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# Measles in Developing Countries

*Anyebe Onoja and Oluwaseyi Ajagbe*

## Abstract

Measles is a major childhood problem which causes significant illness, death and disability. It infects approximately 40 million people resulting in nearly 1 million deaths annually in developing countries. Measles virus accounts for 44% of total deaths among children that are less than 15 years of age. Highest mortality occurs among children living in poor communities especially in areas that are overcrowded, and where there is malnutrition and vaccination coverage is low. Most of the measles infections in the world are recorded in developing countries of Africa and Asia. Endemic areas are largely confined to the tropics, where transmission increases after rainy season. Inability to effectively immunize most children in this area has hampered global measles mortality reduction initiatives and reduction of under-five child mortality. Although, this was initially scheduled to have been met by 2015, recent WHO resolution called for measles elimination in the African Region by 2020. It is not certain that this will be met; hence the need for coordinated and strategic mass vaccination efforts to target unimmunized children in these regions.

**Keywords:** measles virus, genotypes, immunization, vaccination, coverage, Africa

## 1. Introduction

Measles is a serious medical problem in Africa, Latin America, Europe, south-east Asia and eastern Mediterranean [1]. During the pre-vaccine era, 130 million measles cases occurred annually worldwide, and it was the leading cause of childhood deaths [2]. In Africa, about 13 million cases and 650,000 deaths occur annually, with sub-Saharan Africa having the highest morbidity and mortality [3]. In 2018, many developing countries reportedly confirmed measles through laboratory testing with high incidence rates. In AFRO region, Liberia confirmed 218 cases with 412.24% incidence rate. Similarly, Libya confirmed 286 cases with 98.84% incidence rate, Burkina Fasso confirmed 567 cases with 84.2% incidence rate and the southern part of the continent was not left out as Uganda confirmed 531 cases in the laboratory with incidence rate of 65.83%. In the Western Pacific region, Philippines confirmed 1677 cases with incidence rate of 118.5% while Malaysia confirmed 1374 cases with incidence rate of 80.35% [4]. In EURO region, Albania confirmed 1290 cases with incidence rate of 477.05%, Georgia reported 1091 laboratory confirmed cases with 374.74% incidence rate and Kyrgyzstan confirmed 376 cases in the laboratory with 75.22% incidence rate. In EMRO, Afghanistan reported 1846 laboratory confirmed cases with 62.64% incidence rate, Saudi Arabia reported 833 laboratory confirmed cases with 29.99% and 793 laboratory confirmed cases in Yemen with incidence rate of 344.36%. Venezuela in AMRO confirmed 5525 cases in the laboratory with an incidence rate of 23.03% [4].

Despite the comprehensive WHO and United Nations International Children Emergency Fund's (UNICEF's) measles-reduction strategy, and partnership of international organizations for measles mortality reduction, certain countries continue to face recurrent epidemics [5]. The optimal age for infantile measles vaccination is an important since maternal antibodies may neutralize the vaccine antigen before specific immune response develops. Delaying vaccination on the other hand may increase risk of complicated disease [6]. Measles vaccine effectiveness is 84% when administered at 9–11 months of age and 93% when given at  $\geq 12$  months of age [7]. First dose of measles-containing vaccine (MCV1) given at 9 months of age was introduced into the Expanded Programme on Immunization (EPI) in 1977 [8]. Since  $>93$ –95% population immunity is required to prevent measles epidemics, the WHO recommends all children receive two doses of measles vaccine [9]. In Nigeria just like in many developing countries, children are given monovalent measles vaccine at 9 months of age in the EPI [10]. In 2010 and continuing through 2014, DRC experienced the largest nationwide measles outbreak in Africa [11–13]. DRC is a key country for regional elimination efforts because of its large population, central location with nine international borders, and persistent reservoir of circulating measles viruses [14]. The Reaching Every District (RED) approach to strengthening immunization services has been implemented beginning in some developing countries like Democratic Republic of Congo (DRC). A second opportunity for measles vaccination, nationwide measles supplementary immunization activities (SIAs) using a phased approach intended to cover the country every 3 years [15].

## **2. Epidemiology and immunization**

### **2.1 Measles virus detection strategies and sero-surveillance in Africa**

Following a successful polio laboratory platform, The Global Measles and Rubella Laboratory Network (GMRLN) was developed. As at 2018, there are presently 723 laboratories established in 164 countries. It was proposed that in all districts in WHO AFRO surveillance performance should target  $\geq 2$  cases of non-measles febrile rash illness per 100,000 population and  $\geq 1$  suspected measles case investigated with blood specimens in  $\geq 80\%$  of districts [16]. Case-based surveillance with laboratory confirmation of suspected measles cases is in place in many developing countries. Integrated Disease Surveillance and Response (IDSR) was established for aggregate reporting of 18 infectious diseases, including measles. Through the IDSR, aggregate numbers of suspected measles cases and deaths are reported weekly from districts to national level. Through measles case-based surveillance, suspected measles cases were investigated using case investigation form and laboratory testing of blood specimen. Specimens are tested using standard enzyme-linked immunosorbent assays for measles-specific immunoglobulin M (IgM) antibodies. Suspected measles case was defined as an illness with maculopapular rash and fever and one or more symptoms of cough, coryza or conjunctivitis, or where clinician suspects measles. Laboratory-confirmed measles case on the other hand is defined as suspected measles case with positive laboratory test result for measles specific IgM in the absence of measles vaccination within 30 days of specimen collection. An epidemiologically-linked case is suspected measles case having contact (or living in same district) with laboratory-confirmed measles case whose rash onset was within preceding 30 days. Clinically-compatible case is suspected measles case without laboratory test result or established epidemiological link. PCR detection is carried out in specific laboratories with technology for confirm hemagglutinin (H) and nucleoprotein (NP) gene of measles virus.

## 2.2 Circulating genotypes and clades in Africa

Measles virus is monotypic; however, genetic variations occur in the H and NP genes. Currently, the WHO recognizes 8 clades, A-H which consists of 24 genotypes and an additional provisional genotype, D11. Clades B, C, D, G and H each contain multiple genotypes (B1-3, C1-2, D1-10, G1-3 and H1-2) while clades A, E and F each contain single genotype (A, E and F) respectively [17, 18]. Epidemiological findings reveal circulation of several genotypes in Africa. Genotype A has been detected in South America, parts of China and South Africa over the last 40 years [19], and recently in a 3 year old child in Nigeria West Africa [20]. The most endemic genotype circulating in Africa is B3. Studies have shown clade B to be endemic in sub-Saharan Africa [21] with B3 genotype reported in Ghana, Gambia, Nigeria, Libya and Tunisia [20, 22, 23]. The measles viruses isolated in 1983 from Yaoundé, Cameroon, were designated as B1 genotype. However, in 2001 viruses belonging to B3 genotype were found in the country. B3 genotype has been reported in the Gambia. The B3 genotype (2001) in Cameroon were related to B3.1 subgroup, whereas the Gambian (1993) isolates corresponded to B3.2 subgroup. Geographical distribution for period 1993–2001 of these two viruses shows that B3.1 is found from Sudan to Nigeria and Ghana extending to Cameroon, whereas B3.2 genotype is found in West Africa. In Nigeria and Ghana, the viruses co-circulate [3, 14]. Nucleotide sequence analysis show strains from Senegal clustered in B3.1 and B3.3 sub-genotypes. Measles virus detected in Tunisia and Libya from 2002 to 2009 belonged to genotype B3. Viruses isolated from 2002 to 2007 and 2009 were subtype B3.1. Seven of isolates during 2008 and 2009 epidemic were divergent from the B3 isolates and can represent a new subtype of genotype B3 [21]. B3 strain circulates in Addis Ababa, Bahir Dar and possibly elsewhere in Ethiopia [24]. In a 2014 outbreak among refugees from Central African Republic in Cameroon, the genotype B3 found were similar to those circulating in Northern Cameroon in 2010–2011 [25]. Clade B viruses is reported to be endemic in central and western parts of sub-Saharan Africa while genotypes D2 and D4 has been continually detected in southern and eastern parts of Africa. D10 in Uganda is represented by Clade MVi/Kampala. UGA/51.00.1 with accession number AY923185.1. Genotype C2 is found to circulate widely in northern Africa [17, 26–28].

## 2.3 MV complications in developing countries

Measles is characterized by fever of 38°C or more; maculopapular rash of 3 days or more; with one or combination of coryza, cough, conjunctivitis and Koplik spots in the oral mucosa of measles' victims [29]. Mortality rates can exceed 10% in parts of the developing world. Sequela of measles includes giant cell pneumonia, inclusion body encephalitis and sub-acute sclerosing pan encephalitis [SSPE] [30]. A study carried out in the largest children's hospital in Ibadan-Nigeria in West Africa observed several complications ranging from bronchopneumonia (60%), heart failure (12%), gastroenteritis (11%), protein losing malnutrition (8%), encephalitis (5%), croup (2%) and dehydration (2%) [10], whereas bacterial complication is the usual cause of death when measles kills malnourished children [31].

## 2.4 Vaccination and herd immunity

After routine and catch-up vaccinations in 2005 and 2006, as well as follow-up vaccination by 2008 in Nigeria, remarkable level of protection was observed in children. This is attributed to immunological dynamics which is an after-effect of these campaigns [32]. Herd immunity varies between heterogeneous populations in

developing countries. Nigeria is the most populous country in Africa with a population of over 160million. In an assessment of immune status carried out in 2014, herd immunity against measles was 66.8% in Kano State and 73.0% in Ibadan, Oyo State. These are two largely different populations in the north and southern respectively [33]. When history of measles was compared with level of immunity, a significant association was observed between those who had measles and who had protective immunity. There was strong correlation between malnutrition and immune level, a lot of malnourished children who were vaccinated were not protected [33].

## **2.5 Measles vaccination coverage in Africa**

Strategies based on vaccination program have been implemented in order to reduce measles mortality. In 2008, countries in the WHO African Region adopted measles pre-elimination goal to be achieved by the end of 2012. Target was to achieve >98% reduction in estimated regional measles mortality. The goal was to have national measles incidence of <5 cases per 1,000,000 population per year, achieve >90% national coverage with MCV1 with >80% MCV1 coverage target. For SIAs, MCV coverage >95% was targeted in all districts [16]. In the WHO regions, highest percentage of reduction was in Eastern Mediterranean (90%) and African (89%) regions, accounting for 16 and 63% of global reduction [34, 35]. Relatively high measles vaccination in southern Nigeria in West Africa can be attributed to high level of literacy and awareness created by free use of mass media to disseminate information on vaccination activities, without fear of intimidation [33]. The Global Vaccine Action Plan (GVAP) set out a target of reaching 80% coverage with all vaccines including measles vaccine in all districts by 2020 [36]. Health policy decision-making based on spatially heterogeneous vaccination has resulted in shift from pursuing coverage targets at national-level to ensuring high coverage levels evenly distributed across provinces or districts [37]. While this likely represents a more effective strategy over targeting country-level goals, administrative area summaries may still mask important geographical inequities in coverage [38].

## **2.6 Challenges of measles immunization in resource-limited settings**

Vaccination history of children is not documented in hospital's records because many people do not properly keep children's/wards' vaccination records. This is coupled with high illiteracy level found in many developing countries [32]. Many people present as emergencies upon admission, at which point their parents cared less about vaccination status because they were overwhelmed by anxiety. There is need for enhanced comprehensive national vaccination campaigns with intense community engagement and diligent health workers including large number of ad-hoc staff. Weak government support across all levels is responsible for poor surveillance activities hence, their inability to detect new cases. Awareness creation should be intensified to inform concerned citizens about the essence and time of vaccination.

Ability to produce vaccines is a major setback for developing countries. Japan International Cooperation Agency (JICA) is currently supporting transfer of a Measles-Rubella vaccine manufacturing technology to Polyvac® in Vietnam, following the precedent set by multiple previous successful projects. Transfer of an oral polio vaccine (OPV) technology from Biken Co., Ltd. to Bio Farma in Indonesia was pivotal in the global polio eradication efforts. JICA supports UNICEF supply of vaccine cold chain equipment to India, Afghanistan, Angola, Liberia, Zambia and Zimbabwe which has significantly overcome the problem of vaccine failure resulting from inability of most immunization officers to maintain cold chain in remote areas.

Government bodies responsible for ensuring safety and effectiveness of vaccines face serious challenges when protecting the public from harm once the products are used in uncontrolled, real world context [39–41]. Regulations have been moving towards an approach that takes into account the full lifecycle of the vaccine. While this shift has been very slow in countries like Canada, there have been further calls for changes on how regulators safeguard public health and public healthcare resources [42]. These approaches are a far cry from the reality on ground in developing countries, because they utilize whatever vaccines are supplied by donor agencies or vendors who have passed through government's registration processes.

Most countries grapple with unreliable immunization service funding. But in spite of active measles vaccination efforts in several developing countries, re-emergence of measles continues to occur [33]. An interplay of several factors affect immunization. These factors include break in cold-chain of measles vaccine due to long distance to vaccination centers, history of measles, intercurrent infections and malnutrition. In both developing and industrialized countries, loss of public confidence in vaccine due to real or spurious links to adverse events can curtail or even halt immunization activities. This is similar to reports about polio vaccine laced with sterilizing agents which led to decline in vaccination uptake in northern Nigeria. Despite the scientific evidence refuting links between the measles-mumps-rubella (MMR) vaccine and autism, there has been decline in coverage in some countries as a result of this. Measles is making a comeback in several industrialized countries, including Austria, Italy and the United Kingdom. This can be attributed to presence of migrants and refugees from developing countries especially those who are biased against vaccines in light spurious or religious sentiments.

Masking of geographical inequalities in vaccination because of poor administrative summaries is a big problem. Spatial clustering of unvaccinated children sustains disease transmission, even when high overall vaccination coverage is achieved. Continued measles virus circulation occurs as a result of missing age cohorts during routine vaccination. Access to high quality vaccines is important however, there is limited expertise to review technical product information in vaccine regulatory dossiers hence the inability to effectively register and supply vaccines in many developing countries. They lack appropriate expertise and certified personnel to perform good manufacturing practice (GMP) inspections leading to lengthy registration/review process and delays in vaccine registration even in emergency situations. Worrying is the fact that there is limited compliance with good clinical practice standards for some clinical trials. Therefore, improving vaccine supply chain in developing countries is very important. A review of existing data shows freeze exposure occurred in 18–67% of vaccine shipments throughout various stages of storage. Also, heat denatures vaccines when cold chain is not maintained. Such may reduce vaccine potency, ultimately supplying potentially less-effective vaccines.

## **2.7 Sourcing of vaccines**

The developing countries vaccine manufacturers' network (DCVMN) is a public health driven, international alliance of manufacturers trying to strengthen vaccine supply through information and professional training programs, technology improvements, innovative vaccine research and development, encouraging transfer initiatives, to improve availability of safe, effective and affordable vaccines. Three goals were proposed for vaccines. First, to ensure uninterrupted supply of affordable and suitable vaccines for GAVI. Second, improve market dynamics information and expertise to solve vaccine access challenges. Third, strengthening global health and manufacturers' partnerships to enable better alignment of goals, alignment with global strategy and coordination of internal investments [43].

## **2.8 Negative impact of population explosion**

Civil unrest is common in developing countries and this has led to migration of millions of people. There is increased movement by land, air and sea. In Northern Nigeria, activities of Boko Haram terrorist have caused several families to abandon their homelands and converge on Internally Displaced Peoples camps where health care services are poor and even non-existent in some cases. Many children are born in these camps, but vaccination activities may not be sustained at the desired national vaccination level. Wars and famines or other natural disasters increase mortality due to measles. In 2000, measles was responsible for 22% of deaths in children less than 5 years of age and 17% of deaths in children aged 5–14 years in Ethiopia [44]. Increased air travel by people within some regions in developing countries has been reported. For local flights, cabin air flow may not be as reliable a barrier to the spread of measles virus. Several measles reports, including index cases and apparent secondary cases on flights, have been reported in which transmission on board the aircraft appeared likely and which included seating information for both index (primary) and secondary case [45].

## **3. Conclusion**

Regulations for safety and effectiveness of vaccines in the uncontrolled, real world context should be strengthened in developing countries. Perhaps the set of ethical considerations when fully operational in developed countries will be applied to them also. The World Health Assembly established 3 milestones towards eradication of measles. They intend to increase routine coverage with MCV1 by more than 90% nationally and more than 80% in every district; reduce and maintain annual measles incidence to less than 5 cases per million; and reduce estimated measles mortality by more than 95%. Based on current trends of measles vaccination coverage and incidence, and report of the strategic review, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) concluded that the 2015 global milestones and measles elimination goals were not achieved because immunization coverage gaps exist. SAGE recommended focus on improving immunization and surveillance systems to ensure gains made thus far in measles control can be sustained. The situation in developing countries requires serious attention and strict compliance by stakeholders to ensure goals are met.

### **Conflict of interest**

We declare that there is no conflict of interest.

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