including determinants, 164	Measles elimination, 220
3	Measles eradication, 19	Supplementary Immunization Activities, 19	Measles epidemiology, 34	Measles elimination, 67	Outbreak reports, 153	Outbreak reports, 218
4	Supplementary Immunization Activities, 11	Outbreak reports, 13	Measles eradication, 31	Supplementary immunization activities, 62	Measles elimination, 120	SSPE, 146
5	Progress in measles control & elimination, 5	Measles eradication, 11	Studies of costing and economics, 23	Measles epidemiology, 54	Supplementary Immunization Activities, 70	Supplementary Immunization Activities, 84
6	Routine immunization, 4	Studies of costing and economics, 11	Vaccination coverage, including determinants 22	Measles eradication, 47	Progress in measles control and elimination, 62	Progress in measles control and elimination, 77
7	Measles elimination, 2	Mathematical modeling of measles, 4	SSPE, 17	Mathematical modeling of measles, 41	Measles epidemiology, 54	Mathematical modeling of measles, 74
8	Outbreak reports, 2	Progress in measles control and elimination, 3	Mathematical modeling of measles, 13	Autism, 32	Mathematical modeling of measles, 48	Routine immunization, 72
9	Studies of costing and economics, 1	Measles elimination, 3	Supplementary immunization activities, 12	Studies of costing and economics, 24	Measles eradication, 36	Measles epidemiology, 68
10	Vaccination coverage, including determinants, 0	Routine immunization, 3	Progress in measles control and elimination, 8	Progress in measles control and elimination, 22	Studies of costing and economics, 30	Studies of costing and economics, 67
11	Mathematical modeling of measles, 0	Vaccination coverage, including determinants, 1	Routine immunization, 7	Routine immunization, 12	Routine immunization, 29	autism, 50
12	Autism, 0	Autism, 0	Autism, 0	SSPE, 12	SSPE, 9	Measles eradication, 50

Citation counts for each decade are in commas after the name of the topic.

A list of 98 unique keywords was developed, and keywords were grouped into 61 relevant topics (e.g., the terms supplementary, supplemental, and campaign were used to identify articles discussing supplementary immunization activities). Counts were then taken of the number of articles per decade that contained each keyword in their titles. Only articles that employed the pertinent definition of a keyword were included. Topic counts were subsequently obtained by summing the count of each keyword assigned to a topic, taking into consideration any duplicates that might occur from a title containing multiple keywords assigned to the same topic.

Once this analysis was completed, the top twelve most frequently published topics of the present decade were identified. These topics were tracked and arranged in a data table that ranks their frequency in each decade (Table 2). A discussion follows on trends in published discussion of these twelve topics.

The table above shows the number of citations by decade. Table 2, more detailed, shows the frequency distribution of topics by decade.

Limitations/caveats

While this paper presents trends in publications on measles literature, it includes only publications from the National Library of Medicine database; gray literature and other databases were not analyzed. As a result, this paper cannot capture trends in all measles literature (whether published or unpublished), nor can it definitively reveal trends across all instances of published measles literature. At times, topic analyses were limited by this; thus, some references that were not identified through the search method described above were included in topic analyses.

In its exploration of trends on publications in measles literature, this paper used a Boolean search of keywords in titles of articles related to measles. As a result, published papers that did not list keywords directly in their titles were excluded from topic counts, even if the keywords were featured centrally in their analyses. Guidelines were created to establish when the context of a keyword was grounds for inclusion in a topic count. Each keyword was examined by a single reviewer to increase consistency in inclusion. Despite these measures, some amount of error in interpretation and subjectivity likely affected topic counts..

Results

Topic analyses

Vaccination coverage, including determinants: the importance of coverage

In recent years, published citations on measles vaccination coverage have outnumbered those on all other topics, even measles elimination, with 266 citations on coverage from 2010 to mid-2018 in the indexed measles literature.

High vaccination coverage, with one dose or (more recently) two doses of measles containing vaccine, forms the basis for all progress in measles vaccination and for the eventual eradication of the disease. Calculating coverage permits governments and partners to track progress towards meeting the targets of the *Global Vaccine Action Plan 2011-2020* [1] as well as the *Global Measles and Rubella Strategic Plan* [2].

A variety of methods for gauging vaccination coverage have superseded the classic 30 x 7 cluster coverage methodology, which was used from the 1970s well into the present century [3]. The revised WHO guidelines, published in June 2018, enable survey planners more flexibility in making adjustments for confidence intervals and other survey parameters [4].

The 1998 creation of the joint reporting form, now submitted by 192 governments, has permitted WHO and UNICEF to publish, in the *Weekly Epidemiological Record and the Morbidity and Mortality Weekly Report,* increasingly refined estimates of coverage at national, regional and global levels. The article Global Routine Vaccination Coverage, 2016, published in the *MMWR,* provides the most recent published WHO/UNICEF estimates of coverage by antigen and dose. In the words of the article,

"MCV1 coverage in 2016 ranged from 72% in the African Region to 96% in the Western Pacific Region and from 20% to 99% by country. During 2015-2016, MCV1 coverage has remained stable or increased in all regions. Globally, 123 (63%) countries achieved the GVAP 2020 target of 90% national MCV1 coverage [5].

The importance of MCV2 vaccination is that, without it, there is a failure rate of 15 percent among those vaccinated once at 9 months of age. For 2016, according to the *MMWR,*

"MCV2 coverage by WHO region varied from 24% (African Region) to 93% (Western Pacific Region), including countries that have not yet introduced MCV2. In four of six WHO regions (African, Region of the Americas, Eastern Mediterranean, and South-East Asia), MCV2 coverage increased in 2016 compared with 2015, because of both an increase in coverage in multiple countries, as well as an increase in the number of countries introducing MCV2. Globally, MCV1 coverage was 85% and MCV2 coverage was 64% in 2016 (estimated dropout = 21%) [5].

These data show high coverage in some regions, but by no means all. They have led to much work, and to much research work, seeking ways to raise routine vaccination coverage.

Of the six WHO regions, the African region, with 47 member states, lags the others in coverage. However, a 2007 publication noted incremental improvements in vaccination coverage in the African region, largely financed, in low income countries, from external sources [6]. In the current decade, coverage in most African countries has plateaued.

Research and publication on coverage determinants

Many authors have analyzed the determinants of vaccination coverage with a view to increasing coverage. Cochrane reviews and other systematic reviews have sought to summarize the voluminous existing literature on methods for improving routine vaccination coverage [7, 8].

Of course, no efforts at improving coverage can be measured without good data. The early decades of EPI, which was launched in 1974, have few citations on coverage, perhaps because reliable data were generally lacking in the early years of the programme.

By contrast, the current century has been rich in publications on coverage and coverage innovations. For routine coverage, national vaccination registers have been established and documented in Brazil, Israel and Norway. These registers are useful in tracking progress of individual patients in a highly mobile population and a check on the accuracy of parent retained vaccination records. As of this writing, in late 2018, electronic immunization registers are being evaluated in, among other countries, Tanzania and Zambia.

Routine reporting, whether in traditional or electronic form, cannot be accepted without surveys. Most developing countries are the subject of periodic national surveys, such as Demographic and Health Surveys, which serve as a check against administrative coverage estimates, i.e., those estimates which are based on the application of doses given to best demographic estimates of the target population. In addition to the DHS methodologies, the current century has brought about application to coverage monitoring of such methods as LQAS (lot quality assurance surveys), independent monitoring, and cluster coverage surveys, for which the methodology was recently revised by WHO [4, 9].

In the current century, the data quality audit method (DQA) and the less costly data quality self-audit (DQS) have permitted GAVI and governments correctly to gauge the extent to which national administrative figures correspond to the data gathered at the field level [10].

In some countries, national coverage surveys are done in tandem with EPI programme reviews, or preceding them, so that the survey data can feed into recommended corrective measures.

The present century has also seen the introduction of equity analysis in order to ascertain coverage by socio-economic status. It has seen publications on such topics as *"Monitoring equity in vaccination coverage: A systematic analysis of demographic and health surveys from 45 Gavi-supported countries [11]."*

With coverage data now disaggregated both by geography and by socio-economic status, planners can take corrective measures to raise coverage in underserved localities and in underserved socio-economic groups.

Although this century has seen methodological advances in coverage analysis, there is one area which remains under-researched: the coverage status of adults. The following citation is an exception to the general rule of analyzing mainly the coverage status of infants and children: *Why are young adults affected? Estimating measles vaccination coverage in 20-34 year old Germans in order to verify progress towards measles elimination [12]."*

Especially in Europe, where adult measles is emerging as a potential obstacle to regional elimination, new methods, or adaptations of old ones, may be necessary as a step towards elimination.

Measles elimination: elimination and eradication of measles disease

The related topics of elimination and eradication have been among the most discussed in the measles literature. Discussions of elimination and eradication started in the '60s, soon after the 1963 licensing of the vaccine. From 21 citations on these topics in the '60s, citations have soared to 270 in the period since 2010.

In discussions on these related topics, it is well to remember that eradication refers to interruption of transmission on a global scale, with permanent reduction of incidence to zero. Elimination, by contrast, refers to interruption of transmission at the regional or national levels, with the possibility of virus reintroduction from endemic areas [13].

The 20th century

Although David Morley asked as early as 1969 whether measles eradication was possible [14], it was only in 1982 that Hopkins and colleagues published *The Case for Global Measles Eradication",* the first formal advocacy article for global eradication to appear in the indexed literature [15].

In the early decades of measles vaccination, the world was focused on the eradication of smallpox, with eradication declared by the World Health Assembly only in 1980. Resources were not then available for measles eradication. With the 1980 declaration of smallpox eradication, some authors turned to the question *of What next? in terms of feasibility.* The benchmarks of eradicability were such criteria as the absence of a non-human reservoir, the availability of safe and effective vaccines, the presence of political will and financial support, and adequate surveillance and laboratory resources to track progress towards eradication.

The 1980s saw many articles from North America and Europe (especially Czechoslovakia and the Scandinavian countries) on national elimination efforts. Starting in the 1990s, the Pan American Health Organization ran a series of articles, especially in its *EPI Newsletter,* on national elimination efforts in Latin America, and on PAHO/CDC partnership for regional elimination. In the 1990s, PAHO´s *EPI Newsletter* published 38 articles on measles elimination and related topics.

Broadly speaking, the 20th century debates centered on whether measles eradication was feasible. The 21st century debates, noting the elimination of measles from the Americas, have focused on what preconditions must be met before the virus can be cleared from all six WHO regions.

The 21st century

EPI marked four milestones about the turn of the century: the 1998 creation of the Joint Reporting Form, a first step in creating uniform databases shared by W.H.O. and UNICEF; the 2001 creation of the Measles Initiative (now the Measles and Rubella Initiative); the 2002 elimination of measles from the Americas; and the creation, in the new century, of the Global Measles Laboratory Network, an indispensable adjunct to case-based measles surveillance. In the new century, there have been dozens of articles on the status of national and regional elimination efforts, especially from the Western Pacific, the European Region, and the Region of the Americas.

In addition to these milestones, the UN Millennium Development Goal 4 called for steep declines in under-five mortality by 2015 in comparison to 1995 baselines. MDG4 focused attention on measles mortality reduction as a major tool in reaching under-five mortality reduction goals [16].

The Junior Research Fellowship (JRF), which led to improved reporting on coverage and incidence, was a move in the right direction. So, too, was the creation of the Measles Initiative (now the Measles & Rubella Initiative), an international alliance to move forward the measles agenda. However, it was the clearance of measles from the western hemisphere, proof of concept on a continental scale, which lent credibility to the arguments of the eradication advocates. After 2002, published discussions on measles eradication shifted from "whether" to "how." In particular, certain authors laid down prerequisites for the commitment to a global eradication effort, including Heymann and colleagues. Christie and Gay rejected the view that high routine immunization be a prerequisite for measles campaigns or a measles eradication goal [17].

By the year 2000, a group of Center for disease control (CDC) authors was ready to reaffirm the case made by Hopkins and colleagues in 1982. Their reasoning, which reflects that of most eradication advocates, is summarized in their abstract:

Measles eradication would avert the current annual 1 million deaths and save the $1.5 billion in treatment and prevention costs due to measles in perpetuity. The authors evaluate the biological feasibility of eradicating measles according to 4 criteria: (1) the role of humans in maintaining transmission, (2) the availability of accurate diagnostic tests, (3) the existence of effective vaccines, and (4) the need to demonstrate elimination of measles from a large geographic area. Recent successes in interrupting measles transmission in the United States, most other countries in the Western Hemisphere, and selected countries in other regions provide evidence for the feasibility of global eradication. Potential impediments to eradication include (1) lack of political will in some industrialized countries, (2) transmission among adults, (3) increasing urbanization and population density, (4) the HIV epidemic, (5) waning immunity and the possibility of transmission from subclinical cases, and (6) risk of unsafe injections [18].

The support structures for global eradication grew in the current century. Featherstone and colleagues wrote in 2003 on the development of the Global Measles Laboratory Network (GMLN), modelled on the global polio lab network [19].

The GMLN has served, in the current century, to complement case-based surveillance of measles and will serve, in future years, to assist in documenting measles elimination. Both case-based surveillance and the GMLN are essential complements to global eradication.

In the new century, articles appeared on such topics as Future Savings from Measles Eradication in Industrialized Countries [20]. Since measles is no longer a major cause of death in the developed world, such articles buttress arguments in favor of co-financing global eradication on the grounds of self-interest. More recently, Durrheim and Crowcroft have written on "The price of delaying measles eradication," a price already being paid by the countries of the Americas, which must finance sustained regional elimination while waiting for global eradication [21]. These authors noted especially the problem of measles in those aged 15 years and over, a problem which will grow with each passing year as eradication is delayed.

In a widely quoted call to Go Big and Go Fast, S. B. Omer and colleagues noted the build-up of parental vaccine refusals amid declining incidence [22]. They stated that "If a disease such as measles is considered a priority by the global public health community, human and financial resources should be committed up front to a full-scale eradication initiative, conducted with a sense of urgency. If we don't 'go big and go fast,´ we may have to spend a prolonged period on eradication efforts with a diminished likelihood of success."

The debate between integrated and vertical approaches to measles eradication has led to a 2017 call by Goodson and colleagues for a "diagonal approach," with a better balance of integrated and mass campaign approaches than seen in GPEI [23].

In a recent review [24], Hinman listed the following issues in regard to measles: 1) Failure to meet Global Vaccine Action Plan (GVAP) goals; 2) Incomplete implementation of the Global Measles and Rubella Strategic Plan 2012-2020; 3) The GPEI transition, which presents both threats and opportunities; 4) GAVI transition/graduation - many of the same countries affected by GPEI transition are also going through transition/graduation from GAVI support, which entails gradual increases in country co-financing of vaccines up to fully self-financing; 5) Donor fatigue - we are now 17?years late in delivering on polio eradication and donors are increasingly vocal about wanting GPEI to complete so they can address other issues. Many are not enthusiastic about another eradication initiative; 6) Increase in nationalism/isolationism leading to reduced interest in many countries to support issues viewed as primarily affecting developing countries; 7) Need to integrate services - there is now less enthusiasm for categorical programmes and increasing demand for integrated health system development/strengthening.

Midterm review

The most significant recent publication on eradication is the midterm review of the Measles and Rubella Global Strategic Plan, by Orenstein and colleagues, published in 2018 in Vaccine [25]. Key highlights from their review: 1) Measles eradication is the ultimate goal but it is premature to set a date for its accomplishment. Existing regional elimination goals should be vigorously pursued to enable setting a global target by 2020. 2) The basic strategic approaches articulated in the Global Measles and Rubella Strategic Plan 2012-2020 are valid to achieve the goals but have not been fully implemented (or not appropriately adapted to local situations). 3) The report recommends a shift from primary reliance on supplementary immunization activities (SIAs) to assure two doses of measles-containing vaccine (MCV) are delivered to the target population to primary reliance on ongoing services to assure administration of two doses of MCV. Regular high quality SIAs will still be necessary while ongoing services are being strengthened. 4) The report recommends a shift from primary reliance on coverage to measure progress to incorporating disease incidence as a major indicator. 5) The report recommends that the measles/rubella vaccination program be considered an indicator for the quality of the overall immunization program and that measles/rubella incidence and measles and rubella vaccination coverage be considered as primary indicators of immunization program performance. 6) Polio transition presents both risks and opportunities: risks should be minimized and opportunities maximized. 7) A school entry immunization check could contribute significantly to strengthening overall immunization services with assurance that recommended doses of measles and rubella vaccines as well as other vaccines have been delivered and providing those vaccines at that time if the child is un- or undervaccinated. 8) Program decisions should increasingly be based on good quality data and appropriate analysis. 9) The incorporation of rubella vaccination into the immunization program needs to be accelerated - it should be accorded equivalent emphasis as measles. 10) Outbreak investigation and response are critical but the most important thing is to prevent outbreaks.

The elephant in the room of measles eradication

The year 2000 marked the target year for polio eradication, transmission of which persists as of this writing (2018) in three endemic countries (Afghanistan, Pakistan, and Nigeria). The tardy eradication of polio from the world has placed on hold early efforts to shift gears towards measles eradication, since the same governments and donors financing GPEI could not be expected simultaneously to launch a global push for measles eradication. As of 2018, GPEI has set a new target year of 2022 for completing its work. Only after 2022 is it likely that the global community can turn its undivided attention towards eradication of measles or measles and rubella.

The twin problems of increasing measles incidence in adults and increasing vaccine hesitancy amid declining childhood incidence argue in favor of a brief, highly financed push, lasting years rather than decades. This is the "big and fast" approach, in the words of Omer and colleagues [22].

Measles epidemiology, surveillance, and outbreak reports

The related areas of epidemiology, surveillance and measles outbreak investigation have all figured in the medical literature published since the '60s. Measles epidemiology, mostly descriptive, has figured in the literature since the '60s. Remarkably, surveillance and outbreak investigation articles appeared but rarely in the published literature on measles in the decade after the 1963 licensing of the vaccine.

In the 1970s, articles began to appear, especially from North America and the Soviet Union, on outbreak investigations. That decade also saw the appearance of articles on the seroepidemiology of measles. A growing number of authors now advocated for community serosurveys as a tool for planning the age range for measles campaigns [26]. The use of oral fluids has figured in recent literature [27].

It was perhaps the case investigations of highly vaccinated populations that led to the US government´s decision in favor of a two-dose regime, which is now global W.H.O. policy. The 1980s saw a stream of articles, continuing to the present, on the epidemiology of measles at the national and subnational levels, initially from North America, Africa, and South Asia. In the 1980s, after two decades of continuing endemic transmission with the one-dose policy, the problem of persistent measles transmission in vaccinated children was identified. Then, the United States adopted, in 1989, a two-dose vaccination regime, following the example of New York State, which was the first in the U.S. to do so [28]. The internal dialogue among New York decision makers is recounted by Orenstein (op. cit.).

"A small meeting in New York State broke the log jam on moving to a routine 2-dose schedule. College outbreaks in the state captured the attention of the Health Commissioner, David Axelrod. He called together academic infectious disease specialists, led by Saul Krugman and Martha Lepow, state and county health officials and representatives of the CDC to decide how best to address the problem. During the meeting, consultants agreed that the major problem with measles in colleges was failure to make an adequate immune response after a single dose of measles vaccine rather than waning immunity. Led by Saul Krugman, the academic pediatric infectious disease experts had already come to the conclusion that a second dose of measles vaccine would be necessary if measles elimination was the goal. However, the public sector representatives resisted, primarily because of cost considerations. After spirited discussion, the group did not reach unanimity about whether to recommend a routine 2-dose schedule. Near the end of the meeting, Dr. Axelrod came in to hear the conclusions and said emphatically, don´t tell me what it costs, tell me what is the right thing to do." He pointed out that New York State should be preventing outbreaks, not trying to control them, and declared that New York State would implement a 2-dose schedule even if it were the only state. Public sector opposition to a 2-dose schedule rapidly melted."

Subsequently, the World Health Organization recommended two doses of measles-containing vaccine. By 2008, the two-dose regime was policy in 192 of WHO´s 193 member states [29]. The 1990s saw a number of articles on outbreaks of measles transmitted in health care settings. Nosocomial transmission of measles is now a widely recognized phenomenon, though different countries have addressed the issue in different ways.

In addition, the '80s and '90s saw a growing number of publications on outbreaks in schools and universities. The peculiar character of dormitories, which enhance contact between infecteds and susceptibles, can lead to outbreaks in student populations which have received no measles vaccinations, or only one dose.

The 1990s also saw the publication, by the Journal of Infectious Diseases, of a measles outbreak investigation from an athletic event held in a domed stadium [30]. Successive decades have seen publications on outbreaks in public forums, notably the Disneyland measles outbreak of 2015. One '90s publication by CDC reported an outbreak of measles among Christian Scientists [31]. This presaged more recent reports on faith-based opposition to vaccination in Africa [32].

The 21st century saw more and more epidemiology publications linked to the newly established global laboratory network, which also provided information on rubella seropositivity among suspected measles cases. (Rubella, which lies outside the scope of this article, is thought to be a likely co-candidate for eradication, once the world community makes a global commitment to measles eradication).

The 21st century also witnessed the changing epidemiology of measles in Africa, with a shift in age distribution of cases towards older age groups [33]. This led to a recent analysis, in this journal, of the impact on measles of wide age-range campaigns [34]. Not surprisingly, wide age-range campaigns are more effective than under-five campaigns in reducing the number and proportion of measles cases in older age groups.

In Europe, the new century saw several reports on measles in anthroposophical communities. More and more, the results of outbreak investigations have brought social scientists into collaboration on the root causes of vaccine hesitancy in those with philosophical or religious objections to vaccination [35]. Two centers of excellence in this growing area are UNICEF and the London School of Hygiene and Tropical Medicine, LSHTM.

An unpublished 2013 report from the UN Foundation summarized operationally important findings from 21st century outbreak reports, as follows: 1) Adult susceptibility when combined with infant susceptibility can contribute significantly to reaching critical thresholds of susceptibility in the population; 2) Several articles focusing on role of health care workers (HCWs), emphasizing importance of addressing susceptibility in this group. 3) In humanitarian emergencies, need aggressive rapid ORI, at times with multiple rounds. 4) Areas around (refugee and IDP) camps also need to be included [36]. The current century has brought into use the expression pockets of susceptibility, in recognition of the persistence of measles in under-vaccinated sub-populations of states and counties of generally high vaccination coverage [37].

As populations of refugees and displaced persons have risen in the present century, so, too, have articles on measles in refugee and IDP camps [38]. Even where coverage levels are high, the population density of camps makes them particularly vulnerable to outbreaks. Recent work has covered the role of seasonality in measles transmission [39]. Since transmission patterns vary in different countries, this work has not yet led to global recommendations on how best to deal with the seasonality of measles transmission.

The current century has seen more and more detailed surveillance of adverse events following immunization (AEFI), both in developed and developing countries. Such surveillance serves not only to quantify the importance of AEFI, but also, in rare cases, to trigger corrective measures when clusters of AEFI cases are found, either during routine or campaign vaccination. As China approaches elimination, that country is using case-control studies to identify risk factors for measles infection [40]. A consistent finding is that contact with clinical services is a risk factor for measles. This points to nosocomial infection as a likely driver of measles perpetuation in the areas studied.

Subacute sclerosing panencephalitis

SSPE, a disabling and often lethal sequel of measles, was first described in 1950. A Lancet article of 1967 by Connolly and colleagues, Measles-virus antibody and antigen in subacute sclerosing panencephalitis," established the link between measles and SSPE [41]. By 1969, Katz was able to answer, in the New England Journal of Medicine, the question How does measles virus cause subacute sclerosing panencephalitis? [42].

Remarkably, succeeding decades, while witnessing progressive declines in SSPE incidence and mortality, have seen a large and growing literature on clinical and virological aspects of the disease. The '60s saw only 40 SSPE citations indexed. Since 2010, amid declining incidence, there have been 170 publications indexed on SSPE. Discussion articles in the current decade have been entitled, for example, subacute sclerosing panencephalitis (SSPE): The story of a vanishing disease [43].".

Since the disease is increasingly rare, it is not surprising that much of the literature is based on individual case reports. Nonetheless, some authors have synthesized existing knowledge about the disease, its etiology and treatment, in review articles [44]. Given the rarity of SSPE and its long latent period, it is not surprising that the disease is not widely known to the general public. This helps to explain why, in many countries, measles is erroneously dismissed as a maladie banale. No student of SSPE would make such a statement.

Supplementary immunization activities and routine immunization

Almost all measles vaccinations are administered either by routine immunizations (given through health facilities, outreach, and mobile teams) or by supplementary immunization activities. The Measles & Rubella Initiative, like the Global Polio Eradication Initiative before it, has placed great technical and financial resources into SIAs. These are intended, primarily in developing countries, both to raise the level of community protection in endemic countries and to provide the second dose of vaccine, which is now regarded as essential to interrupting transmission. The '60s, '70s and '80s saw publication of mostly descriptive articles on both routine immunization and SIAs (known then as vaccination campaigns). There were many publications on measles/smallpox campaigns from West Africa (the term SIA was not yet in use). These are primarily of historical interest.

Starting in 1985, the Pan American Health Organization, through its *EPI Newsletter,* documented National Immunization Days (PAHO parlance for SIAs) in support of regional efforts to eliminate polio and measles. In the same decade, UNICEF was supporting multi-antigen vaccination campaigns in support of UCI (universal childhood immunization) with a target date of 1990 to achieve global coverage of 80 percent for the basic 6 vaccinations (diphtheria, pertussis, tetanus, measles, polio, BCG). Those experiences were almost entirely documented in donor reports and internal documents. That decade also saw a multi-country effort by UNICEF to reach "UCI (universal childhood immunization) 1990. In the 1980s, UNICEF spent some funds on support to routine immunization but made large outlays on multi-antigen campaigns whose aim was to achieve rapid increases in coverage for the basic 6 vaccinations and, in some cases, tetanus for women of child bearing age. Almost all of the UNICEF reports were internal or to the donors and the UNICEF Board.

The 1990s saw 55 publications on measles and multi-antigen vaccination campaigns, especially from Latin America, UK, Italy and South Africa. Authors were deeply divided in their opinions as to whether the campaigns were a wise use of resources. One article from the *South African Medical Journal asked The winter 1996 mass immunisation campaign--is it the best strategy for South Africa at this time?* [45].

There were several factors which militated in favor of the SIA approach - initially for polio, then for measles: 1) The success of the Americas in eliminating polio largely through use of SIAs, while polio remained endemic in four of the five other WHO regions, which relied on routine immunization (routine immunization coverage being inadequate, outside Europe, to stop polio transmission). 2) The support of Rotary International for the SIA approach to polio eradication; 3) The decision of WHO, after the 1988 polio eradication commitment, to invest heavily in OPV SIAs in the countries still endemic for polio [46]; 4) The successful experience of PAHO in clearing Latin America and the Caribbean of measles, using the SIA approach.

By the year 2000, the target date for polio eradication had been missed, largely because Asia and Africa lacked the health care services, which, in Latin America, had assured high routine coverage. The RED approach (Reaching Every District), launched in 2002, sought to right this balance by a five-pronged approach to routine immunization [47]. The locus classicus for the RED approach is Reaching every District (RED) approach:

a way to improve immunization performance, published by WHO in 2008 and cited 24 times elsewhere [48].

A 2010 published evaluation of RED in the African region found evidence of improvement in delivery of routine immunization services [49]. As of this writing, the World Health Organization´s African Regional Office has prepared revised RED guidelines. The new AFRO guidelines, published in 2018 and place more emphasis on equity, which has been an emphasis in agency and government thinking since the turn of the century. UNICEF, among other agencies, has used quintile analysis to measure differences in coverage among socio-economic strata. Closely related to the RED approach is the interagency GRISP approach (Global Routine Immunization Strategies and Practices), published by WHO.

Remarkably, the present century has seen only 23 published articles on measles SIAs. This probably reflects the predominance of SIAs in the grey literature, including PowerPoint presentations made at EPI meetings. With that said, the dearth of published documentation on measles SIAs limits the readership of the very extensive literature on this subject.

The Either-Or dilemma

As long as many countries lack the infrastructure to deliver vaccinations without SIAs, SIAs will continue. With huge expenditures made on SIAs and, more recently, on Immunization Services Strengthening by GAVI and other partners, many authors have examined such issues as the extent to which the SIA approach can better support routine immunization, and the extent to which SIAs reach children who are missed by routine immunization. Several recent articles have explored these issues [50,51]. WHO has recently published guidelines on the conduct of SIAs, including such items as better microplanning and preparedness assessments [52].

A 2016 Cochrane Reviews covered interventions that will increase and sustain the uptake of vaccines in low- and middle-income countries [7]. In their summary, the Cochrane reviewers found evidence for the following interventions: 1) **Giving information and discussing vaccination with parents and other community members at village meetings or at home** probably leads to more children receiving three doses of diphtheria-tetanus-pertussis vaccine (moderate-certainty evidence). 2) **Giving information to parents about the importance of vaccinations during visits to health clinics combined with a specially designed participant reminder card and integration of vaccination services with other health services** may improve the uptake of three doses of diphtheria-tetanus-pertussis vaccine (low-certainty evidence); 3) **Offering money to parents on the condition that they vaccinate their children** may make little or no difference to the number of children that are fully vaccinated (low-certainty evidence); 4 **Using vaccination outreach teams to offer vaccination to villages** on fixed times monthly may improve coverage for full vaccination (low-certainty evidence). The Cochrane reviewers called for more and better randomized controlled trials to improve information on interventions in favor of routine immunization.

Progress in measles control and elimination

Although few in number, publications examining measles progress were broad in content in the early decades. In the 1960s, publications not only examined progress in controlling and vaccinating against measles but also progress in eradicating the virus at the country level [53,54]. Though picked up by this article´s search for eradication, not progress, the first indexed publication discussing progress at the global-level occurred in a 1982 article in *The Lancet* [55]. While the 1970s produced only three articles examining measles progress, a dip from the prior decade, two of these articles referenced progress in measles immunization alongside rubella immunization [56,57]. Later, WHO highlighted progress in prevention of measles and rubella in an important 2005 article [58].

Publications on progress jumped in the current century, quite possibly a result of the WHO´s 1998 creation of the Joint Reporting Form (JRF) [59]. Changes in global immunization policy brought about a variety of new ways to measure measles progress. September of 2000 saw the signing of the United Nations´ Millennium Development Goals (MDGs) [60], and several articles subsequently appeared in the decade examining measles progress in the context of the goals [61-63]. MDG4, specifically, called for a reduction in under-five mortality [64]; subsequently, the decade produced indexed articles measuring measles-related mortality reduction at regional and global levels [65,66]. National policy, too, appears to have affected measures of progress. In 1989, the Advisory Committee on Immunization Practices (ACIP) issued an official recommendation for the implementation of a two-dose measles regime in the United States [67]. The year 2004 saw a noteworthy article in *The Journal of Infectious Diseases* investigating progress toward implementation of a second-dose measles immunization requirement for all schoolchildren in the United States [68].

Publication frequency on measles progress has remained high in the current decade, with articles examining progress at scales ranging from city to world [69, 70]. The 2010s have seen continued references to mortality reduction and the Millennium Development Goals [71,72]. As in the 2000s, changes in policy designations have resulted in new measures of progress. W.H.O. Africa´s creation of a "pre-elimination" goal [73], a benchmark towards complete measles elimination, has resulted in a number of publications tracking measles pre-elimination progress in the African Region [74,75]. Additionally, the decade has witnessed discussion of post-elimination progress [76]. It remains to be seen if more such articles are published as measles incidence declines.

Mathematical modeling of measles

First indexed in 1973, publications on the mathematical modeling of measles rapidly increased from the 1970s to the present decade, with a modest plateau at the turn of the century. The discussion which follows will focus primarily on those modeling publications which have direct implications for vaccination policy. Of the 13 articles published in the 1980s, nearly one-third specifically examined age-structured models. This topic remains of critical importance, since, with the growth of under-five SIAs, measles in older age groups will play an increasingly important role in measles transmission and in eradication planning. Other articles of the decade were ahead of their time: a 1984 article published in the *Journal of Theoretical Biology*, for instance, examined seasonality in modeling [77]. Additionally, although the measles vaccine had only been in existence for two decades, a 1984 article in the *American Journal of Epidemiology* modeled measles in high-vaccination settings [78].

Though modelling of viral persistence was indexed in the '80s, the topic received greater attention in the '90s, which saw a tripling of citations on modeling of measles. Additionally, more than in years past, modelling articles of the '90s were tied directly to applications, such as assessing economic benefits, evaluating existing vaccination techniques, and crafting immunization policy. These topics continued to be discussed through the 2000s. From the 2000s to the 2010s, publications on measles modeling jumped from 48 to 74. Among modeling studies, some topics may prove to be of interest to policy makers, such as the following: 1) Dynamic transmission models for measles and rubella risk and policy analysis; 2) Modeling of measles transmission to support eradication investment cases; 3) Modeling the impact of HIV infection on measles; 4) Modeling to determine whether mortality reduction goals have been achieved; 5) Modeling to determine the impact of population decline on the dynamics of measles; 6) Modeling the impact of waning immunity; 7) Modeling the impact of vaccination campaigns.

Studies of costing and economics

Early costing and economic studies were largely global, often focusing on both the economic cost of the virus and benefit/cost analyses of vaccination programmes within different countries. As early as 1970, a JAMA article investigated the economic worth of the implementation of the immunization surveillance programme in terms of costs to parents in Rhode Island [79].

Articles indexed on economic and costing topics greatly increased from the '70s to the '80s. Frequency of publication more than doubled in this period. As publication of measles-related costing and economic studies increased, the breadth of the discussion widened. The 1980s saw publications on non-monetary as well as monetary costs (nutritional and energy costs of disease, for instance).

Publications on the subject steadily increased over the next two decades. The 1990s brought a number of articles on cost analyses of immunizing health workers [80-82]. A reference on this subject appeared as early as 1985 [83]. Economic evaluations of two doses of measles vaccine also featured in the decade [84-86]. In the 2000s, a number of articles indexed on the subject discussed the economics of integrated campaigns (e.g., combined campaigns for distributing bed nets while administering measles vaccines) and of supplementary immunization activities [87-90].

In the present decade, publication on economics and costing studies spiked, rising from 30 in the 2000s to 67 in the period 2010 to mid-2018. As MRI expenditures now exceed $50 million annually in agency outlays alone, costing and economics studies have become necessary, both to provide programme managers with the tools for optimal resource allocation and to persuade finance ministries that measles vaccination is bang for the buck. While evaluations of vaccination programmes, supplemental immunizations, and specific outbreaks continue to appear, economic analyses are applied to new tools and challenges in the field. For instance, the current decade has seen studies examining the economic impact of vaccine hesitancy and exemptions [91,92]. The present decade also provides economic evaluations of advances in technology, such as the number of doses per vial, microneedle patches and lab procedures [93-95].

Research on the costs of investigation and contact tracing have been made from developed countries, all showing the expenses associated with measles surveillance [96]. In the US, with the increasing rarity of locally contracted cases, attention has turned to the costs of detection and response to imported measles cases [97]. An important review article estimates the annual costs of measles control at $2.3 billion [98]. Such costing studies lend weight to the arguments in favor of a time-limited global eradication effort..

Discussion

As the expensive GPEI goes into its fourth decade, the relative costs of time limited eradication and long-term control have been increasingly discussed in the literature. The seminal work of Barrett, cited in 14 other articles, makes the case for time limited eradication [99]. Thompson and Badizadegan contrast the costs of high control of measles over a long time period with the costs of time limited eradication. They conclude, like Barrett, that eradication is the better buy [100]. The work of such authors as Barrett and Thompson addresses the question of whether the world should decide to move towards global eradication. Once that decision is made, through a resolution of the World Health Assembly, costing studies may shift their focus to how best to achieve eradication using different strategies.

Autism

Although not discussed in the literature until the late 1990s, publications on measles and autism jumped in the last two years of that decade and substantially increased through the next. While trends for the remainder of the present decade remain to be seen, it appears that publication on this topic has fallen in the 2010s. The first currently indexed article on measles and autism was published in 1998 in the BMJ [101]. This article examines a putative causal link between MMR and autism, first proposed in an article published in The Lancet earlier that year [102] (The Lancet article was subsequently retracted by the editors in 2010 [103]). Thirty-one other articles on measles and autism were indexed by the turn of the century.

In the 2000s, 166 articles were indexed on measles and autism, propelling autism to the most frequently published topic of the decade. Autism-related articles in the 2000s illustrate scientists´ attempts to evaluate the proposed link. Many articles denounced outright the causal link proposed by the 1998 article in The Lancet [104]. In 2001, the Institute of Medicine (IOM) published a report by its Immunization Safety Review Committee concluding that there existed insufficient evidence to assert a causal relationship between the MMR vaccination and the disease; however, the Committee also called for further research [105]. Later, in 2004, the IOM issued another report declaring the absence of a link between autism and the measles-mumps-rubella (MMR) vaccine or the vaccine preservative thimerosal [106].

In 2008, the journal Pediatrics published a paper suggesting that media attention to the controversy had little impact on vaccination rates in the United States [107]. Additional articles published in the present decade continued to investigate whether public discussion of the controversy affected vaccination coverage [108, 109]. While interest in autism appears to have declined, with only 50 articles thus far cited in the present decade, the purported relation to MMR vaccination continues to affect the public. In 2013, an outbreak of measles among pre-teens and teens in Wales is thought to have been the result of autism-related vaccine hesitancy, as was a 2017 measles outbreak among Somali-Americans in Minnesota [110, 111].

Perspectives for future publications

All six of the WHO regions have created time-limited objectives for regional measles elimination. The next logical step would be a resolution by the World Health Assembly in favor of a time-limited eradication effort against measles alone or measles and rubella. Such a WHA resolution is unlikely to predate the current 2022 end date for the Global Polio Eradication Initiative. Discussions on elimination and eradication renew the perennial debate between advocates of integrated approaches and advocates of a vertical approach. Goodson and colleagues have proposed a diagonal approach to measles and rubella elimination based on lessons learned from polio eradication [23]. Biellik and Orenstein have pointed out that measles-rubella elimination can, when properly implemented, strengthen routine immunization [112]. The conflict between elimination initiatives and integrated approaches is, in the view of some authors, an apparent rather than a genuine conflict [24]. Goodson and colleagues propose the following:

"Focusing efforts on MR elimination after achieving polio eradication would make a permanent impact on reducing child mortality but should be done through a 'diagonal approach´ of using measles disease transmission to identify areas possibly susceptible to other vaccine-preventable diseases and to strengthen the overall immunization and health systems to achieve disease-specific goals".

Such an approach, neither vertical nor integrated, would simultaneously serve to stop transmission and to strengthen other components of the Expanded Programme on Immunization. If the next few years see a global commitment to measles eradication, we could expect to see more published research in the following areas: 1) Improvements in the quality of case-based surveillance; 2) Vaccine hesitancy on religious and other grounds; 3) Shifts in age distribution towards adolescents and adults; 4) Sero-surveys as an SIA planning tool; 5) Better predictive models for timing of SIAs; 6) Better understanding of seasonality; 7) Transition of polio surveillance assets to integrated disease surveillance; 8) Wider use of electronics and softwares in epidemiology; 9) Nosocomial transmission and means of combatting it; 10) Epidemiology and economics, with a view to costing measles eradication under different short-term and medium-term scenarios, with or without heavy investments in immunization services strengthening; 11) Combining measles and rubella in a single global eradication initiative; 12) Use of micropatch vaccinations for measles and MR; 13) Methods for identifying high risk districts and localities for pre-emptive vaccination between successive campaigns.

Conclusion

As of this writing, the most recent lists of research topics are those identified at a WHO meeting held at CDC in 2012 [113] and the following list, prepared for the SAGE (Strategic Advisory Group of Experts in 2014, and reproduced in Orenstein et al. [25]: 1) Strategies to increase coverage in difficult populations;2) Novel strategies to increase vaccine coverage; 3) Strategies to address confidence gaps; 4) Outbreaks in settings with high coverage; 5) Optimal age of measles vaccination; 6) Reasons for low confidence in vaccines; 7) Outbreak response strategies; 8) Strengthen routine immunization & surveillance; 9) Susceptibility profiles to measles and rubella; 10) Measures of vaccine coverage; 11) Epidemiology and surveillance for measles & CRS; 12) Point of care diagnostics. Now that MCV2 vaccination has become widespread, it may be time to find out at what level of coverage governments can safely introduce a four-year interval between SIAs without risk of outbreaks.

What is known about this topic

- Since the licensing of the first measles vaccine, there has been an increase in published articles on measles and on measles vaccination;
- The topic has attracted authors from many disciplines, notably clinicians, epidemiologists, biostatisticians, mathematical modelers and social scientists;
- The research agenda for measles deserves careful attention as all six regions of the WHO have targeted measles for elimination.

What this study adds

- This study quantifies the growth of measles publications, decade by decade. The number of index publications on measles has more than doubled since the 1960s;
- This study quantifies trends in measles publications, decade by decade, with special emphasis on the current century;
- This study summarizes several of the most recent reviews of future research priorities on measles, as proposed by specialists in the field.

Competing interests

The authors declare no competing interests.

Authors' contributions

RD conceived the idea for this paper. RK did the statistical analysis and tables. RK and RD contributed equally to the drafting of the individual sections, each author reviewing the other's work. RK prepared the reference section. RD incorporated reviewers' comments into the text. Both authors read and agreed to the final manuscript.

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Editorial

Recent setbacks in measles elimination: the importance of investing in innovations for immunizations

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Abstract

The recent setbacks in efforts to achieve measles elimination goals are alarming. To reverse the current trends, it is imperative that the global health community urgently intensify efforts and make resource commitments to implement evidence-based elimination strategies fully, including supporting research and innovations. The Immunization Agenda 2030: A Global Strategy to Leave No One Behind (IA2030) is the new global guidance document that builds on lessons learned and progress made toward the GVAP goals, includes research and innovation as a core strategic priority, and identifies measles as a "tracer" for improving immunisation services and strengthening primary health care systems. To achieve vaccination coverage and equity targets that leave no one behind, and accelerate progress toward disease eradication and elimination goals, sustained and predictable investments are needed for the identified research and innovations priorities for the new decade.

Editorial

The recent setbacks in efforts to achieve measles elimination goals are alarming [1]. After reaching a nadir of <100,000 estimated measles deaths globally for the first time in 2016, global measles deaths increased to > 140,000 in 2018 [1]. Since 2016, both global measles cases and incidence have steadily increased, to the highest levels since 2011. During 2016-2018, the global number of measles cases increased 167% with increases in measles incidence in five of the six World Health Organization (WHO) regions, including a 246% increase in the WHO African Region (AFR). The increase in AFR measles cases was driven by large outbreaks that occurred in Chad, the Democratic Republic of the Congo (DRC), Madagascar, and Nigeria, while other countries maintained relatively low incidence. In the AFR in 2018, coverage with the first dose of measles-containing vaccine (MCV1) was 74%, coverage with the second dose (MCV2) was 26% [2], and an estimated 52,600 children died of measles [1]. Although the AFR countries established a regional goal in 2011 to achieve measles elimination by 2020, and the World Health Assembly (WHA) endorsed the Global Vaccine Action Plan (GVAP) in 2012, with the objective to achieve measles and rubella elimination in five of the six WHO regions by 2020, it will be important to maintain political commitment and ensure substantial, sustained investments to achieve the global and regional measles elimination goals [1,3-5]. Despite overwhelming evidence of the benefits of strong immunization programs, vaccination coverage among specific populations in certain countries are stagnant or decreasing due to barriers to access, insufficient vaccine investments, and humanitarian crises [5]. To reverse the current trends, it is imperative that the global health community urgently intensify efforts and make resource commitments to implement evidence-based elimination strategies fully, including supporting research and innovations [6].

Measles and rubella elimination research priorities have been identified, including operational research and potential game-changing new tools, such as rapid diagnostic tests (RDTs) [7, 8]. Early and sustained investments in these research priorities could avoid potential future program setbacks and unnecessary excess morbidity and mortality. Evidence generated from this research and the development of effective new tools could be used to shape policy, refine strategies, and strengthen practices of the Expanded Programme on Immunization (EPI). EPI programs aim for control and elimination of vaccine-preventable diseases and reduction of morbidity and mortality [1, 9-11]; elimination efforts reinforce a data-driven focus to reach vaccination coverage and equity targets. When fully resourced, EPI and related research can readily identify gaps in immunization services based on data and field experience and drive innovation through an iterative process of developing and implementing new strategies, field testing, analyzing data, and making evidence-based program adjustments. Strategic recommendations based on the evidence are endorsed by policy-setting bodies including the global WHO Strategic Advisory Group of Experts (SAGE) on Immunization, and regional and national Immunization Technical Advisory Groups.

Strengthening immunization service delivery

Measles outbreak investigations, case-based surveillance data analysis, vaccination coverage surveys, systematic EPI reviews, vaccine-preventable disease impact assessments, and cost-effectiveness studies provide opportunities for research to generate evidence for refinement of elimination strategies. The published literature is rich with evidence that supports simultaneous EPI strengthening and measles elimination, including the impact of the recently updated Reaching Every District strategy; integration of other public health interventions with immunizations service delivery including supplemental immunization activities (SIAs) [12-14]; incorporation of mobile phone use, electronic immunization registries, and recall and reminder systems for vaccination messaging [15]; novel approaches to reduce vaccination dropouts and missed opportunities for vaccination (MOVs); establishing a second-year-of-life (2YL) platform; and SIA microplanning to reach un- and under-vaccinated children [16].

In 2009, an accumulation of evidence led to the WHO recommendation that all countries provide two doses of measles-containing vaccine [17]. Globally, estimated MCV2 coverage increased from 18% in 2000 to 69% in 2018, largely because of an increase in the number of countries providing MCV2 from 98 (51%) in 2000 to 171 (88%) in 2018 [1]. In many AFR countries, MCV2 introduction was the first routine EPI vaccine given to children beyond infancy that required establishing a 2YL clinic visit for scheduled vaccination [2, 18]. Multiple post-introduction evaluations for MCV2 and 2YL initiatives have led to an accumulation of information that can be used to strengthen EPI operations, including using the MCV2 vaccination visit to catch up on previously missed doses of all vaccines [19-22]. Providing two doses of measles-containing vaccine (MCV) to all children has also further highlighted the advantages of using 5-dose vials rather than 10-dose vials of MCV. In 2019, an important comprehensive study by John Snow, Inc. (JSI) showed that using 5-dose vials compared with 10-dose vials was associated with a substantial increase in MCV2 coverage, a significant decrease in MCV1-MCV2 dropouts, and a significantly lower MCV wastage rate (16% compared with 30%). Furthermore, the wastage-adjusted vaccine price per dose was $0.98 for 5-dose vials compared with $0.94 for 10-dose vials, and there was only a 4.9% increase in cold chain space requirements for using 5-dose vials [23]. In November 2019, after careful review of evidence, including the JSI study, the African Regional Immunization Technical Advisory Group now encourages the use of 5-dose vials of MCV in appropriate settings [24].

Risk mitigation and preventive actions

Advances in serological surveys, disease mathematical modeling, measles-susceptibility profiles, and measles risk assessments have facilitated identifying measles population immunity gaps and sub-national areas at-risk [25-30]. However, the results of these studies could be better used to support timely preventive actions, including SIAs to mitigate risk before large measles outbreaks occur. For example, the prescient results from analysis of data from serological surveys published by Winter et al. indicated the risk for a massive measles outbreak in Madagascar; in hindsight, it could have led to immediate preventive action or a timelier outbreak response [27]. Similarly, given WHO and United Nations Children's Fund (UNICEF) estimates of national immunization coverage indicating low population immunity in DRC, a decision could have been made to repeat a measles SIA earlier than the three-year interval between the 2016 and the 2019 measles SIAs, at least mitigating the scale of the current outbreak.

Periodic nationwide SIAs are a long-established cornerstone of elimination efforts that include special strategies and microplanning for reaching zero-dose and under-vaccinated children previously missed by routine immunization services. Starting in 2016, however, global measles donor funds were redirected toward organizations that focused on health systems strengthening rather than measles elimination [31]; this was followed by funding reviews that suggested that countries downsize nationwide measles SIAs to subnational SIAs, extend the interval between SIAs, or restrict SIA target age groups to young children [32]. It was thought that the cost savings from the proposed smaller SIAs could then be used flexibly on additional immunizations systems strengthening activities in districts not included in the SIA [33]. However, pilot testing of this approach found that data quality was not high enough to support decisions to exclude certain districts from SIAs.

SIA frequency and target age groups should be based on epidemiological analyses, and adequate resources made available to ensure optimal implementation of the indicated target population and SIA timing [34, 35]. Previous published studies in the AFR have shown negative impacts of narrow target age groups, delayed SIA implementation, subnational phased implementation, and long gaps in SIA frequency [36-40]. The impact of suboptimal SIA implementation can be devastating, including, for example, the deadly measles epidemics that have continued to occur predictably in DRC, including 327,959 reported cases and 6,256 reported deaths during December 31, 2018-January 19, 2020 [41]. Any proposed alternative strategies, including methods that aim to identify subnational target populations, limit the geographic scope, or decrease the frequency of SIAs should be carefully evaluated to provide evidence of impact on disease burden and long-term cost effectiveness compared with existing elimination strategies.

Changing measles epidemiology, vaccine effectiveness and immunity

Measles epidemiology has changed over time, following decreases in measles incidence in all regions since 2000. Studies have documented this changing epidemiology, including in the AFR [42], and recent reviews have described some fundamental aspects of current measles epidemiology related to elimination strategies [43-45]. For example, with increased vaccination coverage, there has been a shift from protective immunity developing primarily after wild-type measles virus infection to one that is derived from vaccination, with less opportunity for natural boosting from exposure to wild-type measles virus. This has resulted in a shift in measles-susceptibility to older age groups, including young adults [8, 38, 42]. In addition, infants become susceptible to measles at an earlier age [46, 47]. Studies have shown that maternally derived measles antibodies passively transferred to infants via the placenta from vaccinated mothers are lower and wane faster below the protective threshold than from mothers who had measles from wild-type infection [45, 46, 48]. A recent study in an elimination setting found 92% of infants became susceptible to measles by 3 months of age [46].

Similarly, a recent review of the measles reproduction number (R0), the measure of transmissibility that drives herd immunity and subsequent vaccination coverage levels needed to interrupt measles virus transmission, showed that R0 estimates vary considerably by setting and more widely than the often-cited 12-18 range, and they are dependent on context-specific factors including population density, birth rates, and age-mixing patterns [49]. Better understanding of the contributors to transmissibility in various settings may improve elimination efforts in specific contexts.

With changing measles-susceptibility, a recent review of the effect of age at first dose and time since vaccination on measles vaccine effectiveness (VE) was completed. It showed that, in measles-endemic settings, one-dose VE increased by 1.5% (95% confidence interval=0.5, 2.5) for every month increase in age at first dose and found no evidence of waning VE. More data, however, are needed to answer the question of whether measles VE wanes in measles-elimination settings [50]. Recent studies in some elimination settings have suggested that waning immunity among older children and adults might have led to emerging measles susceptibility and that breakthrough infections might have played a role in some outbreaks. However, this phenomenon has been observed only in a small number of elimination settings that likely experienced gaps in cold chain and/or vaccine mishandling in the past [51-53]. Detailed case investigations and laboratory evaluations are needed to confirm measles cases as breakthrough cases and provide clearer evidence of potential waning measles immunity, to support decisions to revaccinate populations experiencing re-emerging measles susceptibility [54, 55].

Measles virus infection leads to severe viremia and lymphopenia and can cause immunosuppression that can last for months to years [43]; however, the long-term impact of measles on the immune system is not fully understood [56]. Recent studies have demonstrated that measles virus can infect up to 70% of memory T-cells during the first 3-10 days after infection [57, 58], and measles virus infection diminishes specific preexisting antibodies that were providing protection from other pathogens [51-60]. Further studies are needed to quantify the impact and implications of the long-term susceptibility to other pathogens caused by measles infection.

Potential game-changing tools

Important innovative tools are on the horizon, including a measles rapid diagnostic test (RDT) and a measles-rubella (MR) vaccine microneedle patch that are among the highest priorities for measles and rubella elimination research [8]. A measles RDT is currently being field tested in several studies in Ghana, India, Malaysia, and Uganda, and a rubella RDT is in development. RDTs have the potential to substantially reduce time to case confirmation and fundamentally change approaches to outbreak response and infection control measures [61]. For example, rapid confirmation of a suspect measles outbreak by a district health officer or diagnostic testing of suspect measles cases at the clinic could lead to more timely outbreak response immunization, and appropriate triaging and isolation of cases in hospitals and health centers. The MR microneedle patch is widely recognized as a potential game-changer for elimination strategies. The MR patches will require minimal storage and disposal capacity, are easily transported, do not require reconstitution with diluent, cannot be re-used because they dissolve in the skin, do not generate sharps waste, and are easily administered, permitting vaccination by minimally trained personnel [62]. The patch will eliminate adverse events following immunizations due to human error during reconstitution and make house-to-house vaccination campaigns possible, a key strategy for elimination and eradication efforts [63, 64]. Despite the clear potential positive impact on vaccination coverage and equity, and long-standing urgent calls for investments in MR microneedle patches [65, 66], securing sustained predictable funding commitments has been challenging, adding unnecessary years to licensure and use [67]. The current optimistic timeline for developing and commercializing MR patches, even with timely funding, is estimated to be 7-8 years. Novel product development to improve upon existing products often requires formation of global public-private partnerships, similar to the partnership that supported development of the N. meningitides group A vaccine, MenAfriVac™, to firmly establish the public health need, advocacy, and to make the business case for shared costs and risks of the development process [68].

Build synergy for common goals

With the decade of vaccines coming to an end in 2020, global immunization partners are establishing the "Immunization Agenda 2030: A Global Strategy to Leave No One Behind" (IA2030) [69] to be approved by the WHA in May 2020 for the next decade. This new global guidance document builds on lessons learned and progress made toward the GVAP goals. The IA2030 includes research and innovation as a core strategic priority and identifies measles as a "tracer" for improving immunisation services and strengthening primary health care systems. Measles has proven to be an effective tracer for EPI performance and as a driver for efforts to strengthen health systems and innovations [70]. Key factors that make this possible include: 1) very high measles vaccine effectiveness, 2) very high transmissibility of measles virus among unimmunized people, and 3) the absence of silent measles virus transmission, a characteristic which distinguishes measles from polio. All measles cases have a well-defined clinical presentation of maculopapular rash and fever, sometimes seen with the pathognomonic Koplik spots; therefore, are detectable by disease surveillance. Measles epidemiology accurately reflects measles susceptibility in the population, thereby identifying areas and communities with low vaccination coverage. Also, measles is frequently the first vaccine-preventable disease detected when weaknesses in immunization service delivery occur. Therefore, measles is often referred to as the "canary in the coalmine" for EPI and as such, can be effectively used as a signal and driver for overall immunizations systems strengthening [71]. Achieving measles elimination in AFR will focus efforts to deliver two doses of measles vaccine safely and effectively to ≥95% of children in a timely manner, as well as detect, prevent, and respond effectively to measles cases and outbreaks. These efforts can dovetail synergistically with the aims of the Global Health Security (GHS) and the Universal Health Coverage (UHC) agendas to strengthen primary health care systems, immunizations and preventive services, disease surveillance, and outbreak preparedness and response capacity [3, 72-75]. To achieve these common goals, attain vaccination coverage and equity targets that leave no one behind, and accelerate progress toward disease eradication and elimination goals, sustained investments are needed for the identified research and innovations priorities.

Competing interests

The author declares no competing interests.

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