PROGRESS TOWARDS MEASLES ELIMINATION IN MOROCCO

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Abstract
In order to eliminate measles in Morocco, a mass vaccination campaign targeting children aged from 9 months to14 years was conducted on May-June 2008. The vaccination coverage was estimated to be 99%. This study aims to assess the impact of the measles mass vaccination campaign on measles incidence based on sensitive surveillance system. For this purpose, a laboratory case-based surveillance was set up during 2010. Epidemiological definition of suspected measles cases was fixed. Specimens were collected through all primary health centers and hospitals at national level and suspected cases were confirmed by serological tests. Measles strains isolated during outbreaks were genotyped. The performance of the surveillance system was evaluated according to the World Health Organization indicators. The incidence was calculated based on the epidemiological surveillance data, and compared to the World Health Organization incidence, which is 1 case per million per year. 1214 suspected cases were notified and 1083 measles samples were analyzed and 45 % (491/1083) were serologically confirmed and 115 cases were confirmed by epidemiological linkage. Molecular

epidemiology shows that genotype D4 is endemic since 2008. The WHO indicators show that the sensitivity of surveillance system is low. Despite this weak sensitivity, epidemiological data show that measles incidence is higher than that recommended by WHO, and reached 19.18/1 000 000. In conclusions, Measles mass campaign did not reach the goal expected. A second mass campaign should be planned in the near future to eliminate the disease in the country.

Keywords: Measles elimination, mass campaign, epidemiology, laboratory confirmation/genotyping, Morocco

Introduction

  Measles is one of the most contagious human diseases caused by Measles virus (MeV), a member of the family *Paramyxoviridae*, genus *Morbillivirus*. It can induce complications such as pneumonia, encephalitis, and death, especially among children under 5 years of age, under adverse conditions. In 2008, 164 000 measles deaths globally were reported worldwide, of which 95% occurred in countries with low-income and weak health infrastructures (Ciofidegliatti et al., 2006; Wichmann, 2009; Sternfeld et al., 2010). However, measles can be prevented with efficient vaccination programmes, aiming to reach the goal of its elimination (Adetunji, Macklin, Patel, & Kinsinger, 2003; Moss & Griffin, 2006; Chang et al., 2010).

  WHO has established a global strategic plan for measles elimination, based on a theoretical target of maintaining a herd-immunity threshold of 95% according to mathematical models. In practice, to assess the progress towards measles elimination, WHO proposed three main indicators: 1°) achieving and maintaining annual vaccination coverage of more than 95% with 2 measles doses in all districts in order to interrupt the endemic measles transmission 2°) implementing sensitive surveillance including a dynamic laboratory case-based investigation with the aims to ensure the detection of measles virus and 3°) reaching and maintaining a low incidence, set at less than one case per 1 million inhabitants per year (WHO-WPRO, 2010).

  The sensitivity of the surveillance system is assessed by WHO indicators namely the reporting rate, the proportion of provinces reporting non-measles cases per 100.000 population, the proportion of measles cases investigated within 48h, and the proportion of laboratory confirmation for sporadic cases and outbreaks (WHO, 2009).

  In Morocco, measles vaccine (MV) was introduced in 1981. The number of cases reported, declined from 120 000 registered annually before the introduction of measles vaccine to 4 216 in 1984. However, there was an increase again in 1987, when 26 621 cases of measles were reported (MoH-Morocco/WHO, 2005). Consequently, the government of Morocco launched

the National Immunization Days to increase vaccination coverage which evolved from 73% in 1987 to more than 90% since 1996 (WHO/Morocco, 2008). In 1997, Morocco joined the WHO/EMRO Measles elimination program and continued to improve the vaccination coverage of one dose vaccine at 9 months (MoH-Morocco, 2010).

Based on the one-dose vaccination strategy maintained for 23 years, measles remained an endemic disease in Morocco with epidemic cycles that occurs every 4 to 5 years. The number of the annually reported cases ranged from 1 324 cases in 1996 to 11 000 cases in 2003 with the highest incidence was among children aged 5 to 9 years.

In response to the WHO recommendations, a second dose of MV was introduced in 2003 and covered all children at school entry (6 years old) (MoH-Morocco/WHO, 2005; MoH-Morocco, 2009). The introduction of the second dose of measles vaccine and the evolution of reported measles cases shows a significant decrease in the following three years. The annual reported measles cases decreased from 10 841 in 2003 to 1 217 in 2006 but in 2007, measles cases notification increased again and reached 2248 cases (figure 1).
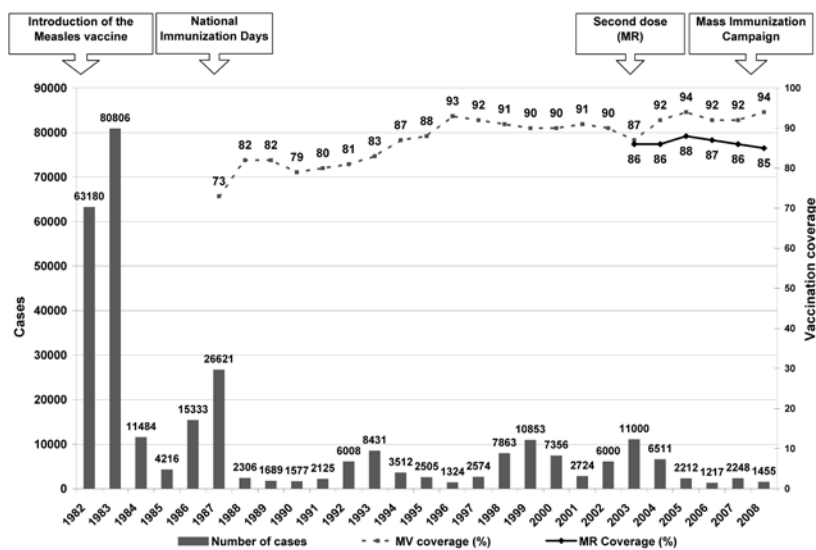

Figure 1: Reported Measles cases and vaccination coverage in Morocco by year, 1982-2008 (MR: Measles/Rubella Vaccine; MV: Measles vaccine).

Outbreaks investigated in Morocco before September 2008 were associated with imported genotype as D7, B3.2 (Alla et al., 2006; WHO, 2006) and D8 (unpublished data) which became endemic strains in 2007 and 2008 as the susceptible population was high enough to maintain the chain of transmission.

In order to reduce measles-susceptible population and to interrupt the endemic chain of transmission, a mass vaccination campaign (MVC) with Measles-Rubella (MR) vaccine was organized in May-June 2008 and targeted 3 547 548 children aged between 9 months and 14 years with a focus on hard-to-reach population (MoH-Morocco/DP, 2008). In this strategy, the ministry of health (MoH) had excluded children who received a second dose from 2003 till 2008. The immunization coverage registered was estimated to be 99% (WHO-EMRO, 2010). Moreover, for the purpose to monitor the incidence of confirmed measles cases and document the interruption of measles endemic transmission after the mass campaign, a laboratory case-based surveillance was set up at the national level on 2010 (MoH-Morocco, 2009).

Based on the assessment of the sensitivity of the surveillance system and on laboratory case based surveillance, this review will assess the impact of the mass campaign on measles endemic transmission in Morocco with the aim of reaching the elimination goal.

Methodology:
1- Establishment of Laboratory case based surveillance

Measles is notifiable infectious disease in Morocco. In 2002, the MoH implemented laboratory confirmation, initially focused on outbreaks investigation by confirming 5 to 10 cases per outbreak. Sentinel laboratory surveillance was established in 2007 to monitor sporadic measles cases in five provinces and all outbreaks at the national level. In 2010, after the mass campaign, the case based surveillance was set up at the national level and included 69 provinces, 2600 primary health centers, 16 regional hospitals and 68 provincial hospitals. The population was estimated to 31 894 000 (HCP, 2010).

Specimen were collected from all suspected measles cases according to WHO definition; including any person with, fever, a maculopapular rash, and either cough, coryza or conjunctivitis, or any person suspected by a clinician

- Specimen collection

During 2010, specimens were collected from patients that met measles clinical case definition. All sporadic cases and five to ten cases from each outbreak were subject to sera or oral fluids specimen collection for serological confirmation using specific kits (UTM-RT Transport Medium / COPAN, Cat# 305 for the oral fluid and Oracol Saliva collection system / MMD for saliva specimen). Oral fluid specimens were recommended in case of difficulty to collect blood samples especially among infants less than 2 years old. In addition to sera or oral fluid specimens, urine and nasopharyngeal specimens were collected for measles virus isolation and

genotyping analysis. All specimens were shipped to the National Measles Reference laboratory at the National Institute of Hygiene, in cold boxes with an investigation form including clinical and epidemiological data

- Serological analysis

Serum or Oral fluid was collected within 28 days of rash onset. Specimens were tested first for IgM specific to measles. As recommended by WHO, all negative samples for measles IgM were tested for rubella IgM. Suspected cases with negative measles laboratory results were discarded as non-measles cases.

Serological confirmation was done using two commercial ELISA test kits provided by the WHO; the Enzygnost® Anti-Measles virus (Siemens) (Marburg, Germany) for serum samples and Measles IgM capture EIA (Microimmune Ltd) (Hounslow, UK) for oral fluid samples, performed according to the manufacturer's instructions.

The serological data of the national measles surveillance was analyzed according to the age group and to the vaccination status, and used to assess the surveillance performance and to calculate measles incidence.

- Measles genotyping

Measles virus was isolated from urine or throat swab samples collected from outbreaks within 3 and 5 days of rash onset. Virus isolation was performed on Vero Slam cells.

RNA extraction was performed from positive cell culture using the QIAamp viral RNA mini kit (QIAGEN) (Hilden, Germany). RT-PCR analysis was done using primers provided by The Centers for Disease Control and Prevention-Atlanta-GA (CDC). MeV216 (Forward): 5' TGGAGCTATGCCATGGGAGT   3'   and   MeV214 (Reverse):   5' TAACAATGATGGAGGGTAGG 3' to amplify a 634-bp fragment of nucleoprotein coding gene, using superscript one step reverse transcription – PCR (cat# 210210/210212, QIAGEN) according to the manufacturer's instruction.

The PCR product was then purified using the Wizard® minicolumn. The purified amplicons were sequenced using the BigDye Terminator V 1.1 kit and   analyzed on ABI PRISM 310 automatic sequencer.

Sequence data were analyzed using Seqscape Software Version 2.5. Nucleotide sequences (450 pb) alignment, phylogenetic tree and molecular evolutionary analysis were performed using MEGA5 software (Tamura et al., 2011).

2-Assessment of the surveillance system

The surveillance system was evaluated based on the following WHO indicators:

a- The reporting rate, should be at least two non-measles suspected measles cases per 100 000 population.

Reporting rate= number of non measles cases/ total population x100.000

b- The annual measles detection should be at least one non-measles suspected case per 100 000 population in at least 80% of provinces (WHO, 2001).

Annual measles detection= number of provinces reporting at least one non-measles suspected case per 100 000 population / total of provinces.

c- Measles case investigation should be done within 48 hours of notification for a minimum of 80% of all reported suspected measles cases.

Measles case investigation= number of reporting cases within 48 h / total of reporting cases.

d- Laboratory confirmation of at least 80% of suspected measles cases,

Laboratory confirmed cases= number of laboratory confirmed cases/ total of cases notified.

e- Viral detection from at least 80% of laboratory-confirmed outbreaks

Viral detection of laboratory-confirmed outbreaks= number of confirmed outbreaks with virus isolation by Cell culture/total of outbreak notified.

3- Determination of measles incidence

The incidence of confirmed measles cases per 1 000 000 habitants after mass campaign was calculated based on laboratory data and epidemiological linkage. Measles incidence after the mass campaign was compared to the WHO indicator fixed to 1 case per million habitants for reaching the elimination goal.

Incidence of measles per million of habitants = number of measles confirmed cases/total population.

▪ **Results:**

1-Laboratory case based surveillance

During 2010, 1214 measles cases were notified. The NML received samples from 1104 cases, from which 1083 had specimen for serological analysis (930 sera and 153 oral fluid), and 192 samples for virus isolation (93 urine and 99 throat swab). 21 specimens were inadequate for serological analysis.

Among 1083 samples, 491 (45%) were IgM positive. 592 cases were classified as non-measles cases. All negative samples were tested for rubella IgM. One case was confirmed rubella IgM positive. 115 measles cases were

confirmed by epidemiological linkage. Thus, the incidence in the general population reached 19 per million inhabitants.

According to the distribution of confirmed cases by age group, the most susceptible population to measles infection were age group [0-4] followed by the age groups [5–9], [15–19] and [20-24].

Furthermore, the incidence of measles per million, and by age groups, shows a high incidence in the age group <=4 years, 44% (47/106) of confirmed cases among this group were aged less than one year. The second high incidence was observed among the age group [5-9], followed by [15-19] and [20-24]. In contrast, the incidence is low in the age groups older than 35 years (Table 1).

Table 1: Distribution of confirmed measles cases and measles incidence by age groups, Morocco, 1st Jan. - 30 Dec. 2010

Age groups (years)	Number of population by age group (2010)	Clinically suspect measles cases	Confirmed measles cases	Incidence (per Million)
0 - 4	2903000	456	106	36,51
5 - 9	2865000	224	88	30,72
10 - 14	2986000	63	22	7,37
15 - 19	3215000	118	86	26,75
20 - 24	3106000	86	64	20,61
25 - 29	2928000	66	52	17,76
30 - 34	2503000	47	39	15,58
35 - 39	2194000	24	19	8,66
40 - 44	1877000	5	3	1,60
>=45	7317000	15	12	1,64
Total	**31894000**	**1104**	**491**	**15,39**

Information on vaccination status was available for 358/491 confirmed cases (73%), the overall rate of vaccinated cases was 48%, 8/172 cases had received two doses (figure 2).
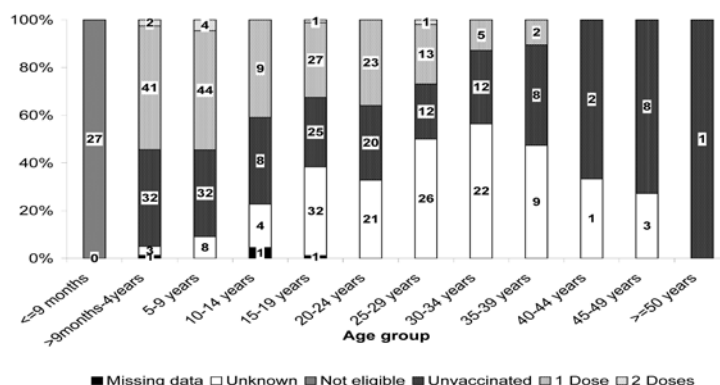

Figure 2: Distribution of the laboratory confirmed measles cases by immunization status and by age group, Morocco, 1st Jan.-31 Dec. 2010. (The monovalent measles vaccine was administered for the one dose at 9 month of age and the bivalent measles/rubella vaccine for the second dose).

Virus isolation and molecular data analysis

Phylogenetic analysis shows that all viruses isolated from cases reported during 2010 belong to D4 genotype and had identical N gene sequences. They are closely related to the WHO genotype D4 reference strain (MVi/Montreal.CAN/89), and to the D4 strains that were isolated in 2008 after the mass campaign (MVi/Midelt.MAR/37.08/, GenBank accession numbers: FJ595981 and FJ595982). They also showed 100% identity with the strain MVs/Enfield.GBR/14.07/ isolated in the UK in 2007 (GenBank accession no: EF600554) and to the D4 genotype that was isolated all over the world during 2007 and 2008 (Chironna et al., 2007; Rota et al., 2011), suggesting that this virus may have been imported (figure 3). The sequence analysis comparison was done with 11 measles reference strains from GenBank (accessions numbers: HQ338080, HQ338077, HQ338078, HQ338073, HQ338074, HQ338075, HQ338076 and HQ338079).
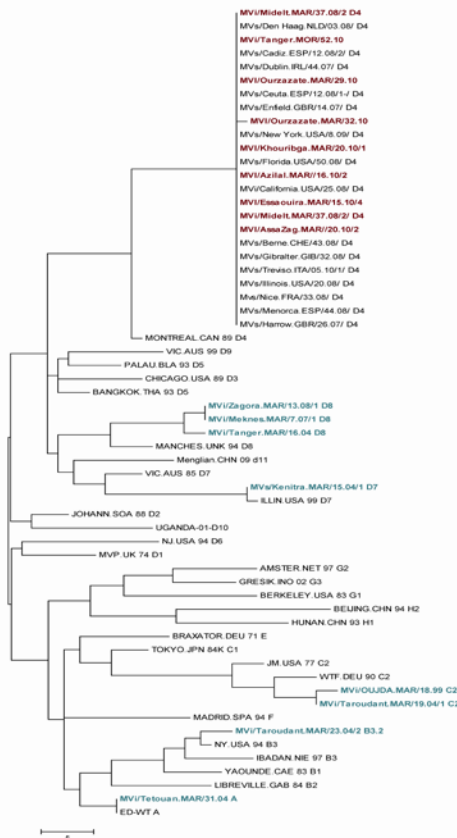

Figure 3: Phylogenetic analysis of measles strains collected between 1998 and 2011 based on the C-terminal of the N gene and were compared with the WHO reference sequences. The Phylogenetic tree shows the representative genotype strains identified in Morocco before (in Green) and after (in red) the mass campaign organized in June 2008. An unrooted tree is drawn after analysis using maximum parsimony.

Assessment of epidemiology surveillance indicators

Based on WHO-EMRO measles elimination indicators, the surveillance system in Morocco reported the following results (table 2):

Table 2: Measles surveillance indicators, Morocco, 2010.

Indicators	Target	Morocco (2010)
National reporting of non-measles suspected cases	> 2/100 000	1.86/100 000
Percentage of districts reporting ≥ 1/100,000 non-measles suspected cases	> 80%	88%
Percentage of suspected cases with adequate investigation within 48 hours of notification	> 80%	84%
Laboratory confirmation of suspected measles cases	> 80%	89%
Viral detection from at least 80% of laboratory-confirmed outbreaks	>=80%	61%

Based on laboratory results, 592 suspected measles cases were discarded as non-measles. The incidence rate at the national level is 1.86 per 100 000 inhabitants.

Among 69 provinces, 61 (88%) have a rate >=1 per 100 000 inhabitants measles cases.

Eighty four percent 84% (922/1104) of all reported suspected measles cases were investigated within 48 hours of notification.

The national measles laboratory confirmed 89% (1 083/1214) of reported cases.

NML received adequate samples for viral detection from 11 outbreaks, which represent 61% of all outbreaks (18) reported during 2010.

Discussion

The current study shows that in 2010, the performance of the surveillance system was adequate for only two of the elimination indicators. Despite the low sensitivity of the surveillance system, measles incidence remains higher than one measles confirmed case per 1000000 population. The wide distribution of confirmed measles cases and the large number of outbreaks confirms the circulation of the virus among a high population of susceptible.

The epidemiological analysis of confirmed cases shows that all age groups were affected by measles. However, the incidence of measles was higher for age groups under 9 year and 15-24 years. For the age group under 9 months that is not eligible for the vaccination, the current vaccination strategy did not protect children of getting the disease through the herd immunity as supposed. For the age group 17-24 years; this group had received only one dose of measles vaccine at 9 months, which led to the

accumulation of susceptibles. Indeed, the efficiency of the measles vaccine at 9 month is only 85% (Lee & Nokes, 2001; Bauch et al., 2009).

The children aged between 2 and 16 years, were also reported as susceptible to develop the disease. According to the national immunization strategy, this group belongs to the population that received two doses of measles vaccine, with an estimated coverage of 90% (MoH-Morocco/DPRF, n.d.). A high number of measles confirmed cases among this age group led us to suppose an underestimation of the population targeted by the mass campaign. Moreover, the fact that the population targeted by the second dose implemented since 2003 had been excluded during the 2008 mass campaign may contribute to increase measles cases among this age group. Indeed, WHO recommended strategy for the first mass immunization campaign specifies to vaccinate the target population regardless their previous immunization status (WHO-EURO, 2005; WHO-EMRO, 2006; WHO, 2012).

The group, including adults older than 25 years, has also been affected, but not with a high incidence, as before the introduction of measles vaccines in 1980 in Morocco (Bouskraoui & Braikat, n.d.), nearly all children contracted measles.

Molecular characterization of measles virus shows that 83% of investigated outbreaks belong to the D4 genotype. Retrospective molecular analysis of measles cases in Morocco reported during outbreaks in 1998 and 1999 revealed that C2 genotype was the only genotype circulating in Morocco (Alla et al., 2002). Later studies, conducted between 2003 and 2005, show that multiple genotypes co-circulated; C2, D7, B3.2 and A virus were isolated in 2004 (Alla et al., 2006). Phylogenetic analysis suggests an importation from Europe and Sub Saharan African countries (WHO, 2005; Griffin & Oldstone, 2009; Kremer et al., 2010; Peña-Rey et al., 2010). Strains isolated in 2005-2006 belong to genotype D8 that was circulating in all Moroccan regions (unpublished data). D8 genotype was identified in recent study of 9 samples collected before the mass vaccination campaign, during outbreaks that occurred between 2007 and 2008 (unpublished data). D8 genotype had been circulating for more than 12 months and appeared to replace C2 as the endemic genotype. After the mass vaccination campaign, molecular characterization of the measles virus isolated during the outbreaks that occurred in September 2008, revealed the predominance of the genotype D4, which has had a worldwide distribution during the last three years (Chironna et al., 2007). Phylogenetic analysis shows that strains isolated in Morocco had sequences identical to the Enfield D4 strain (EF600554) isolated in England in 2007, which has been widely implicated in outbreaks all over the world during 2007 and 2008 especially in Europe (Kremer et al., 2008; Peña-Rey et al., 2009; Rota et al., 2011). The isolation of viruses with

the identical sequences in Gibraltar supports the hypothesis of the importation (Nieto Vera et al., 2010). Viruses associated with outbreaks that occurred during 2010 in different provinces of Morocco have identical N gene sequences suggesting the spread of the 2008 D4 lineage. Thus, the D4 genotype has become the endemic genotype in Morocco.

Conclusion

The results of this study show that there are still major challenges to reach the 2015 measles elimination goals in the country. Although vaccine coverage improved over time, this assessment confirms that high coverage in children documented by epidemiological data is inevitable to avoid the spread of the virus. Also, it's necessary to maintain a high level of vaccination in each birth cohort to avoid new reservoirs of susceptible persons.

The ministry of health has to strengthen its efforts by taking action to reach high population immunity by conducting sero-surveillance after each vaccination campaign, identify susceptible population and conduct supplementary immunization activities.

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Conflict of interest statement

The authors confirm that there are no known conflicts of interest associated with this publication.

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Abbreviations:
MeV: Measles virus
WHO: World Health Organization
WPRO: Western Pacific Region
MV: Measles vaccine
MoH: Ministry of Health
WHO/Morocco: Moroccan WHO Office
EMRO: Eastern Mediterranean Regional Office
MVC: Measles vaccination campaign
MR: Measles Rubella bivalent vaccine
DP: Population Department
NLM: National Measles Laboratory
DPRF: Planning and Financial resources Department
EURO: European Regional Office