



Field evaluation of measles vaccine effectiveness among children in the Democratic Republic of Congo



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ABSTRACT

Background: Large-scale measles outbreaks in areas with high administrative vaccine coverage rates suggest the need to re-evaluate measles prevention and control in the Democratic Republic of Congo (DRC). Monitoring of measles Vaccine Effectiveness (VE) is a useful measure of quality control in immunization programs. We estimated measles VE among children aged 12–59 months in the Democratic Republic of Congo (DRC) using laboratory surveillance data from 2010–2012.

Methods: We used the case-based surveillance system with laboratory confirmation to conduct a case-control study using the test negative design. Cases and controls were selected based on presence ($n = 1044$) or absence ($n = 1335$) of measles specific antibody IgM or epidemiologic linkage. Risk factors for measles were assessed using unconditional logistic regression, stratified by age.

Results: Among children 12–59 months, measles vaccination was protective against measles [aOR (95% CI)], 0.20 (0.15–0.26) and estimated VE was 80% (95% CI 74–85%). Year of diagnosis, 2011: 6.02 (4.16–8.72) and 2012; 8.31 (5.57–12.40) was a risk factor for measles when compared to 2010. Compared to Kinshasa, children in Bas-Congo, Kasai-Oriental, Maniema and South Kivu provinces all had higher odds of developing measles. Measles VE was similar for children 12–23 months and 24–59 months (80% and 81% respectively).

Conclusions: Repeated occurrences of measles outbreaks and lower than expected VE estimates suggest the need to further evaluate measles vaccine efficacy and improve vaccine delivery strategies in DRC.

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1. Introduction

An estimated 1.5 million deaths among children under five are attributed to vaccine-preventable diseases [1,2]. Measles is among the most infectious of diseases and is associated with complications such as encephalitis, pneumonia, and blindness [3]. Despite the

availability of a safe and effective vaccine, measles continues to be a major cause of vaccine-preventable disease mortality among children under five in resource-limited countries, with up to ten out of every hundred measles cases leading to death [3]. Globally, measles immunization coverage has improved tremendously over the last ten years; measles has been eliminated in most high and middle-income countries. In 2012, there were 122,000 estimated measles deaths worldwide, over 95% of which occurred in resource-limited settings [4].

In the African region, increased routine vaccination coverage coupled with Supplementary Immunization Activities (SIAs) has led to significant reductions in incidence and mortality [5]. Between 2000 and 2010, measles-related mortality was reduced by 85% [6]. However, throughout the region, deficiencies in routine

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immunization persist. Of the 28 countries reporting measles outbreaks in 2009–2010, 18 reported <90% vaccine coverage with the first dose of Measles Containing Vaccine (MCV) [7,8]. Additionally, 13 had held SIAs with <90% coverage, less than 24 months before the outbreak [7,8]. These occurrences of measles outbreaks post campaigns have raised concerns about the loss of vaccine effectiveness (VE) in areas where vaccine storage, handling, distribution, and cold chain requirements are difficult to maintain. VE is of particular concern in resource-limited settings, where refrigeration and electricity are limited, and cold chain maintenance represents a substantial economic and logistical burden [9].

Since 2004, the Democratic Republic of Congo's (DRC) effort to reduce measles mortality has consisted of a 3-pronged approach: (1) increasing routine immunization coverage of MCV1, given at 9–11 months of age, (2) implementing SIAs to provide second dose of MCV, and (3) expanding epidemiologic surveillance [2,10]. Despite these efforts, in 2010, DRC saw a resurgence of measles with large scale outbreaks throughout the country [10].

DRC suffers from inadequate roads and limited electricity and water, coupled with a lack of human resources. Consequently, DRC struggles to implement international vaccination guidelines effectively, including cold chain maintenance. Despite these problems, reported administrative vaccine coverage levels are high, with 223 of 516 health zones reporting >90% coverage in 2010 and SIA coverage reportedly above 100% in many health zones [11].

Monitoring of measles vaccine effectiveness is a useful quality-control measure for immunization programs. It can highlight areas of weakness and inform policy decisions [12–14]. The effectiveness of a vaccine depends on both potency and proper administration [12,13]. In addition to serologic studies, which assess vaccine uptake post-vaccination, laboratory-based techniques can test measles vaccine potency; unfortunately, the complexity and expense of these studies make implementation in resource-limited countries infeasible [12–15].

The test-negative case-control design has proven an effective epidemiologic approach to estimate influenza and rotavirus VE [14–19]. This design selects cases and controls from a pool of subjects with “measles-like illness”, which are subsequently laboratory-confirmed positive or negative. The design is non-traditional as the marginal ratio of cases to controls is unknown during enrollment; however, its efficient way of mitigating selection bias due to health seeking behaviors makes it useful for measuring VE [16,20]. Using this approach, we estimated VE using case-based measles surveillance data collected among children in DRC between 2010 and 2012.

2. Methods

2.1. Case-control study

We utilized data from the Case-Based (CB) measles surveillance system with laboratory confirmation collected from January 1, 2010 through December 31, 2012. The system was first implemented in 2002 to coincide with the start of SIAs. Individuals presenting to health centers with measles-like-illness (MLI), or found through active case searching, are reported to the Integrated Disease Surveillance and Response (IDSR) and CB surveillance systems, and a blood specimen is collected and tested for measles specific antibodies (IgM).

Human Subjects Protection boards at both the Kinshasa School of Public Health and UCLA approved the study protocol.

Case Definition: Individuals reported to the CB measles surveillance system are persons presenting with MLI, i.e. any person with

fever and maculopapular rash and cough or coryza or conjunctivitis, or a person in whom a clinician suspects measles [21]. Individuals were confirmed as a recent infection through either (1) Siemens Enzygnost® indirect enzyme immunoassay (EIA) for measles IgM antibody; or (2) by epidemiologic linkage, i.e. a case meeting the clinical case definition who had contact with a lab-confirmed case, with rash onset within the preceding 30 days or living in same district [21]. All laboratory analyses were conducted at the National Institute for Biomedical Research in Kinshasa, part of the Global Measles and Rubella Laboratory.

Case selection: Case patients were selected if they met the case definition (confirmed infection) and were 12–59 months of age, living in DRC and reported to the CB measles surveillance system, with available vaccination history.

Controls: Individuals were eligible to be a control if they were 12–59 months of age, living in DRC, reported to the CB measles surveillance system because of MLI, and testing IgM-negative for measles virus with available vaccination history.

Vaccination status ascertainment: Measles vaccination history was obtained through maternal recall when vaccination cards were unavailable (Fig. 1). All subjects were considered vaccinated if a vaccination date was recorded and occurred >1 month prior to disease onset. Children were also considered vaccinated if ≥ 2 doses of vaccine were recorded. Children with one dose and no date of vaccination were excluded from the main analysis because we could not confirm if vaccination occurred before disease onset.

Age calculation: We calculated age (in months) when birth-date was available; date of birth was subtracted from the date of specimen collection to calculate the age in months. If an exact birthday was unavailable, the variable “age in years” was converted to months and added to “age in months” to create overall age (in months).

Statistical analyses: All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary NC). Unconditional multivariate logistic regression was used to assess risk factors for recent measles infection among children aged 12–59 months. In multivariate analyses, vaccination status, sex, age, year of diagnosis, province, and health zone of residence (rural/urban) were included.

VE estimation: VE was estimated using the standard case-control protocol, with the formula $VE = (1 - \text{odds vaccinated/odds unvaccinated}) \times 100$, where the odds vaccinated/odds unvaccinated was the adjusted odds ratio for receiving ≥ 1 dose of measles vaccine compared with no doses [12]. Children with unknown vaccination history were excluded from multivariate models used to estimate VE. Attack rates in each province were low (<10%), satisfying the rare disease assumption; the odds ratio therefore approximates the risk ratio [12,13,22]. A sub-analysis was performed to assess year-to-year variation in VE estimates.

3. Results

Between 2010 and 2011, reported measles cases in DRC had surged to 134,041, with >70% occurring in children under five years of age [23]. The epidemic may have started in Katanga province and then spread throughout the country, with the highest incidence rates in province Orientale, Equateur and Kasai Orientale [10,23] (Table 1).

Since 2004, 16,789 samples have been tested for measles specific antibodies, with 28.51% confirmed positive by measles IgM and an additional 11.19% confirmed by epidemiologic linkage. Of the 8650 samples tested between 2010 and 2012, 4208 (48.6%) were considered measles-positive; 1734 (41.2%) were confirmed through epidemiologic linkage and 4379 (50.6%) tested negative. Negative samples were further tested for rubella IgM; 25.5% were positive.

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