AMERICAN UNIVERSITY OF BEIRUT

MEASLES ELIMINATION IN SUDAN: INCIDENCE TREND AND VACCINE COVERAGE

by
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A thesis
submitted in partial fulfillment of the requirements
for the degree of Master of Science
to the Department of Epidemiology and Biostatistics
of the Faculty of Health Sciences
at the American University of Beirut

Beirut, Lebanon
June 2015

AMERICAN UNIVERSITY OF BEIRUT

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ACKNOWLEDGEMENTS

This dissertation would not have been possible without the guidance and valuable assistance of several individuals. I am highly indebted to the *Expanded Programme of Immunization* – Sudan for providing the necessary information and facilitating the approval process for implementation of the study.

It has been great honor and privilege to work with *Dr. Salim Adib*, (Department of Epidemiology and Population Health, FHS-AUB). All the thanks with special gratitude for his technical support and the sincere attention; he spared no effort in advising me all through the process of thesis writing. His knowledge made me understand in great depths this project and its manifestations.

I am very much thankful with high appreciation to all *others committee members* at FHS -AUB for the kind support and sharing of their valuable comments that made me able to meet this project requirements.

AN ABSTRACT OF THE THESIS OF

Linda Awad Mustafa Haj Omar for Master of Science
Major: Epidemiology and Biostatistics

Title: Measles Elimination in Sudan: Incidence Trend and Vaccine Coverage.

Introduction: Measles remains a leading cause of vaccine-preventable deaths among children worldwide, despite the availability of vaccines and global activities in mortality reduction. In 1997, The EMR adopted a resolution to eliminate measles by 2010 in all countries of the region. However, constrains and challenges forced the delay of the elimination date to year 2015. Sudan is one of the countries still affected by relatively higher measles morbidity and mortality rates. Control activities have been conducted under the Extended Immunization Programme (EPI) – Sudan to reach elimination by 2015, but that goal has not been reached yet.

Aim: To highlight gaps and challenges facing the programme toward achieving the EMR goal of measles elimination by 2015.

Methodology: A descriptive cross–sectional analysis of recorded surveillance and vaccination data was conducted covering all related records between the year 2006 and 2013.

Results: Through-out the 8-year period, the programme reported 17,974 cases and 261 deaths (Case-Fatality Rate 1.5%). Most cases (94.3%) reported over that 8-year period occurred during an outbreak period, which started in 2011 (n=5616), peaked in 2012 (n=8523) and receded in 2013 (n=2813). Cases belonged mostly to the (1-5 years) and (>15 years) age-groups (32.5% and 27.9% respectively). The majority were either epidemiologically–linked (73%) or laboratory-confirmed (23%). Vaccination history of cases showed that out of the total case-load, only 19% had been previously vaccinated and almost all (97%) had single dose of MCV vaccine. The vaccination distribution was highest among age-group (1-15 years) (82%). Nevertheless, only 33% among the vaccinated cases were laboratory confirmed with IgM, indicated a large rate of vaccine primary failure. The analysis of measles surveillance indicators found that all WHO targets for measles elimination had been met since 2007. MCV1 coverage and Supplementary Immunization Activities (SIAs) had reached (>85%) all over Sudan States. However, gaps were mainly detected in MCV2.

Conclusion: EPI-Sudan to face a double challenge in measles elimination. First, it should reach high vaccination coverage across all ages and all States. Second, it has to elucidate the relatively important rates of vaccine primary failure, either by evaluating the integrity of the cold chain and/or assessing the possibility that the virus may have shifted and is now displaying increased resistance to the usual vaccines.

Recommendation: Allocation of more financial resources and trained human personnel to maintain the measles surveillance activities, in addition to implementation of further studies toward measles sero-surveillance as a baseline for geno-shifting of the virus.

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ILLUSTRATIONS

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ABBREVIATIONS

AFP	Acute Flaccid Paralysis
CBS	Cases – Based Surveillance
EMR	Eastern Mediterranean Region
EMRO	Eastern Mediterranean Regional Office
EPI	Expanded Immunization Programs
GAVI	Global Alliance for Vaccines Initiative
IgG	Immunoglobulin G
IgM	Immunoglobulin M
MCV1	Measles Coverage Vaccination with 1st Dose
MCV2	Measles Coverage Vaccination with 2nd Dose
MMR	Measles, Mumps and Rubella Vaccine
MR	Measles and Rubella Vaccine
MV	Measles Vaccine Only
PCR	Polymerase Chain Reaction
SIA’s	Supplementary Immunization Activities
UNICEF	UNICEF United Nations Children’s Fund
WHO	World Health Organization

SUDAN BACKGROUND

Sudan is a strategic link between the Arab world and Sub-Saharan Africa. It shares borders with eight countries. The Sudanese population and that of neighbouring countries move freely and interact across these borders. The latest 10-year population census in 2008 showed a total resident population of 30.9 million. The rural population represents about 65%, in which nomads represent 10%; and 43% of the population is less than 15 years of age. The governmental system is Federal, composed of eighteen States and 180 Districts. The states have uneven population distributions and financial and manpower resources. Differences are often determined by the rural-urban, multi-ethnic and multi-cultural composition of the respective communities (1). The country has passed through many humanitarian and natural emergencies related to civil wars, and natural disasters such as drought, flooding and major infectious diseases outbreaks. Poverty remains widespread with 46.5% of the population living below the poverty line according to the national definition of poverty (about 0.30 USD per person/day). This resulted in loss of qualified working personnel to migration and decreased access required to essential social and health related services especially in rural areas (1). Health services are provided by the Federal and state ministries of health, the Armed Forces, university health facilities, the private sector and the non-profit civil society. However, these providers are performing in isolation with unequal distribution of health care services between the center and the states. This contributed to the ill-defined managerial system for coordination and guidance. Many others barriers and challenges toward health improvement are considered within the country. These are; poor health system infrastructure, lack of population accessibility for vaccination and appropriate health care, inadequate funds for non-emergency interventions, limited human resources and rapid turnover of staff. To address these challenges, the Federal Ministry of Health (FMoH) increased the efforts to enhance the existing health systems by strengthening the national capacities and development of sustainable policies and resources required for provision of health and immunization services and improving their quality. Nevertheless, Sudan is still suffering from huge health barriers, such as the double burden of communicable non-communicable diseases, as well as malnutrition and re-occurrence of some vaccine preventable diseases and multiple outbreaks such measles, diphtheria, watery diarrhea, yellow fever and bacterial meningitis. This uneven epidemiological situation is clearly indicated by maternal and child mortality rates highest among EMR region[(1)].

To
My Beloved Family

CHAPTER 1

INTRODUCTION

1.1. Measles Facts

Measles is an airborne infectious disease caused by an RNA virus of the family paramyxoviridae, transmitted by droplets or by direct contact with infected nasal or throat secretions. It is marked clinically by fever, cough, coryza or conjunctivitis, and maculo-papular rash covering the body. The incubation period of the disease is 10 days, but it could range between 7–18 days from the exposure to the onset of fever and/or rash(2). Measles can induce outbreaks that occur in different seasonal patterns. In moderate climates, outbreaks generally occur in late winter and early spring. In tropical climates, transmission appears to increase after the rainy season(3).

Measles is confirmed by the detection of elevated anti-measles (IgM or IgG) antibody titers and/or direct detection of viral RNA using Polymerase Chain Reaction (PCR) test. Both IgM and IgG are produced, but IgM represents the first immunological response and evidence of primary viral exposure. IgM antibodies production peaks at 7–10 days and is rarely detected beyond the 8th week after the rash onset. The absence of IgM detection in a fever-rash case does not exclude infection, as sensitivity of some of IgM assays may be low or weak. IgG antibodies production follows that of IgM, and peaks about 2 weeks following the rash onset. It can be detectable for years after infection, as a second immune response(4).

Measles is considered as one of the leading causes of death among young children, worldwide in many developing countries particularly. In 2010–2012, there were 122,000–145,000 measles deaths globally and more than 95% of these deaths occurred within the countries of low per capita incomes and weak health infrastructures. In developing countries the Case-Fatality Rate (CFR) due to measles is estimated to be 3%–6%, and among infants aged between 6–11 months CFR could reach as high as 20%–30%. In developed countries, CFR tends to be low, ranging between 0.1–1.0 per 1,000. Measles leads to serious complications appear mostly in young children below 5 years. Measles complications usually involve the lower respiratory tract and may cause deafness. Others like encephalitis and corneal ulcerations were also reported, which resulted in blindness that estimated to be between 15,000 and 60,000 cases annually worldwide [(2)].

1.2. International Measles Vaccination Schedule

Measles is a childhood vaccine-preventable disease, and measles vaccine has been included in immunization programme schedules globally. The available vaccines are the live attenuated monovalent Measles Containing Vaccine (MCV) or combined vaccines. The most common combinations are Measles-Mumps-Rubella (MMR) or Measles-Rubella (MR) vaccines. Both measles vaccines types are equally effective and expected to produce a stable life-long immunity. The efficacy of measles vaccine is 85% when administered at 9 months of age and increases to 90%–95% when administered at 12–15 months. Children in most of countries like European countries and USA usually get two doses of MMR vaccine, the first dose starting at 12 through 15 months of age, and the second dose at 4 through 6 years of age. Others national immunization programmes like Sudan and Jordan vaccinate children providing MCV in two doses MCV_1 at age of 9 months or at 12 months, the second dose MCV_2 at age of 15–18 months [(5)]. Recently countries like Lebanon have moved to add a third measles dose at their vaccination schedule at age of 4 – 5 years[(6)]. Worldwide, two vaccination strategies are used:

- Routine Vaccination (RV) performed in health services as part of the national EPI programs.

- Supplementary Immunization Activities (SIAs) performed through campaigns as needed. The SIAs include “Follow-up vaccination” activities targeting children up to age 5, and conducted every 2– 4 years. They also include “Catch-up vaccination” activities targeting children up to age 15. These SIAs are recommended globally for the following purposes:

  - To enhance the immunity of children, in particular older ones, who either have never been exposed to measles or never got vaccinated or failed to respond to vaccination, accordingly did not develop neither natural nor acquired immunity. This had been demonstrated by serological studies that showed approximately 15% of children vaccinated at 9 months of age and 5% vaccinated at 12 months of age could fail to seroconvert (primary failure) and are therefore not protected after vaccination.

  - To interrupt the virus circulation and outbreak occurrence. Measles induce periodical outbreaks when a critical number of susceptible populations is reached, due to primary failure even where routine vaccination is done as per regular schedules. Outbreaks also occur in some countries where people have no regular access to routine vaccination. SIAs represent focused one-time efforts to reach out susceptible individuals, thus preventing measles virus, when reintroduced in the community, from spreading widely in population (5).

1.3. Measles Vaccination in Sudan

The EPI programme in Sudan had been launched in 1976 under the supervision of the Federal Ministry of Health (MOH), Department of Basic Health Care. Sudan vaccination schedule follows WHO recommendation; the routine vaccination composes of MCV in two doses; MCV_1 at age of 9 months and MCV_2 at age of 18 months. This routine immunization schedule is accompanied with SIAs activities, follow-up (up to 5 years) and catch-up (up to 15 years) campaigns. In order reach measles elimination phase, the programme conducted several vaccination activities, by developing plans and adoption of technical guidelines[(7)]. Also the programme established well collaborations and partnerships with different international UN agencies such WHO, UNICEF and Global Alliance for Vaccines Initiative (GAVI). These partners contributed in achieving a considerable progress in measles vaccination and control. This resulted in achieving more than 80% of measles (MCV_1) coverage rate for consequent 4 years (2008–2011). Furthermore, the second measles vaccine dose (MCV_2) was introduced for the first time in 2012, with initial coverage ranging between 54% and 57%. The programme conducted several catch-up campaigns in 2004 – 2005 and 2013, besides several follow-up campaigns in 2007 – 2011. These series of campaigns have had a substantial impact on the reduction of measles morbidity at each governmental level[(7)]. Additionally, the program has moved to the 2nd step in elimination, which is shifting from enhanced population surveillance to case-based surveillance, as number of cases was dwindling. This case-based surveillance system was implemented in all states with the laboratory as an integral part for establishing effective measles surveillance. This led to the strengthening of the laboratory capacities, contributing to meeting the WHO standard requirement for case investigation (>80%). In 2009, the National Public Health Laboratory (NPHL) became able to isolate the virus circulating during the outbreak in North Darfur, West Darfur, River Nile (B3), Kassala and South Kordofan (D4)[(7)].

1.4. Problem Statement and Justification

Although of all these vaccination achievements at international and local level, only 78% of deaths were dropped between 2000 and 2012 worldwide. Adding to that in 2011 there were eightfold increase of measles cases between 2003 and 2010.

In Sudan, since 1990 and 1994 the coverage reached only 51% of children less than one year were reached, hence efforts intensified more by the EPI-Sudan but up to year 2001 and 2003, vaccination coverage ranged between 50% and 79%[(7)]. In 2003, a large outbreak of >3000 measles cases was reported from all Sudan states (15 States). The central states like Khartoum and White Nile states, accounted for approximately 54% of reported cases. A population-based study conducted in Sudan in 2004 to estimate the burden of the disease due to the outbreak in 2003, found that that CFR was (0.9%; 95% confidence interval 0.16–1.91), which is lower than expected for the region but remains 10 times higher than that in developed countries[(8)]. Furthermore in 2015 Sudan reported a new outbreak, with a total of 2,023 suspected cases, of whom 924 confirmed by laboratory and 610 hospitalized for severe signs or complications. The outbreak affects mainly the Darfur zone and two states from the eastern zone. It is believed that this new outbreak is caused by relentless security circumstances which have delayed the implementation of the SIAs vaccination campaigns in those states[(9)].

Adding to that many others constrains still impede the progress such as the internal emergencies and conflict situations that passed in states such as Southern Kordofan and parts of Darfur Region, vast geographical distribution with the limited financial recourses available and the massive measles outbreaks that hit the country.

1.5. Research Aim and Objectives

The Extended Immunization Programme (EPI) increased work and had considerable efforts toward measles elimination, however it still facing challenges contribute not to reach the optimal elimination goal by 2015.

The available data at the EPI-Sudan during 2006 and 2013 are analyzed to highlight gaps and challenges facing vaccine coverage and surveillance performance quality. As well as the findings and the ultimate recommendations of this study will be shared with the national program in Sudan with the aim of optimizing measles elimination efforts. To achieve this aim, the following objectives will be targeted:

- To determine the incidence of measles in Sudan during 2006 – 2013 and characterize these cases by time, place and person.
- To identify variations in measles vaccination routine and SIAs coverage during 2006–2013, in-term of time of vaccination and the administered number of doses.
- To assess measles surveillance indicators during 2006-2013, such as reporting timelines, investigations outbreaks, system sensitivity and ability of confirmation by lab.

CHAPTER 2

MEASLES ELIMINATION (PROGRESS AND FAILURE)

2.1. Global Vaccination Responses toward Measles Elimination

Globally, as a response to reach elimination and improve health of children, the fourth Millennium Development Goal (MDG 4) called for the worldwide reduction of the under-five mortality rate due to measles disease by two-thirds between 1990 and 2015. Since 1997 tremendous progress in vaccination activities were considered. Therefore the following strategies have been considered:

- *Measles Strategic Planning (MSP):* It's a designed tool by the WHO to help countries in identifying the best possible measles vaccination strategies, based on their programme objectives and financial considerations, to reach measles mortality reduction goal by 2010. Along with these actions three sequential phases for measles immunization programmes are present, as follow:

  - Measles Control Phase: Also known as mortality reduction phase. This phase targets the reduction in measles incidence and mortality, when high levels of vaccine coverage are attained (>80%).
  - Outbreak Prevention Phase: This phase considers aims at maintaining low incidence by improving surveillance in order to understand the changing epidemiology of the disease, identify outbreaks and intervene rapidly to control their dissemination.
  - Measles Elimination Phase: Targets the complete interruption of the measles virus circulation, reaching an incidence of (0 cases) by implementing measles immunization activities (SIAs) in addition to routine

vaccination, with coverage >90%. In this phase, surveillance strategies and activities continue to be improved[(7)].

- *Global Measles and Rubella Initiative Strategy:* It was launched in 2001 in collaboration between the Centers for Disease Control and Prevention (CDC) and the UN agencies: UNICEF and WHO. The Initiative provides technical and financial support to governments and communities for measles vaccination campaigns worldwide. The Measles Initiative has supported vaccination of more than 500 million children. This has resulted in reducing measles deaths by 68% at the global level. In 2009 the number of deaths decreased from 63% to 91% in the African region alone, compared to 2000 (8), within the same region, between the years 2001 and 2011 MCV_1 coverage increased from 56% to 85%. Also in 2012 the African region introduced the second dose of measles vaccination MCV_2 as part of the routine immunization and a total of 568.4 million children were vaccinated through SIAs in that year in the 43 Member States. [(10)].

In 2012, the Initiative was re-organized as a new Global Strategic Plan for both Measles and Rubella elimination, covering the period 2012-2020. By the end of 2015, the goal is to reduce global measles deaths by at least 95% and to achieve regional measles and rubella/congenital rubella syndrome (CRS) elimination. By the end of 2020, the targeted goals are:

- To achieve measles and rubella elimination in at least 5 WHO regions.
- To maintain vaccination coverage by 2 doses of measles-and rubella containing vaccine.
- To develop and maintain outbreak preparedness, respond rapidly to outbreaks and manage cases.

- To communicate and engage to build public confidence and demand for immunization.
- To perform the research and development needed to support cost-effective operations and improve vaccination and diagnostic tools [9].

- *Regional (EMR) Measles Elimination:* the EMR total mortalities due to measles dropped by only 78%, much less than the drop targeted by the WHO. Therefore, members of the Eastern Mediterranean Region (EMR) had resolved to eliminate measles from their region by 2010. The generated strategy composes of two main compounds; vaccination and surveillance compounds that both targeted to achieve the following objectives:[11]

- To achieve ≥95% vaccination coverage of children with the first dose of measles-containing vaccine (MCV1) in every district of each country through routine immunization services.
- To achieve ≥95% vaccination coverage with the second dose of measles-containing vaccine (MCV2) in every district of each country either through a routine 2-dose vaccination schedule or through supplementary immunization activities (SIAs).
- To conduct high-quality, case-based surveillance including proper reporting system in all countries.
- To provide optimal clinical case management, including supplementing diets with vitamin A.

Achievements toward elimination varied across countries: 12 of 22 countries had achieved 95% for MCV_1 in 2011; 19 EMR members had implemented the 2nd dose of measles vaccine through routine services in 2012. Adding to that five countries have adopted a 3-dose measles vaccine strategy, these are Jordan, Lebanon, Saudi Arabia, United Arab Emirates and Iraq. This was followed by the vaccination of 30 million children through measles SIAs, reaching 95% coverage. Other countries as Afghanistan, Egypt, Iran and Sudan conducted smaller-scale and focused immunization campaigns in high-risk areas as a response to measles case-clusters. These efforts by EMR countries had finally resulted in reduction of measles mortality by 90% in 2012, compared with 2000[(10)].

For example; in Somalia and despite of enormous challenges like: poor infrastructure of health system and political instability. It would be found that the country was able to establish and accelerate measles control activities since 2005. Measles incidence was reduced by >80%, in particular after implementation of catch-up campaigns in 2005 and 2007. While case-based surveillance was still in its early stages, it included a network with a proper number of sentinel sites. Laboratory confirmation of cases is performed at the nation laboratory to provide measles confirmation based on IgM results[(12)].

2.2. Surveillance Measures toward Measles Elimination

With the above mentioned elimination strategies, measles surveillance should evolve with each phase of control and elimination. An efficient surveillance system characterized with completeness and timeliness of reporting is arguably the most important public health tool for to ensure proper control of any communicable preventable disease. Countries in the mortality reduction phase (control) should concentrate on raising routine measles immunization coverage and strengthening their surveillance and case-reporting capacities. Countries in the elimination phase have achieved high levels of population immunity against measles and low measles incidence of (< 1 case), with or without periodic outbreaks. Therefore these countries have been recommended to shift from routine surveillance system to Case-Based Surveillance (CBS)[11]. Surveillance system shifting requires reporting and outbreak investigating for every suspect case immediately with laboratory confirmation whenever possible, to be included in the weekly reporting system. In presence of others cases with rash illnesses such as rubella or scarlet fever, the laboratory process plays a central role in the confirmation of suspected measles cases and outbreaks, beside identification of circulating strains of measles viruses. Information regarding the circulating strains are useful to track genotype of measles virus when a country is in the elimination phase. Hence it’s recommended that during outbreaks specimen collection should be limited to the first 5 suspected cases[7],[12]. To ensure proper identification of true measles cases and facilitate notification process within the countries’ elimination targets, WHO recommends a unified case definition, as follow:

- *Clinical case definition*: Any person in whom a clinician suspects measles infection, or

any person with fever and maculopapular rash and cough, coryza or conjunctivitis.

- *Surveillance case definition (suspected case):* this is a country-specific definition. It consists of a clinical case presentation (Goblet Spots) or presences of fever & rash or suspected by a clinician. This type of definition is most commonly reported in a situation of outbreak or among contact of a confirmed case.

- *Confirmed case:* for measles case confirmation two ways are considered:
    - Laboratory confirmation includes titers of measles antibodies (IgM or paired IgG), OR direct viral isolation, or viral RNA detection. As recommended by the WHO two types of samples should be obtained: one of serum blood or dry blood or oral fluid for immunoglobulins detection; and another of urine or throat swab for viral detection.

- Epidemiological linkage is defined as direct contact with another laboratory-confirmed measles case in which rash onset occurred 7-18 days before the present case[7], [12] .

Also to attain sustainable achievements regarding measles elimination and carry out more intensive surveillance, the EMRO recommends specific measles surveillance performance indicators to be considered during the elimination phase and vaccination coverage in different countries. Therefore many of EMRO countries have set up micro-plans based on their countries situation to strengthen measles surveillance particularly after implementing catch-up campaigns with emphasis on case reporting and laboratory confirmation of suspected cases. For each of these indicators, the WHO defined a specific percentage as the targeted achievement. These indicators include [12]:

1.	Completeness and timelines of reporting	**≥ 80%**
2.	Case investigated < 48h after notification	**≥ 80%**
3.	Cases with adequate blood sample	**≥ 80%**
4.	Laboratory-confirmed cases	**≥ 80%**
5.	Laboratory results available within 7 days	**≥ 80%**
6.	Outbreaks source identified	**≥ 80%**
7.	Reporting rate of non-measles, non-rubella among fever/rash cases	**≥ 2 /100, 000**
8.	Incidence rates	**0 /1,000,000**
9.	Population Coverage	**≥ 95%**

2.3. Global and Regional (EMR) Challenges toward Measles Elimination

Even with significant progress still outbreak reported at several countries and regions globally. In fact since 2008, measles outbreaks have occurred in many countries worldwide, even in some which had declared measles elimination such as the USA and European countries. However the major set-back on measles elimination occurred in the 2009-2011 global outbreaks and beyond. In that year, there was an eightfold increase of measles cases over the previous annual average. Europe contributed to a rise in the global number of reported cases from 7,499 in 2009 to 30,625 in 2010, with most cases and outbreaks occurring in western European countries[(10)]. Furthermore, between January 2014 and March 2015, WHO received notification of over 23,000 cases of measles in the WHO European Region, now mostly from Eastern Europe and Central Asia. Kyrgyzstan reported over 7,000 cases in just the first seven weeks of 2015. Significantly higher numbers of measles cases have also been reported in Bosnia and Herzegovina, Croatia, Georgia, Germany, Italy, Kazakhstan, Russian Federation and Serbia [(13)]. Similar situation was observed as well as in the American Region, in 2010 a total of 1,290 cases were confirmed as measles and higher numbers have been reported since, although with decreasing loads annually. Cases in the USA have been reported from 18 states and the District of Columbia. Over 80% of the cases occurred among persons who were unvaccinated or had unknown vaccination status[(14)].

In the African Region in year 2010, 28 countries experienced measles outbreaks with incidence levels up to 165 cases per million population, as compared to incidence levels of 10 – 40 per million between years 2007 – 2009 within the same region.

In the EMR the situation was more complex; several countries of the region have encountered major measles outbreaks between 2009 and 2012. The recent situation of internal conflicts, political changes and financial constraints in numerous EMR countries constitute major challenges to reach measles elimination goals by 2010. Only 9 out of 22 have reached a measles incidence of (<1- 5 case) per million (the 6 GCC countries plus Jordan, Tunisia and Lebanon). It would be found that the total confirmed measles cases reported in 2011 – 2012 was 9,315 and 7,827 cases respectively. Of those, 87% - 90% were reported from Afghanistan, Pakistan, Sudan and Yemen. Sudan alone accounted for 50% of the case-load in 2011 and 62% in 2012[10]. Majority of EMR's countries had success to conduct case-based surveillance, except (Morocco, Somalia and Pakistan). However, countries with CBS achieved reporting rate of suspected measles case of 2.19 cases per 100,000 persons. Also 19 countries only could achieve target of >80% in all others indicators. To improve virologic surveillance, 17 (77%) of the 22 national laboratories received training and now have the capacity to do measles and rubella virus isolation or reverse-transcription-polymerase chain reaction (RT-PCR) testing[12].

A number of studies have been conducted either within EMR countries or not to addressed the related elimination challenges by these countries. One of these studies had conducted in Pakistan to estimate the proportion of measles susceptible children in Karachi, the largest metropolitan city of Pakistan, after the nationwide measles SIA in 2007-2008. Oral fluid specimens of 504 randomly selected children aged 12-59 months were collected to detect measles IgG antibodies. Results found that measles antibodies were detected in only 55% of children. The proportion varied between children whose families reported receiving a single dose (78%) or two doses of measles vaccine (12%). Among the children who had received a single dose of measles vaccine 58% had serologic immunity against measles, while among those who received two doses 64% had evidence of measles immunity. The study concluded that it is important to strengthen routine immunization services using high quality mass vaccination campaigns to achieve measles elimination in Pakistan [15].

Although majority of EMR countries introduced CBS, measles surveillance system is not functioning at the same levels of optimal performance among all of them. Relevant to that, a retrospective review of records was conducted in Qatar, a country in the elimination phase of measles, to evaluate the timeliness of notification and completeness of surveillance data. The review was conducted in 2008 and studied the measles notification and investigation forms based on WHO recommendations. The elements of the study considered data related to vaccination history, date of birth, geographical distribution, date of case investigations and notification, beside the results of measles serology. Results showed that the prominent deficiency was in the notification forms that lacked information on vaccination history and blood specimen collection. Overall, 85.0% of notification forms missed at least 2 of the 6 minimum required data elements. Compared to WHO recommended benchmarks, the percentage of suspected cases reported within 48 hours was only 27.8% (compared to recommended ≥ 80%), while 43.6% were reported between 2 and 7 days (also compared to ≥ 80%). The study also concerned with notification quality from various sources. It found that only 33.3% of the notifications from PHC centers had legible information on vaccination history, and an even lower rates (6.9%–17.9%) from other facilities (p=0.005)[16].

In addition to a performing surveillance system, an effective program to eliminate and eradicate an infectious disease such as measles requires existing of a qualified laboratory able to provide adequate confirmation of suspected cases. A retrospective study was conducted in Zimbabwe for the period 2004–2009, to assess measles laboratory performance against predefined WHO indicators.

Data was retrieved from the National Measles Virology Laboratory of Zimbabwe. The report showed that 66.8% of the samples were received in the lab within three days and that 92% of serum specimens arrived in the laboratory in good condition. For the feedback, 77% of the results were sent back to the national centers within 7 days. Also for quality certification the laboratory sent 13% of representative sera for regional reference laboratory co-testing and the concordance of results was

98%. An average of 27% of patients showed positive measles IgM although of their positive vaccination history[18].

2.4. Adapted Measles Elimination Strategy by EMR

The persistent challenges and reoccurrence of massive measles outbreaks at global level general and at regional level (EMR) particularly, had end with a negative impact toward total achievement of the elimination target by 2010. To cope with these new challenges in 2011 the Regional Committee of the Eastern Mediterranean resolved to revise the target date of measles elimination to be 2015, with emphasis on increased vaccination coverage and improved surveillance systems. Due to this variation and to prevent invalid reports of measles cases among the region, the Regional Committee of the Eastern Mediterranean categorized the countries into 3 groups:

- Countries ready for validating elimination (reporting 0 cases for ≥2 years or more in presence of with a nationwide measles case-based surveillance, high measles coverage for both (MCV1 and MCV2) such as Kuwait, Qatar, Bahrain, UAE, KSA, Oman, Jordan.

- Countries close to elimination (incidence < 5 cases/1,000,000 with a nationwide measles case-based surveillance, high measles coverage for both MCV_1 and MCV_2), such as Palestine, Egypt, Iran, Iraq, Tunisia, Lebanon.

- Countries with high burden of disease, including; Afghanistan, Djibouti, Libya, Morocco, Pakistan, Somalia, *Sudan* and Yemen [14].

In addition to that, the WHO recommended countries in the elimination phase to achieve high levels of population immunity against measles and low measles incidence, with or without periodic outbreaks, through;

- Ensuring and maintaining of proper routine and SIAs vaccination activates.

- Ensuring of proper identification of true measles cases, by using of the recommended unified case definition.
- Shifting from Routine Surveillance System to Case-Based Surveillance (CBS), therefore it requires outbreak investigating for every suspect case immediately with laboratory confirmation whenever possible, to be included in the weekly reporting system
- Following of measles surveillance performance indicators considered during the elimination phase as recommended by EMR.

CHAPTER 3

MATERIALS AND METHODS

3.1. Study Design

A descriptive cross–sectional analysis of recorded surveillance and vaccination data was conducted covering all related records between the year 2006 and 2013.

3.2. Sources of Data

The source of data was the EPI programme at FMOH – Sudan, including all the reported cases data in addition to the vaccination records at the surveillance and vaccination departments of the programme.

3.3. Data Management and Analysis

As a policy at EPI programme in Sudan, both measles and rubella cases are reported at one surveillance system. Nonetheless, to achieve the research objectives of measles cases descriptive part, *only measles cases* were considered in the analysis. Rubella and others discarded cases (non- measles or rubella) were considered in the analysis to assess the overall quality of reporting of the surveillance system and elimination standards.

Cleaning and coding were performed prior to analysis, and some variables were grouped as needed. During analysis, missed data were not considered nor included in the total. Data were analyzed using SPSS version 20.

For the descriptive analysis, data are presented as frequencies and percentages for categorical factors, or with measures of central tendency (mean, standard deviation

(SD), range) for those continuous ones. Specific associations (cross-tabulation) between some aggregate variables were investigated and calculated using Spearman coefficient such as, correlations between vaccination status with sex and age groups and vaccination coverage by age-groups with vaccination strategy and number of doses. The correlation significance level was defined for a (p-value ≤ 0.05).

3.4. Study Variables

A total of 30 variables were available at the surveillance entry sheet to be studied as aggregated from the national statistics. All variables were defined and tabulated and presented in figures. The required data are described in a table below and some have been defined below also. However, for facilitation purposes theses data have been grouped into:

- Cases Demographic Data.
- Cases Outbreak Investigation Data.
- Cases Vaccination Data.
- Cases Laboratory Investigation Data.

Study Variables

1. Year of reporting
2. State
3. Total Population per Year
4. Number of Cases per Year
5. Age in years
6. Age groups (≤ 1year, 1 – 5 year, 5 – 15 year & > 15year)
7. Sex
8. Definition of fever and rash cases

9. Measles Case Classification
10. Source of Notification
11. Date of Notification
12. Date of Investigation
13. Vaccination Status
14. Vaccination Strategy
15. Number of Vaccination Doses
16. Date of Last Vaccination
17. Sample Collection Obtained
18. Type of Sample Collected
19. Condition of Sample Collected
20. Date of Sample Collected
21. Date Sample Sent to Laboratory
22. Date Sample Received at the Laboratory
23. Laboratory results of Measles Cases
24. Laboratory results of Rubella Cases
25. Date of Result Sent to EPI
26. Outcome: full recovery, disability (mostly blindness), death
27. Incidence Rate /1,000,000 per Year
28. Outbreak Investigation Response Time in Days
29. Outbreak Investigation Response Time Grouping (On–time/Late)
30. Laboratory Feedback Result Time (On–time /Late)

3.5. Definition of Variables

- *Fever and rash cases:* The EPI programme – Sudan follows the WHO standard case definition of fevers and rashes which eventually classifies them into either well-defined Measles or Rubella cases or Discarded (non- measles or non-rubella) cases.

- *Measles case classification:* This includes measles cases classification and definition recommended by the WHO as considered earlier in the introduction part on page13. In this analysis, for the laboratory confirmation of cases based on positive results from either Ig levels or PCR results. Some clinically-suspected cases were temporarily defined as "equivocal" (EQUI) when the first tests did not yield conclusive results. Also, the cases that had samples for (Ig and PCR) are reflected in the analysis with "Combined". Also to confirm a measles outbreak, WHO guidelines require to test and confirm 5–10 cases.

- *Source of Notification:* This variable describes the site from which the report was initiated to the surveillance system. These sites include: hospitals, health centers, community practice or other private care settings. Hospitals and health centers are considered the main source of notification, as several of these sites already fulfill the criteria of sentinel sites accredited by the Sudan surveillance system.

- *Vaccination Strategy*: EPI – Programme at Sudan has 2 main vaccination strategies according to WHO recommendation; routine and campaigns vaccination strategies. The routine includes MCV1 vaccination that targets children at the age of 9 months and MCV2 that added at age of 15 – 18 months after the first dose. To interrupt the transmission of measles, Supplementary Immunization Activities (SIAs), are included and achieved through; follow-up campaigns that conduct at appropriate intervals every 2 – 4 years, targeting children up to age 5 and the Catch-up campaigns targeting children up to age 15.

- *Vaccination Doses*: Two doses of measles vaccine are recommended

(MCV1) (MCV2), through the routine strategy, while other doses can also be obtained when SIAs activities are conducted.

- *Incidence rate*: A zero incidence rate is a required indicator for measles and rubella surveillance performance to reach elimination certification according to WHO recommendations. However for epidemiological characteristics analysis incidence rate will be calculated of measles cases only.

- *Outbreak Investigation Response Time in Days:* This is a time calculated according to the formula: *{Date of Investigation – Date of Notification}.* This variable reflects the time consumed to conduct the outbreak investigation activities. The "*On-time*" investigation response time is within 1–2 days (24–48 hours). A response time of more than 2 days indicates a **"*Late*"** investigation.

- *Laboratory Feedback Result Time*: This is a time calculated according to the following formula {*Date of Results Feedback – Dates of Samples Received by Laboratory*}. This time reflects the duration of the feed-back from the Laboratory to the EPI – Programme at the MoH. The results should be sent back to EPI–Programme within 7 days to be considered "*On – time*". If more time is used, the feed-back is considered as **"*Late*".**

3.6. Study Strength and Limitations

3.6.1. Strength

- Accessibility of the data due to the collaboration of the EPI-Sudan for providing of the required information required for the study.

- Availability of good and adequate date for both surveillance and vaccination data, in addition played a major role in having a considerable amount of information within a short period of time.

3.6.2. Limitation

- Such huge amount of data possibility of having missing data could limit the analysis for some certain variable which could lead to under-estimations of the complete and true dimensions of the process.
- Availability of large amount data and information could sometimes barrier the possibility to of conduction all the analysis required easily.
- Possibility of having under or over reporting of the routine surveillance data is still there, also vaccination data as recorded officially is subject to the veracity of the reports by civil servants who may not be willing to show gaps in their performance, and would tend to white-wash unsatisfactory situations.

CHAPTER 4

RESULTS

To cover the study objectives probably the results of the study will be divided into 2 parts as follow:

Part I: to cover objectives no.1:

- Determine the incidence of measles in Sudan during 2006–2013 and characterize these cases by time, place and person.

Part II: to cover objective no. 2 and 3:

- Identify variations in measles vaccination routine and SIAs coverage during 2006–2013, in-term of time of vaccination and the administered number of doses.
- Assess measles surveillance indicators during 2006–2013, such as reporting timelines, investigations outbreaks, system sensitivity and ability of confirmation by lab.

4.1. Part I: Measles Dynamics in Sudan 2006-2013

4.1.1. Epidemiological Characteristics of Reported Measles Cases

The total number of reported measles cases between 2006 and 2013 was 17,974, with the minimum reported cases in 2009 (68 cases) and the maximum in 2012 (8,523 cases). The number of cases remained relatively constant low and fluctuating at less than 300 per year between 2006 and 2010, but then increased to reach the peak in 2012 with 8,523 cases. Across the eight years of follow-up period, measles cases were more frequent in male (57.7%) than in female (41.9%). Age trends showed that age-group (1–5 years) had the highest reported case-load with 5,808 (32.5%), then age-groups (>15 and 6-15 years) to be 4,994 (27.9%) and 4,293 (24.0%) consecutively, while the least case-load was among age-group (<1 year) with 2,798 (15.6%). The case incidence rate corresponded to the number of reported cases that remained at lower levels (about 1–2 cases per million) between 2006 and 2010. However, it increased thereafter with an incoming outbreak to reach a maximum of 243.1 per million in 2012. All related details are showed in Table A1.

According to available data, deaths started to be reported within EPI surveillance system in 2010, so the total of deaths between 2010 and 2013 was 261 yielding a Case-Fatality Rate (CFR) of 1.5%, which increased by years from 0.8% in 2010 to 1.9% in 2013. Mortality Rates also available after 2010 fluctuated in parallel with the magnitude of the epidemic, as detailed in Table A1.

The geographical distribution of cases among Sudan States reflected differences in social and environmental characteristics. Hence the number and relative proportions of the case-load showed variation among the country states, accordingly. The higher relative case-loads during the study period came from Northern Kordofan State (27%), compared to Kassala and Khartoum States who shared the same percentage (12.0%) and (11.0%), in addition to River Nile Sate that reported (10%). On the other hand, percentage distribution of cases among other states ranged between (1 – 10 cases). More details are showed in Figure A1.

4.1.2. Measles Cases Classification, Sources of Notification and Outbreak Response Rates

In non-epidemic years 2006 – 2009, most of the reported cases were clinically diagnosed that presented with highest percentage of (83.6%) and lowest of (36.8%). Then the tendency reversed towards the epidemiological link during the outbreak years to reach (82.6%) in 2011 and (77.0%) in 2012. The laboratory confirmed cases showed remarkable increase from (57.7%) in 2008 to (69.0%) in 2010, but then stated to decline when the outbreak became massive as in 2012 (22.3%). However, this increase in laboratory confirmation compared to clinical confirmation in non-epidemic years reflects the start of an appropriate case-based surveillance with clear standards and resources made available for laboratory confirmation. Details are shown in Table A2. Regarding the source of notification, it would be found that the majority of cases were reported by hospitals (68.5%), then by health centers (17.4%). Nevertheless some of these clinics and health centers work as sentinel sites according to specific selection criteria by the EPI-Sudan. Active search by surveillance officers in affected communities was also reported, but with a lower percentage (4.0%) compared with clinical sites. Considering response time, results showed that (95.5%) of outbreak investigations were on time, while (4.0%) were late investigations, according to recommended timelines for investigations. Table A3 shows these details.

4.1.3. Laboratory Case-Confirmation

Results showed that out of 17,974 cases, 4,303 (23.9%) provided specimens for laboratory testing. In almost all cases had positive confirmation (99%), while the other results were either clearly negative (0.3%) or equivocal (0.7%) even after testing twice for IgM levels. Considering the type of specimen collected, it would be found that only (20%) of specimens provided allowed for combined testing by Ig analysis and PCR, while all other provided specimens for Ig analysis only, most commonly serum blood samples (70%). Also (98.7%) of the tested specimens had arrived at the laboratory in adequate conditions. The relative proportion of positively identified cases by age-groups mirrored the overall case-load, except the older group (>15 years) that composed about

(21%) of laboratory-confirmed cases, while it represented about (28%) of the entire case-load. Males confirmed cases were more relatively frequent (56.8%) than females (43.2%), also mirroring the sex distribution of the overall case-load. Details are in Table A4.

4.1.4. Vaccination Status of Measles Cases

Out of 17,974 measles cases, only 3,406 (19.1%) had previously been vaccinated, while 14,568 (80.9%) had not. Compared to not previously vaccinated cases, the majority (82.8%) of those vaccinated tended to be from age-groups (1-15 years), reflecting the phasing-in of larger measles coverage in more recent years. In contrast, the largest relative proportion in non-vaccinated cases was found in the older than 15 years group, with significant changes of ($p < 0.01$). The results showed that females were significantly more represented in the vaccinated cases (45.6%) than in the non-vaccinated (41.2%) with ($p < 0.01$). According to the measles case classification it would be noticed that the clinically confirmed cases were relatively low among the both vaccination groups, while the epidemiologically linked cases were considerable high among the vaccinated and non-vaccinated groups to be 59.2% and 76.7%, consecutively. The laboratory confirmed cases showed higher percentages (33.4%) among the vaccinated group compared to non-vaccination, and all showed statically difference ($p < 0.01$). Related details are presented in Table A5. By geographical distribution, all Sudan states showed similar low proportions of vaccination coverage among the previously vaccinated cases. Conversely, States like Northern Kordofan, Kassala and Southern Kordofan States, showed high percentages of non-vaccinated cases compared to vaccinated to be (30.1%), (13.7%) and (1.3%), respectively, as shown in Figure A2. Further analysis for vaccination strategies and doses by age-groups showed that routine vaccination strategy was covered among all ages, but the highest percentages were among age groups ≤ 1 year and >15 years (76.6% and 57.0% respectively). Compared to campaign strategy the highest percentage was among age group of 6-15 years (51.5%) with good statistical difference ($p < 0.01$). Vaccination with one dose was the dominating pattern among all age–groups (93.4%), ($p < 0.01$) and it was enough to generate immunity as indicated by positive IgM results in almost all cases (98.7%). Although this showed no statistical differences, but obviously could be too late to stop an infection already nearing symptomatic levels. Details are presented in Table A6. Analysis was conducted on those cases with a previous history of vaccination. Data showed that coverage of previously vaccinated cases by routine strategy was highest in 2013 (74.7%), while coverage through vaccination campaigns was highest in 2011 (58.8%). Details are presented in Table A7.

4.1.5. Outcome Characteristic of Measles Cases

Outcome data started being recorded since 2010, and were available for 17,207 cases. Out of those cases, 16,756 (98.5%) recovered, 261 (1.5%) died and only 2 recovered but remained blind. The peak number of death was reported in year 2012, which was also the peak year of the epidemic, as shown previously in Table A1. Age-group 1–5 years was more represented among deceased cases (41.8%) than expected from its proportion in the overall case-load (32.5%). In all other age-groups, the relative proportions were almost similar. The sex-distribution among deceased cases mirrored that of the overall case-load, with a male predominance (54% and 46%) respectively. Epidemiologically-linked cases predominated (93.1%) in the dead case-load. The vast majority (91.2%) of dead cases had not vaccinated cases. Although results showed that majority of the deaths were among whom routinely vaccinated (52.2%), but all (100%)

had received only single vaccination dose. The epidemiological characteristics of deaths are detailed in Table A8. The geographical distribution of fatal measles cases was represented in Figure A3, where North Kordofan State had the highest percentage of deaths (22.2%), followed by Kassala State (21.8%), White Nile (12.0%) and then Khartoum State (9.2%).

4.2. Part II: Population Vaccination, Measles Elimination Surveillance Indicators in Sudan

Two elimination indicators are considered: total population coverage and the incidence rates reported in the surveillance system for both measles and rubella case.

4.2.1. Population Coverage

On average, national routine vaccination with MCV_1 dose had been increasing over the eight-year of surveillance period from (76%) in year 2007 to reach the peak (87%) in 2011, but decreased again to be (85%) in 2012 – 2013. However; in general the improvement was reported from all states with few exceptions; like South Kordofan which was going through a period of civil unrest from 2011 and North Kordofan where coverage unexpectedly decreased from (83% or more) in 2009 to 62% in 2013. In comparison with others states such as Gadarif State coverage increased through years from (73%) as in 2008 to (91%) in 2013. in. The second dose (MCV_2) was introduced in year 2012, and coverage started improving slowly from 24% in 2012 to 57% in 2013. Further details are shown in Table A9.

In addition to routine coverage, SIA campaigns have been conducted periodically, in two different forms: follow–up and catch–up campaigns. Follow–up covered age-groups up to five years during 2007-2008 and 2010-2011. For these years, coverage percentage was constantly high (95%–100%) in all states (Figure A4). During the years of study, a “catch-up” campaign was also conducted in 2013 to cover age-groups up to 15 years, as a response to the mounting epidemic. The target population for the “catch-up” campaign was estimated at 15 million and was covered at a rate of (98%). All states reported high coverage (>90%), except in Southern Kordofan (64%), where political instability limited the campaign’s outreach (Figure A5). F-test showed no significance difference between vaccination strategy and number cases, (p 1.636). Conversely, No significance different was found between number of cases and vaccination doses (MCV_1 and MCV_2), ($p < 0.01$) at α level of 0.05. A summary of the various strategies of the national coverage by year is presented in Figure A6.

4.2.2. Incidence Rates

According to WHO recommendation, elimination is defined as a zero incidence. This level has not yet been reached for measles or rubella in Sudan, even outside the epidemic period. Data compiled for both entities showed that incidence rates were relatively low in non-epidemic years (2006 – 2010) (14.6 –24.6/1,000,000), compared with the epidemic years that reached a peak in 2012 (250/1,000,000). Details are presented in Table A10.

4.2.3. Measles Surveillance Indicators

The WHO recommends certain indictors to measure a country surveillance performance towards measles elimination. These indicators have been analyzed using data for measles and rubella, as compiled in the system. Results presented in Table A10 show the following:

- Completeness: high annual percentages (97%-100%)

- *Timeliness:* high annual percentages (97%-100%)
- *Case investigation within ≤ 48h of notification:* Sudan showed slow but steady improvement in investigation within recommended times, from 60% in 2006 to 97% in 2013.
- *Laboratory Indicators:* For case–based surveillance, WHO recommends 3 indicators for laboratory performance:
- *Adequacy of blood samples:* Sudan reported above 93% rates of adequate sampling throughout the eight years of study.
- *Laboratory-confirmed cases:* The year-to-year performance was inconsistent and presented no clear pattern, with some years showing extremely poor performance.
- Laboratory feedback obtained within 7 days of testing: Data found an unexpectedly lower performance in years 2010 -2011.
- *Reporting Rate of Non- Measles and Non-Rubella Cases:* This rate reflects the specificity of surveillance of cases of "fever-rash", where measles and rubella should be ruled out. WHO recommends having at minimum of 2/100,000 cases detected as non-measles, non-rubella as an indicator of good performance for elimination. Results showed that this rate reached a peak in 2010 (3.8/100,000) only to drop back unexpectedly in following years.

4.2.4. Uncoupling Morbidity and Mortalities from Vaccination, 2006 -2103

To assess measles incidence in the study years (2006 – 2013), we have used the Northern Kordofan State as a benchmark. This State has reported the highest percentage of cases (27% or 4,865 cases) and deaths (22% or 58 deaths) of the total nationwide reported cases and deaths. In fact, the state reported un-matching finding between its regular vaccination activities and reported cases among the study years. The peak of cases was reported in 2011 (2054 cases) and of deaths in 2012 (33 deaths), despite high MCV1 average coverage percentage (80%) and conduction of SIAs in both years. In comparison, in 2013, the state reported (779 cases) and (7 deaths) while reporting lower routine coverage percentage (62%). Details are shown in Table A12. Other states also have shown un-matching findings: Kassala and Khartoum States. Both states also reported respectively the second highest percentage of cases (12%) and (11%) and deaths (22%) and (9%) of the total reported cases and deaths in Sudan. However, both were among the states that were reporting continuous high MCV1 coverage percentages reaching 85% or more in addition to SIAs conducted repetitively. These findings are presented in Figure A7.

CHAPTER 5

DISCUSSION

5.1. Measles Elimination in Sudan

Before measles vaccines became available, virtually all individuals contracted the disease with an estimated 130 million cases each year, worldwide. Improving vaccination coverage and reaching an elimination phase were declared as global aims between 1990 and 2015. Practically all countries have introduced MMR/MCV vaccines in their routine immunization schedules [9]. In Sudan important progress towards the goal of measles elimination has been achieved. During the 8-year period covered by this analysis, most of Sudan States reported adequate coverage of MCV_1 (80%–100%), but some had a coverage percentage at 75% or less. The gap in routine coverage across States has not yet been totally covered with the second dose (MCV_2) which has been introduced incrementally only since 2012. MCV_2 national coverage has thus increased from 24% in 2012 to 57% in 2013. Nevertheless full routine coverage with 2 doses of vaccines as recommended now by EPI-Sudan remains a weakness point towards measles elimination across the national territory.

Sudan faces huge challenges in reaching optimal vaccination coverage across the territory. Its geographical vastness means that a lot of financial and human resources are required to be able to distribute the vaccines and administer them under ideal conditions. Insufficient vaccine storage and cold chain in a large and economically challenged country such as Sudan may reduce the efficiency of the vaccine and produce low immunity levels leading to outbreaks. A scenario involving logistical gaps leading to lost potency of the vaccine is suggested in the situation of the River Nile State.

Despite being a stable, safe state and having high measles routine coverage (83% - 98%) all through the 8 years of this study, but it reported 10 % of the case-load, comparing to State of Gazera that had almost the same level of coverage (>95%) and reported much lower numbers of cases. Other scenarios like variation of regional demographic characteristics, population movement from the rural areas to urban or central areas and subsequent crowding and overpopulation in urban/suburban areas as in Khartoum State, can render regular complete vaccination difficult. Therefore, the reported morbidity and mortality can be particularly higher in such areas during outbreaks periods.

To address the weakness in routine coverage, SIAs “follow-up” campaigns which target age-groups up to five years, regardless of their previous measles vaccination status, are conducted periodically. They have reached high coverage (95%–100%) rates in all states during the four years 2007-2008 and 2010-2011. Further activities can also be implemented in response to periodic outbreaks, typical of the one reported in 2012. These activities consist of a “catch-up” campaign such as the one conducted in 2013 which reached an estimated 15 million children aged up to 15 years. The estimated coverage rate was 98% in all Sudan states, except Southern Kordofan (64%) which was experiencing political instability in 2011-2013. However, the negative effect of longer intervals between SIAs has to be considered in addressing the problem of recurrent outbreaks. In Bavaria (Germany), records were reviewed after an outbreak in 2013, which showed that in 1988, among 86,000 children aged 10–12 years, 54.8% of the children were found to have had one dose of measles vaccine. Due to a lack of concerted catch-up campaigns of measles vaccination many children who were unvaccinated in that year were a good foci for low herd immunity within the Bavarian community, so the accumulation of considerable susceptible cases led to several major outbreaks of measles in the area over the previous years [25].

Slow but steady progress in immunization coverage has been accompanied by the construction of an increasingly valid and complete case-based surveillance system in all Sudan States, which refers to one national accredited laboratory of reference (National Public Health Lab-NPHL). Since 2007, most of the recommended surveillance indicators including investigation of each suspected measles case, collection of clinical and epidemiologic data, case-reporting and collection of serum (IgM) and other specimens for virus isolation, have met the WHO standards of more than 85%. Besides that, the NPHL has acquired the capacity to identify viral genotypes in specimens obtained from suspected cases. As per EMRO standards, a country is considered as reaching the elimination phase when it reports an incidence rate of (0) cases over three consecutive years. Sudan's incidence rates have widely varied over the 8-year period of the study, without ever reaching less than 5 cases per million. While this may be a disappointing result, it should be benchmarked against countries going through similar economic and political hardships. Within the EMR, Afghanistan, Djibouti, Somalia, Iraq and Yemen, are also lagging behind the elimination goal, due to the poor financial resources, huge political instability and natural disasters [13]. For example Somalia since 2001 reported a routine coverage between 20% - 40%, with lack of measles case investigation [17]. In countries that reached elimination phase such as Qatar, limitations appear on surveillance indicators as reported in a study in 2008. They were related to incomplete notification and/or investigation forms, which may mean that cases are occurring but are just not being reported [16]. Overall, measles will remain a difficult disease to eliminate. Even full coverage rates or surveillance completeness cannot always protect any country from surges in incidence and related mortality.

5.2. Measles Outbreaks in Sudan

Amidst improvements in measles vaccine coverage and surveillance, periodical outbreaks still occur worldwide, although they tend to become less frequent and smaller in size, in parallel with the depletion of the pool of initially non-vaccinated adults. However, the persistence of special adverse circumstances and challenges in some EMR countries may limit this favorable progress causing low immunization. In Sudan an unexpected rise in measles cases was recorded in 2011 (n=5616) compared to the previous two years (n=69 and n=255), suggested the start of a new outbreak. In fact, the outbreak peaked in 2012, to slowly disappear in 2013. The analysis showed that almost all Sudan states and age-groups have been affected by the outbreak, although the case-load was concentrated in heavily populated Northern Kordofan, Kassala and Khartoum States, and among the age-group 1–15 years. The analysis found that several states with high bulk of cases had as well a history of low vaccination coverage. Therefore the accumulation of susceptible individuals in pockets or clusters because of lack of complete vaccination particularly in communities that are hard-to-reach such as Northern Kordofan State, or do not wish to be vaccinated as in the Eastern Zone (Kassala and Red Sea States), or population in forced migration and overcrowding situations such as Khartoum State, may understandably increase the risk of reducing of the herd immunity with communities leading to outbreaks. It is natural that lower coverage would result in regular outbreaks. Qatar conducted a study to assess the demographical and epidemiological characteristics of a measles outbreak in 2007. The study found that out of 362 confirmed cases, unvaccinated cases represented 35.9%, and 47.0% were of unknown vaccination status. The bulk of unvaccinated cases were among age group of < 1 year and > 15 years [(26)].

Low vaccine coverage, while present, does not tell the whole story of the recent measles outbreak in Sudan. Results in this analysis have shown that some states such as Northern Kordofan, Khartoum, Kassala and River Nile with high vaccination coverage in both routine and SIAs, have also reported local outbreaks of larger relative dimensions. This can be due either to higher probability of vaccine failure as well as to large intervals between supplemental vaccination campaigns. Both situations would cause the accumulation of susceptible children which subsequently results in generating current outbreaks. Recent outbreak studies refer to the possibility of having vaccination failure (primary or secondary) that should be detected by presence of IgM and IgG. Therefore, case-based surveillance and serological investigation of every suspected case and contacts can provide solid evidence to sort out the role of vaccine failure in the genesis of a new outbreak [(27), (28), (29)]. Unfortunately, in places with resource constraints such as Sudan, complete investigation is stretched out in an outbreak, and may be limited to the first 5-10 cases coming from the same area. This means that full data regarding the immune response among previously vaccinated cases are not always available. Laboratory investigation was conducted on 24% of all cases and showed that a substantial proportion of about 1/3rd were previously vaccinated. As per documented studies, patients' serology indicates that an initial immune response may be failing in 5%–10% of children after vaccination at 12 months [(5)]. However, almost all (97%) had received at least one single dose of MCV.

Several conditions mostly related to economic hardships and violent conflicts may contribute to higher rates of primary vaccine failure in Sudan. The immune status of infants and children may be adversely affected by malnutrition and infectious co-morbidities. Civil unrest may also be causing higher levels of break-down in the cold chain, a problem relatively easy to detect and correct. Of more serious concern would be the emergence is the genetic shifts in prevalent viral strains, which cause larger resistance to the vaccine. The existence of such shifts would signal a public health problem of global dimensions, which goes beyond the borders of Sudan and would require the development and industrial production of new vaccines. Suggestions of ineffectiveness of vaccines due to genetic shifts in strains have already started to emerge from other vaccine-preventable disease such as diphtheria, as well as measles. Many researches are now taking place to interpret the epidemiological changes of measles vaccine era, particularly in countries that are still facing severe measles epidemics and outbreaks even among fully vaccinated cases and reached or close to reach elimination phase. A population study was conducted in Germany to identify causes behind the shifting of measles genotype. The study concluded that shifts may be attributable to differences between the fitness of the new and the old genotypes, as well as the diversity of strains isolated from cases can be high. This could occur in populations have been immunized, at the time most cases may be linked to other areas with different genotype (30). In the same regard, Uganda conducted a study to identify the genotype of measles virus, after the repeated outbreaks among vaccinated people. The study analyzing the laboratory data from 2000 to 2002 for 36 viruses isolated from 6 districts. The study documented isolated virus suggested (d10) genotype, which is not known to be reported previous by WHO among the African countries that commonly affected by genotype D2 and D4 with minimum percentages for H and N genotypes (31).

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

Improvement in routine and additional vaccination activities coverage have resulted in better control of measles in Sudan. Even when outbreaks occur, their scope and adverse effects have remained relatively limited compared to previous years. SIAs campaigns are expected to compensate for low routine coverage especially in disadvantaged states. These positive trends have to be maintained and improved, while conducting SIAs every 3–4 years until elimination is achieved. Increased efforts are needed to target and reach high-risk and hard-to-reach subgroups such as migrant workers and nomadic groups, with MCV_1 and MCV_2.

The persistence of outbreaks among vaccinated children should be further investigated. It is important to provide the evidence to distinguish primary vaccine failure, which is partially preventable, from outbreaks due to new viral strains which may eventually require the production of a new vaccine. Similarly, during outbreaks it is recommended to enhance the surveillance system and not to neglect a full laboratory confirmation of cases.

At any rate, case-based surveillance should be reinforced in outbreak situations as well as with sporadic cases, to generate the evidence needed for better understanding and effective control of those outbreaks in the future. This would require the allocation of more financial resources and trained human personnel to be surveillance activities in Sudan.

Improvements must be documented through on-going analyses of accumulated data, similar to the process delineated in this study also further advanced studies related to sero-surveillance or prevalence are highly recommended to be consider as baseline to identify the possibility of having geno-conversion of the measles virus.

APPENDIX I

TABLES AND FIGURES

PART I: Measles Dynamics in Sudan 2006-2013

Table A1. Epidemiological Characteristics of Reported Measles Cases in Sudan, 2006–2013 (N= 17974)

Year	**Total population**	**Cases**	**Cases by Sex (%)**		**Cases by Age Groups (%)**				**Incidence per million (95% CI)**	**Deaths**	**Case Fatality Rate (CFR%)**	**Mortality Rate (MR) per 100,000 (95% CI)**
			Male	**Female**	**<1 year**	**1 – 5 years**	**6 –15 years**	**>15 years**				
2006	30,741,233	238	110	82	63	74	44	12	7.7 (7.4 – 8.0)	-	-	-
2007	31,573,870	350	168	142	75	158	57	24	11.1 (10.7 -1.4)	-	-	-
2008	32,981,933	111	77	34	18	33	5	55	3.4 (3.1 – 3.5)	-	-	-
2009	34,747,589	68	38	30	11	24	22	11	2.0 (1.8 – 2.1)	-	-	-
2010	32,670,898	255	165	90	31	91	60	73	7.8 (7.5 – 8.1)	2	0.8	0 (-0.0-0.01)
2011	33,975,593	5616	3448	2168	662	1641	1343	1970	165.3 (163– 66)	73	1.3	0.2 (0.2 – 0.3)
2012	35,055,538	8523	4911	3612	1446	2710	2077	2340	243.1 (241– 44)	134	1.6	0.4 (0.3 – 0.4)
2013	37,964,000	2813	1446	1367	492	1077	735	509	74.1 (73.2-74.9)	52	1.9	0.1 (0.9 – 0.1)
Total	**69,710,654**	**17,974**	**10,363 (57.7)**	**7,525 (41.9)**	**2,798 (15.5)**	**5,808 (32.5)**	**4,293 (24.0)**	**4,994 (27.9)**	**66.6 (65.4-67.8)**	**261***	**1.5**	**0.18 (0.6 – 0.9)**

*** Represents the experience of 2010 – 2013**

Table A2. Classification of Measles Cases in Sudan, 2006–2013 (N= 17,974)

Year	Clinically Diagnosed (n=519)	Epidemiologically Linked (n=13125)	Laboratory Confirmed (n=4260)	Total
2006	199 83.6%	0 0.0%	39 16.4%	238 100.0%
2007	200 57.1%	5 1.4%	145 41.4%	350 100.0%
2008	44 39.6%	3 2.7%	64 57.7%	111 100.0%
2009	25 36.8%	16 23.5%	27 39.7%	68 100.0%
2010	27 10.6%	52 20.4%	176 69.0%	255 100.0%
2011	31 0.6%	4641 82.6%	944 16.8%	5616 100.0%
2012	62 0.7%	6562 77.0%	1899 22.3%	8523 100.0%
2013	1 0.0%	1846 65.6%	966 34.3%	2813 100.0%
Total	589 3.3%	13125 73.0%	4260 23.7%	17974 100.0%

Table A3. Distribution of Measles Cases by Reporting Sites and Response Time in Sudan, 2006–2013(N = 17,974)

	n	%
Reporting Sites		
Active Search	722	4.0
Community	786	4.4
Health Center	3128	17.4
Hospital	12315	68.5
Other Sources*	236	1.4
Total	**17,207****	**100**
Response time		
On time	17,018	95.9
Late	728	4.1
Total	**17,746*****	**100**

* Include private clinics or dispensaries.
** 4.3% (787 cases) had missing data on reporting sites.
*** 1.2% (228 cases) had missing data on response time

Table A4. Characteristics of Laboratory-Confirmed Measles Cases in Sudan, 2006-2013 (N =4303)

Characteristics	n	%
Results of Samples Collected		
Positive confirmation	4260	99.0
Negative confirmation	14	0.3
Equivocal*	29	0.7
Type of Sample Collected		
Combined (specimens for Ig analysis and PCR)	867	20.2
Dry Blood only**	2	0.0
Oral Fluid only**	449	10.4
Serum Blood only**	2982	69.3
Condition of Sample Collected at Time of Arrival to the Laboratory		
Adequate	4246	98.7
Inadequate	51	1.2
Age distribution of confirmed cases		
< 1 year	751	17.6
1 – 5 years	1534	36.0
6 – 15 years	1087	25.0
>15 years	888	20.8
Sex Distribution		
Male	2420	56.8
Female	1839	43.2

* Equivocal results even after being checked twice for IgM

** In these cases, immunoglobulins (Ig) analysis is possible but not PCR testing

Table A5. Vaccination Status of Measles Cases in Sudan, 2006–2013 (N=17,974)

Characteristics	**Yes**		**No**		**Total**	
	n	**%**	**n**	**%**	**N**	**%**
	3,406	**19.1**	**14,470**	**80.9**	**17,876**	**100**
Age groups (p< 0.01)						
<1 year	349	10.4	2446	16.9	2795	15.6
1 – 5 years	1772	52.0	4028	27.8	5800	32.5
6 – 15 years	1051	30.9	3238	22.3	4289	24.0
>15 years	234	6.8	4758	32.8	4992	27.9
Total	**3,406**	**100**	**14,470**	**100**	**17,876**	**100**
Sex (p< 0.01)						
Male	1852	54.4	8501	58.8	10,353	65.1
Female	1553	45.6	5968	41.2	7521	34.4
Total	**3,405**	**100**	**14,469**	**100**	**17,874**	**100**
Measles Cases Classification (p< 0.01)						
Clinically Diagnosed	253	7.4	248	1.7	501	2.8
Epidemiologically Linked	2017	59.2	11107	76.7	13,124	73.4
Laboratory Confirmed	1136	33.4	3122	21.6	4,258	23.8
Total	**3,406**	**100**	**14,477**	**100**	**17,883**	**100**

Table A6. Characteristics of Previously Vaccinated Measles Cases by Age - Groups, Sudan 2006–2013 (N=3406)

Characteristics	**Age – Groups (N)**				
	<1year	**1-5 year**	**6-15 year**	**>15 year**	**Total**
	349	**1772**	**1051**	**234**	**3406**
Vaccination Strategy (p < 0.01)					
Routine	239 76.6%	819 50.8%	473 48.2%	131 57.0%	1662 53.0%
Campaign	71 22.8%	792 49.1%	506 51.5%	99 43.0%	1468 46.8%
Vaccination Doses (p < 0.01)					
1 dose Only	333 97.1%	1602 93.0%	945 91.5%	228 98.7%	3108 93.4%
2 or > 2doses	10 2.9%	119 6.9%	88 8.5%	3 1.3%	220 6.6%
IgM Measles Results (p= 0.08)					
Positive	102 96.2%	591 98.8%	371 98.9%	73 100%	1137 98.7%
Negative /Equivocal	4 3.8%	7 1.2%	4 1.0%	0 0.0	15 1.3%

Table A7. Vaccination Strategies of Measles Cases by Years in Sudan, 2010–2013, (N=3406)

Years	Routine		Campaign		Total	
	n	%	n	%	n	%
2010	33	50.7	32	49.2	65	100
2011	345	41.7	517	58.3	826	100
2012	821	51.8	763	49.2	1548	100
2013	463	74.7	156	25.2	619	100
Vaccination Strategies data stated to be reported in EPI system in 2010						

Table A8. Characteristic Deaths of Measles Cases in Sudan, 2006 – 2013 (N=261)

Characteristic	n	%
Age groups		
<1year	38	14.6
1 – 5 years	109	41.8
6 – 15 years	40	15.3
>15years	74	28.4
Sex		
Female	120	46.0
Male	141	54.0
Measles Case Classification		
Measles Clinically Diagnosed	1	.4
Measles Epid-Linked	243	93.1
Measles Laboratory-Confirmed	17	6.5
Vaccination Status		
Yes	23	8.8
No	238	91.2
Vaccination strategy		
Routine	11	52.2
Campaign	12	47.8
Vaccination Doses		
1 dose	261	100

*17 (6.5%) of death had samples and all were IgM (+ve)

** In these cases, immunoglobulins (Ig) analysis is possible but not PCR testing

Table A9. Routine Vaccination Percentage by Years – Sudan States, 2006–2013

States	**MCV_1 %**								**MCV_2 %**	
	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2012**	**2013**
Blue-Nile	90	89	94	100	100	95	96	100	88	100
Darfur-C	-	-	-	-	-	-	67	70	16	46
Darfur-E	-	-	-	-	-	-	77	74	7	38
Darfur-N	50	65	69	81	87	89	74	73	17	50
Darfur-S	75	98	73	77	76	85	82	92	17	66
Darfur-W	74	83	85	85	97	83	72	73	21	48
Gedarif	73	61	73	72	72	84	86	91	27	60
Gezera	82	87	87	94	96	94	93	92	32	64
Kassala	75	73	81	78	78	89	85	84	23	53
Khartoum	78	77	80	85	90	91	91	86	19	49
Kordofan-N	80	83	79	83	86	89	89	62	26	62
Kordofan-S	71	76	75	80	81	66	69	54	25	39
Kordofan-W	-	-	-	-	-	-	-	82	-	51
Northern	64	65	72	73	83	90	95	91	16	68
Red-Sea	72	71	98	64	68	84	77	90	20	60
River-Nile	84	83	89	91	95	98	97	92	37	72
White-Nile	80	77	81	79	89	83	86	85	22	54
Sennar	74	72	79	78	88	90	91	89	26	62
National %	**76**	**80**	**80**	**83**	**86**	**87**	**85**	**85**	**24**	**57**
No. Cases	**238**	**350**	**111**	**68**	**255**	**5616**	**8523**	**2813**	**-**	**-**

Table A10. Measles Elimination and Surveillance Indicators – Sudan, 2006 – 2013

	WHO Standards	2006	2007	2008	2009	2010	2011	2012	2013
Elimination Indicators Rate									
Incidence rates	**0 /1,000,000**	14.6	15.6	22.5	24.6	52.5	154.7	250.6	72.2
Surveillance Indicators (%)									
Completeness and timelines of reporting	**≥ 80%**	97	98	100	100	100	100	99	100
Case investigated < 48h after notification	**≥ 80%**	60	78	93	97	98	80	97	97
Cases with adequate blood sample	**≥ 80%**	98	98	93	97	98	98	99	99
Laboratory-confirmed cases	**≥ 80%**	15	42	25	30	25	98	98	95
Laboratory results available within 7 days	**≥ 80%**	98	100	86	86	66	70	80	81
Reporting rate of non-measles, non-rubella among fever/rash cases	**≥ 2 /100, 000**	0.51	0.85	0.72	1.00	3.80	1.80	2.50	0.21

Table A11. Measles Cases and Deaths VS. Measles Coverage (MCV1) in Northern Kordofan State by Years, 2006 - 2013

Years	No. Cases (%)	No. Deaths (%)	MCV_1 Coverage %
2006	2 (0.0%)	-	80
2007	5 (0.0%)	-	83
2008	0 (0.0%)	-	79
2009	21 (0.4%)	-	83
2010	64 (1.3%)	1 (1.7%)	86
2011	2054 (42.2%)	17 (20.0%)	89
2012	1940 (39.9%)	33 (56.9%)	89
2013	779 (16.0%)	7 (12.1%)	62
State Total (%)	**4865 (26.0%)**	**58 (22.0%)**	**80%**
Sudan Total	**17,975**	**261**	**80%**

Figures

PART I: Measles Dynamics in Sudan 2006-2013:

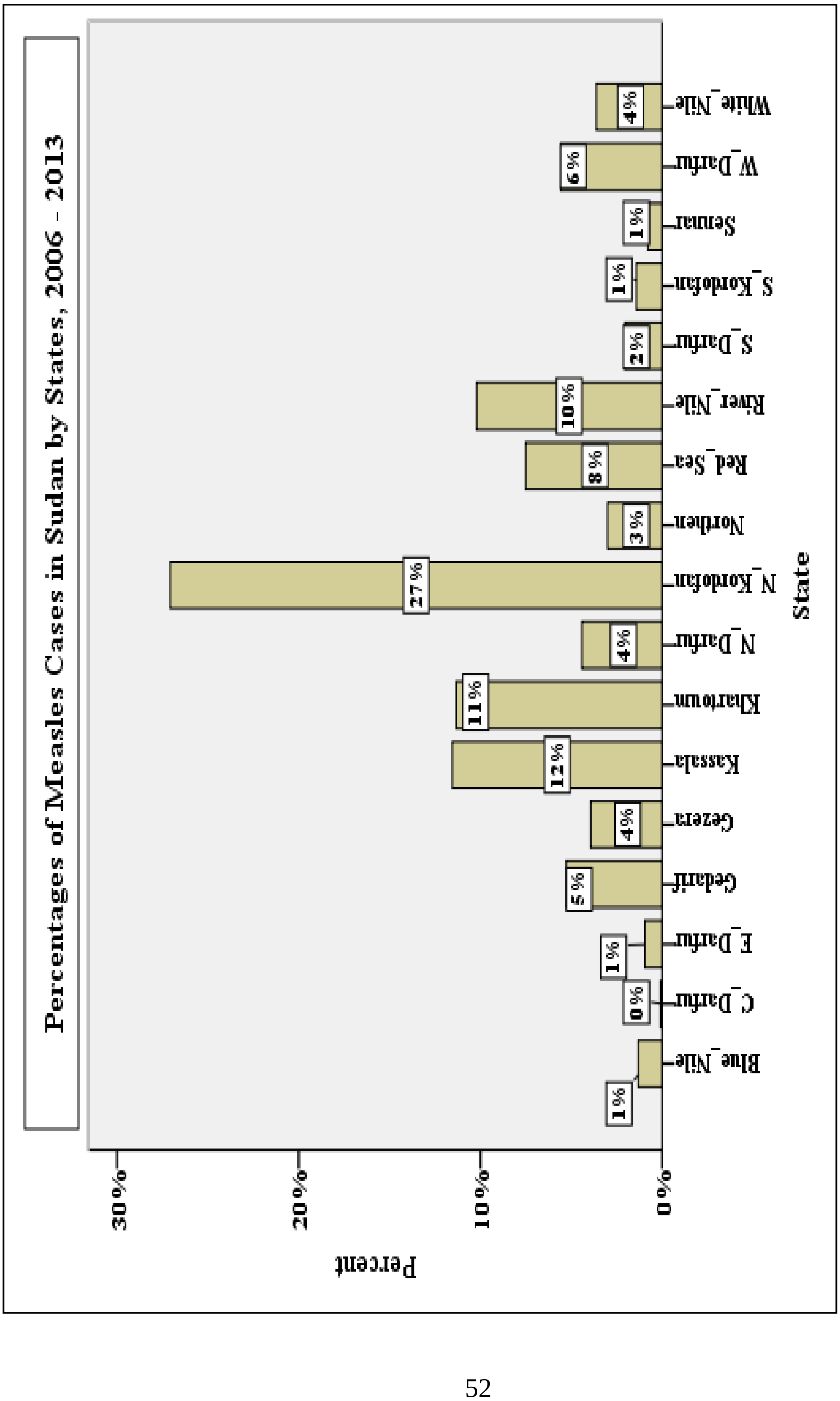
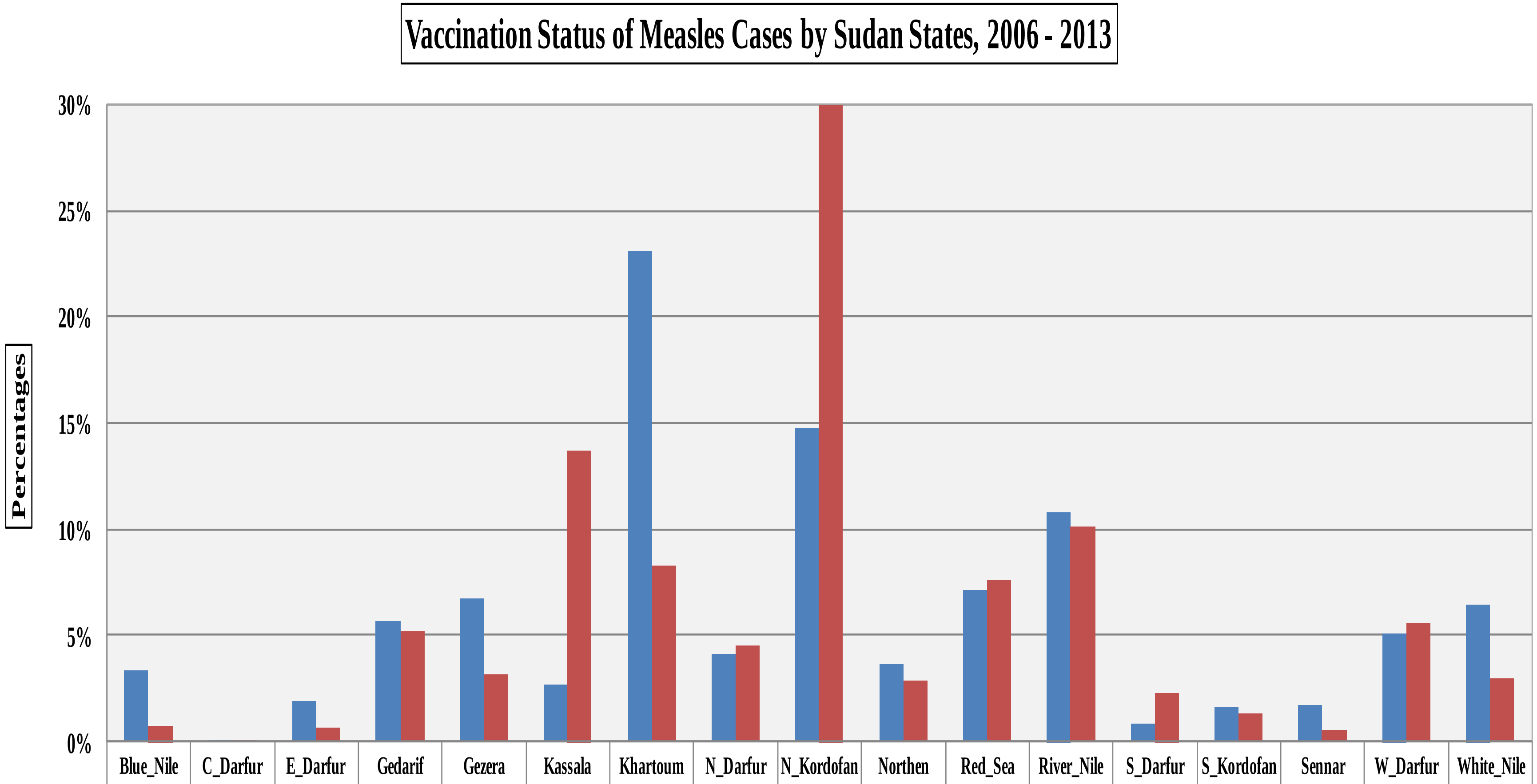


Fig. A1. Measles Cases Distribution, Sudan (N= 17974)



	Blue_Nile	C_Darfur	E_Darfur	Gedarif	Gezera	Kassala	Khartoum	N_Darfur	N_Kordofan	Northen	Red_Sea	River_Nile	S_Darfur	S_Kordofan	Sennar	W_Darfur	White_Nile
Yes	3%	0%	2%	6%	7%	3%	23%	4%	15%	4%	7%	11%	1%	2%	2%	5%	7%
No	1%	0%	1%	5%	3%	14%	8%	5%	30%	3%	8%	10%	2%	1%	1%	6%	3%

Fig. A2. Vaccination Status of Measles Cases, Sudan (N= 17,883)

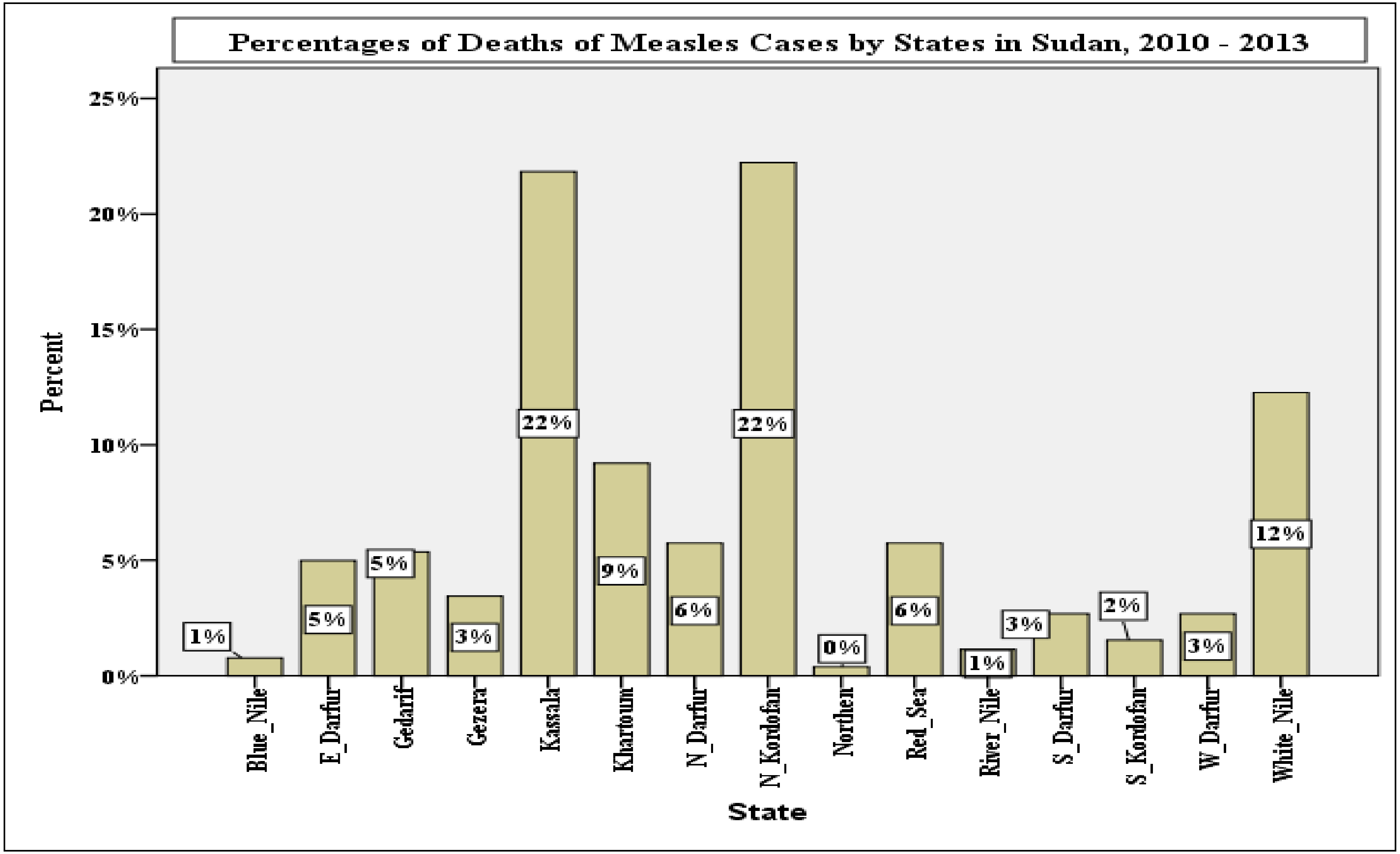


Fig. A3. Distribution of Measles Death, Sudan (N= 261)

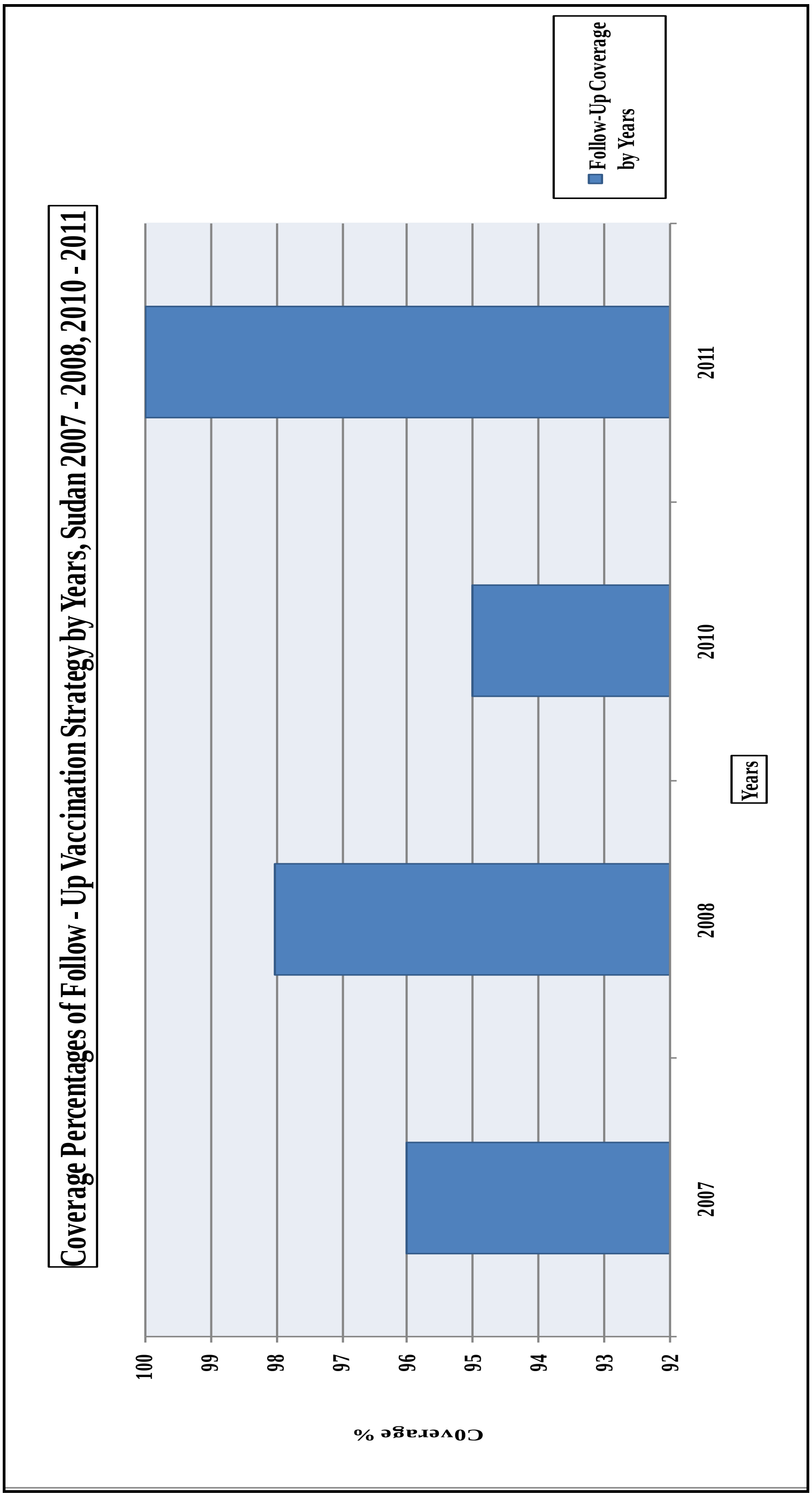


Fig. A4. Follow-up Vaccination Coverage* (N= Un Defined)
* All Sudan states Reported Follow-Up Coverage Percentage > 90%

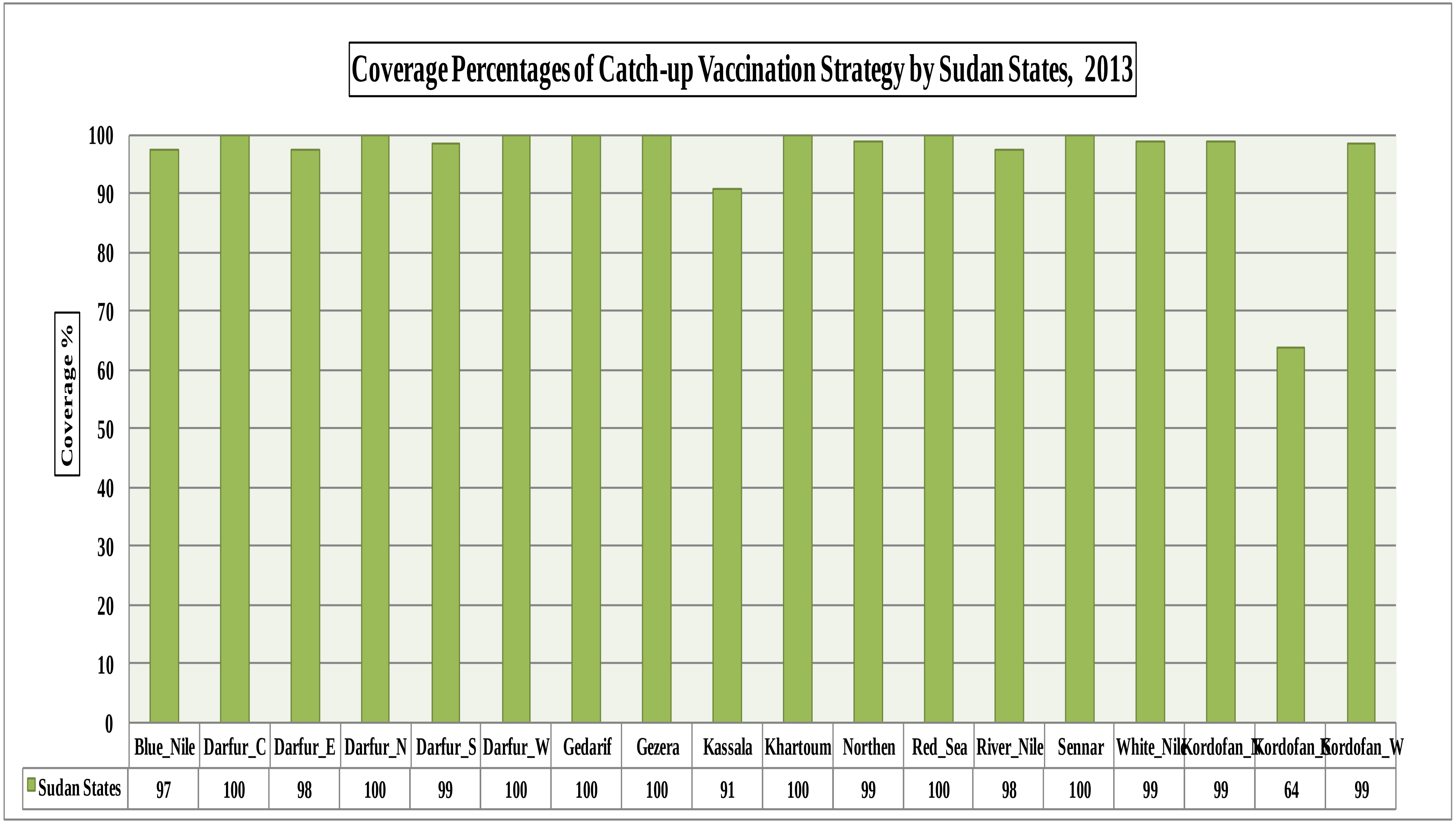


Fig. A5. Vaccination Coverage of Catch-Up Vaccination Strategy, Sudan (N = 15,295,794 Pop)

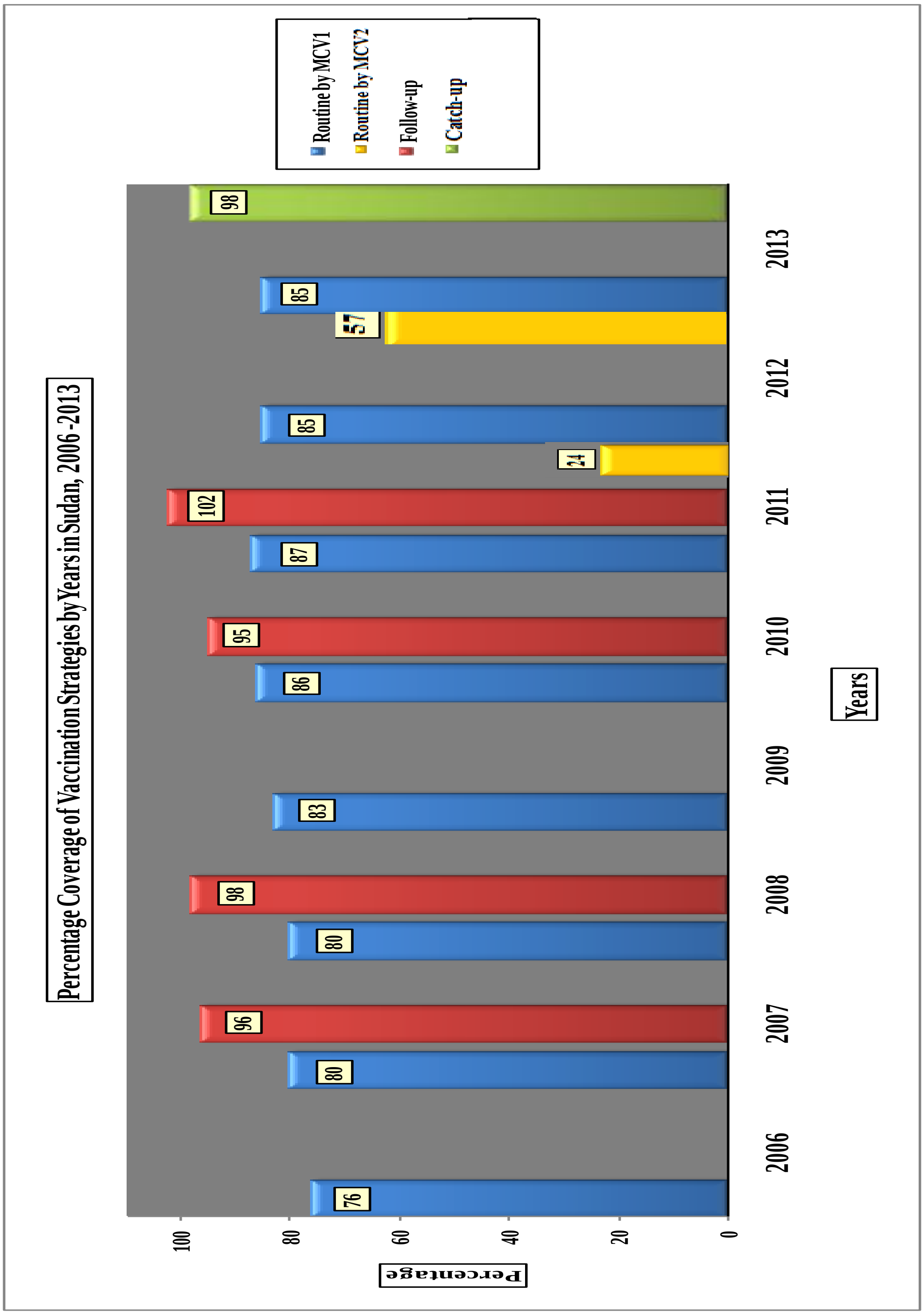


Fig. A6. Population Vaccination Strategies Coverage of Measles, Sudan 2006-2013794 Pop)

Vaccination Strategy	**Population Covered**
Catch-up	Targets age-group (9 months – 5 years)
Follow-up	Targets age-group (9 months – 15 years)
Routine	MCV1 = Targets age-group (9 months) MCV2 = Introduced 1.5 year from the 1st dose (MCV1)
P. value (Vaccination Strategies and Number of Cases) (p< 0.01)	

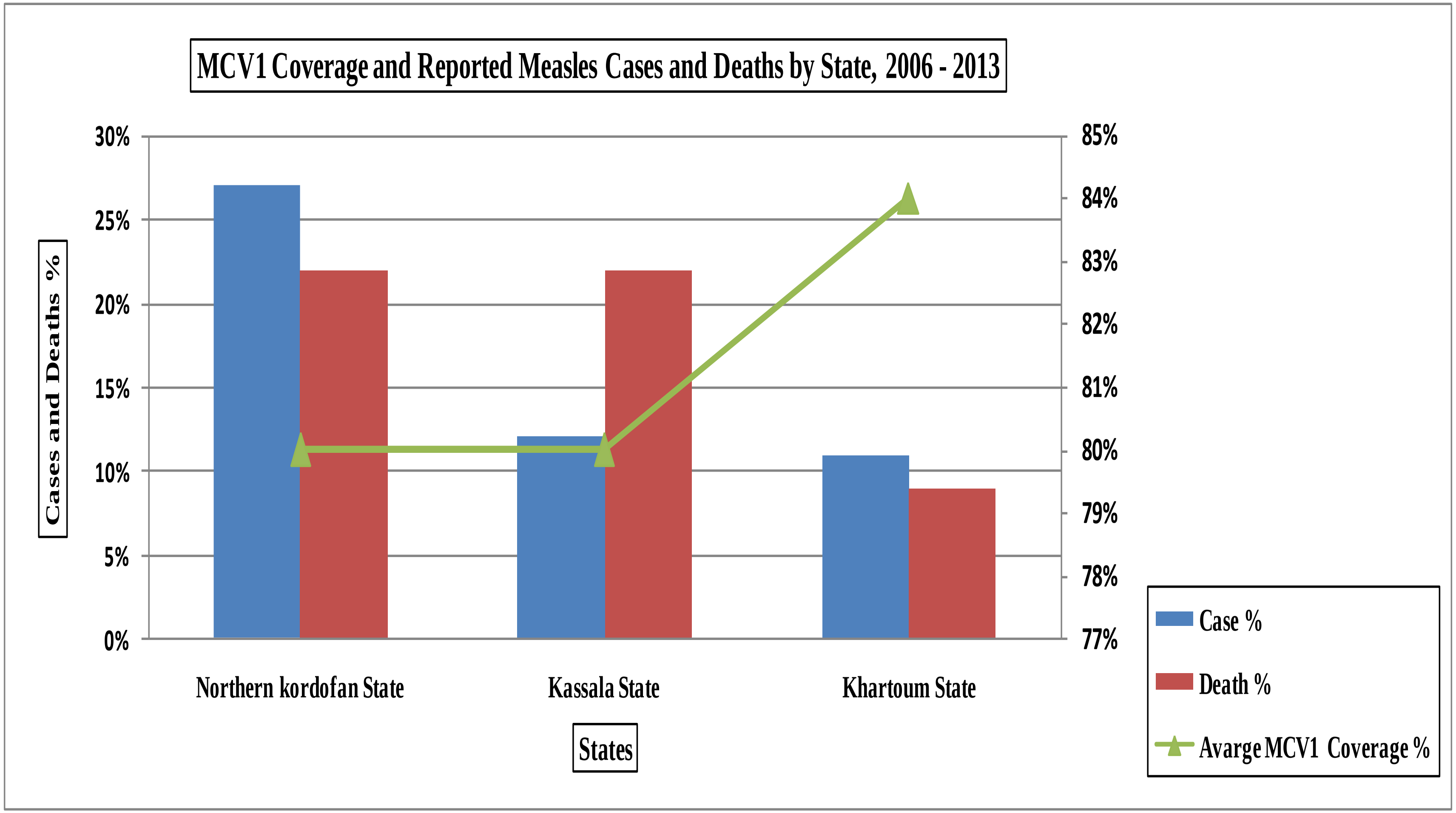


Fig. A7. Measles Cases and Deaths Vs. MCV_1 Coverage in Northern Kordofan, Khartoum & Kassala States,794 Pop)

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