

Full Length Research Paper

Factors associated with detection of measles-specific immunoglobulin M (IgM-positive) in Côte d'Ivoire from 2015 to 2019: A nested case-control study from a measles national surveillance programme

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Measles outbreaks are regularly reported in Côte d'Ivoire districts although on-going measles vaccination coverage has increased. The objective was to identify the factors associated with measles IgM-positive in a population with suspected measles. A case-control study nested in the national surveillance of 9337 registered measles suspected cases from 2015 to 2019 in Côte d'Ivoire was conducted for identification of factors associated with laboratory-confirmed case-based measles. The independent factors associated with detection of IgM in blood were determined from logistic regression. Among suspected measles cases, 88.84% had blood samples taken to test for measles IgM antibody. The proportion of IgM-positivity was 10.03% among the 8295 blood samples tested at the measles reference laboratory. The median age of the population tested was four years (y) with an interquartile range (IQR) [1.5-9 years]. The majority of IgM-positive subjects (71.28%) were aged from 1 to 15 years. Of the IgM-positive subjects, 52.05% had an unknown vaccination status. The independent factors associated with the presence of IgM were: Unvaccinated status against measles (adjusted odds-ratio [aOR]=2.82, 95% confidence interval (CI) 2.19 to 3.64), increasing age (aOR(95% CI): 1.37(1.06 to 1.78), 1.54(1.18 to 2.00), 1.56(1.14 to 2.12) for age groups 1-5 years, 5 to 15 years, 15 years +, respectively compared with the age group 0 to 1 year, and health regions of residence located in the west of Côte d'Ivoire aOR ranged between 1.68 (Haut Sassandra) and 2.87 (Marahoue). Interventions considering factors associated with measles IgM-positive will help to control the spread of measles in Cote d'Ivoire.

Key word: Measles-specific M-immunoglobulin, measles, vaccination, logistic regression, surveillance programme, Côte d'Ivoire.

INTRODUCTION

Measles is one of the main causes of vaccine-preventable death, especially in children under 5 years (WHO, 2015; Durrheim and Crowcroft, 2017; Yang et al., 2019). Vaccination helped to reduce measles incidence (66%) and deaths (73%) worldwide from 2000 to 2018 (Patel et al., 2019). However, Africa remains the most affected area in terms of morbidity and mortality. In 2019, 44 out of 47 countries in the World Health Organization (WHO) African Region reported 54% (286 542 confirmed cases) of the world's cases. The Democratic Republic of Congo registered 15292 confirmed cases and 6412 deaths in 2019 (WHO, 2020). In addition, measles is one of the most contagious viral infections with a basic reproduction number (R_0) ranging from 10 to 20 (Collèges des Universitaires de Maladies Infectieuses et Tropicales, 2016; Guerra et al., 2017) which underscores the public health emergency in case of an outbreak.

In Côte d'Ivoire, the first dose of measles-containing-vaccine (MCV1) through an expanded programme on immunization (EPI) was recommended for children at nine months of age. The global measles control strategy recommended by the WHO and United Nations Children's Fund (UNICEF) implemented in Côte d'Ivoire reduced cases and deaths from 24789 cases and 992 deaths in 2001 to 30 confirmed cases and 0 deaths in 2014 (MSHP Côte d'Ivoire, 2014). Encouraged by this progress, Côte d'Ivoire adopted the measles elimination strategy recommended by the WHO African Region in 2011 (WHO, 2015). However, since 2015, incidence has been increasing, although vaccination coverage seems to be increasing. Detection of measles-specific immunoglobulin M (IgM-positive) in the blood has become the standard diagnostic method for laboratory confirmation of measles (Helfand, 1998).

In Côte d'Ivoire, measles surveillance is performed in all health districts by the Epidemiological Surveillance Office of the National Institute of Public Hygiene (INHP) with coordinating directorate of the Expanded Programme Immunization (DCPEV) collaboration and the Measles Reference Laboratory (Institut Pasteur of Côte d'Ivoire).

In light of the recent epidemiological indicators, an analysis of factors associated with measles IgM-positive in Côte d'Ivoire from 2015 to 2019 was conducted in suspected cases of measles.

METHODOLOGY

Study location

The study was conducted in Côte d'Ivoire, a country located in West

Africa, with a population of 22,671,331 inhabitants in May 2014 (INS Côte d'Ivoire, 2014) over an area of 322642 km². Côte d'Ivoire had 86 health districts in 2018 (MSHP Côte d'Ivoire, 2015) grouped into 20 health regions. Since 2019, the country has grown to 103 health districts with 33 health regions, a change that became effective in 2020.

Measles surveillance

The surveillance of diseases with an epidemic risk is carried out as part of the Integrated Disease Surveillance and Response (IDSR) technical guidance developed by the WHO African Region (WHO 2010), which includes measles surveillance in Côte d'Ivoire. It is based on case-by-case surveillance. Case-based surveillance for measles requires an investigation of all suspected measles cases using an individual case investigation form. A blood specimen is collected for serologic confirmation of acute infection at the time of the initial contact with the case (WHO, 2015; Murray and Cohen, 2017).

Case definition

A suspected case of measles is defined as any person with generalized maculo-papular rash and fever and either cough, coryza or conjunctivitis or any person in whom a clinician suspects measles. A measles confirmed case is defined by serologic detection of measles-specific immunoglobulin M (IgM-positive). In order to strengthen surveillance, case-based surveillance for measles requires that all suspected measles cases be investigated and that a blood specimen be collected for serologic confirmation of measles infection (WHO, 2015).

Study period, population, and data sources

The study covered the period from 2015 to 2019 and was based on the data of the National Institute of Public Hygiene (INHP) and the Pasteur Institute of Côte d'Ivoire (IPCI). All suspected measles cases (9337 cases) were reported on individual forms and were then recorded in electronic databases by the health districts. The Epidemiological Surveillance Office of the INHP systematically received the recorded data. All blood samples from the health centres were transported to the IPCI laboratory with individual case forms from the health districts. The laboratory performed serological tests based on anti-measles IgM detection (8295 samples) (Figure 1).

Statistical analysis

In descriptive analysis, quantitative variable was described with means, standard deviation, median, interquartile range and range values and qualitative variable was described with sex ratio, number, and percentage. Regarding factors associated with measles IgM-positive, odds-ratios (crude OR and adjusted OR) and 95% confidence interval (95% CI) were calculated with univariate and multivariate logistic regression. Vaccination status, year of registration, gender, age group, and region of residence, were chosen as independent variables in our model. For the univariate analysis, all variables which had a *P*-value of <10% were included

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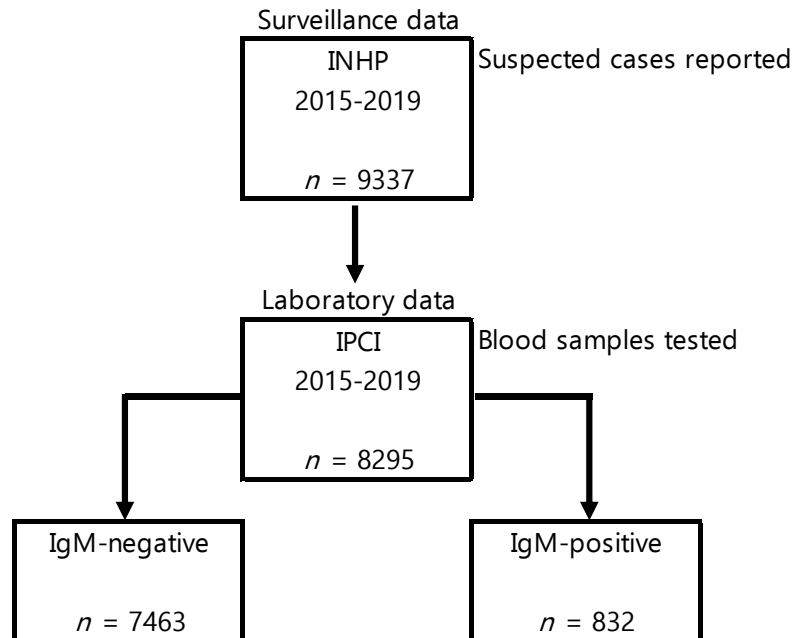


Figure 1. Measles surveillance and laboratory data from 2015 to 2019 in Côte d'Ivoire.

Sources: Surveillance data and laboratory data.

in multivariate model. A *P*-value of <5% was considered in the multivariate model. The data were analysed with Epi-Info 7 and the maps were depicted with QGIS 2.18.

Ethics

This study was approved by the Directors of the National Institute of Public Hygiene (INHP) and the Direction of Coordination of the Expanded Programme on Immunization (DCPEV). Both institutions respectively host epidemic disease surveillance and vaccine-preventable disease surveillance. Measles is a mandatory notification disease in Côte d'Ivoire. In this retrospective study, laboratory data were previously anonymised and surveillance data were anonymised prior to analysis.

FINDINGS

Socio-demographic characteristics of measles IgM-positive cases

A total of 9337 suspected cases of measles were reported of which 8295 blood samples were tested (88.84%). By year five (2015 to 2019), the median IgM-positive proportion was 8.09% (2017) with a range from 4.03% (2016) to 13.93% (2018). (Figure 2). The sex ratio (M/F) of IgM-positive cases was 1.03. The median age of IgM-positive cases was 4.38 year with an interquartile range (IQR) of [1.58-9.29 year]. There were 71.28% of IgM-positive cases aged between 1 and 15 years. Among the vaccination target population (<1 year), 57.02% were

unvaccinated. In the entire population, 28% were vaccinated against measles, 19.95% were unvaccinated and 52.05% had unknown vaccination status against measles (Figure 3).

Incidence of measles IgM-positive and measles vaccination coverage

Many of the health regions in the west of Côte d'Ivoire had among the highest incidence of measles IgM-positive (≥ 1 case per 100 000 inhabitants) (Figure 4). Vaccination coverage for measles in Côte d'Ivoire averaged 89.28% (\pm SD 3.12%). This coverage was heterogeneous across the country and ranged from 80 to 90% in most western regions (Figure 5).

Factors associated with measles IgM-positive cases among suspected cases

The presence of measles IgM was associated with vaccination status, year of registration, gender, age and region/area of residence. Unvaccinated cases had a higher risk of confirmed infection compared with vaccinated cases [aOR=2.82, (95%CI 2.19, 3.63), $P<0.0001$]. The risk of being infected with measles increased with years ($P<0.0001$) and age ($P=0.043$). The regions in the west of the country were more at risk than the regions of the economic capital of Abidjan, located in

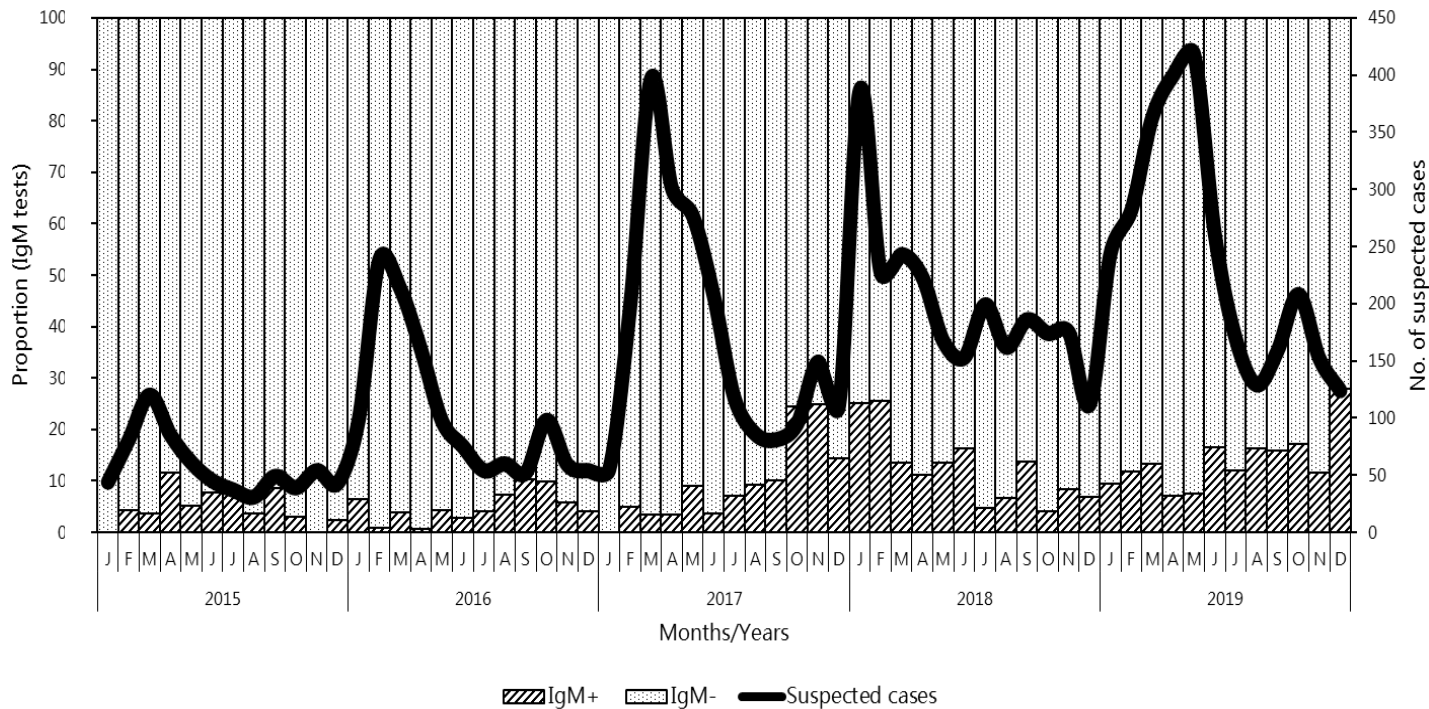


Figure 2. Proportion of cases tested ($n = 8295$ with IgM+ = 832 / IgM- = 7463) among measles suspected cases ($n = 9337$) per month, from 2015 to 2019, in Côte d'Ivoire.
Source: Surveillance Data and Laboratory Data (Côte d'Ivoire, from 2015-2019)

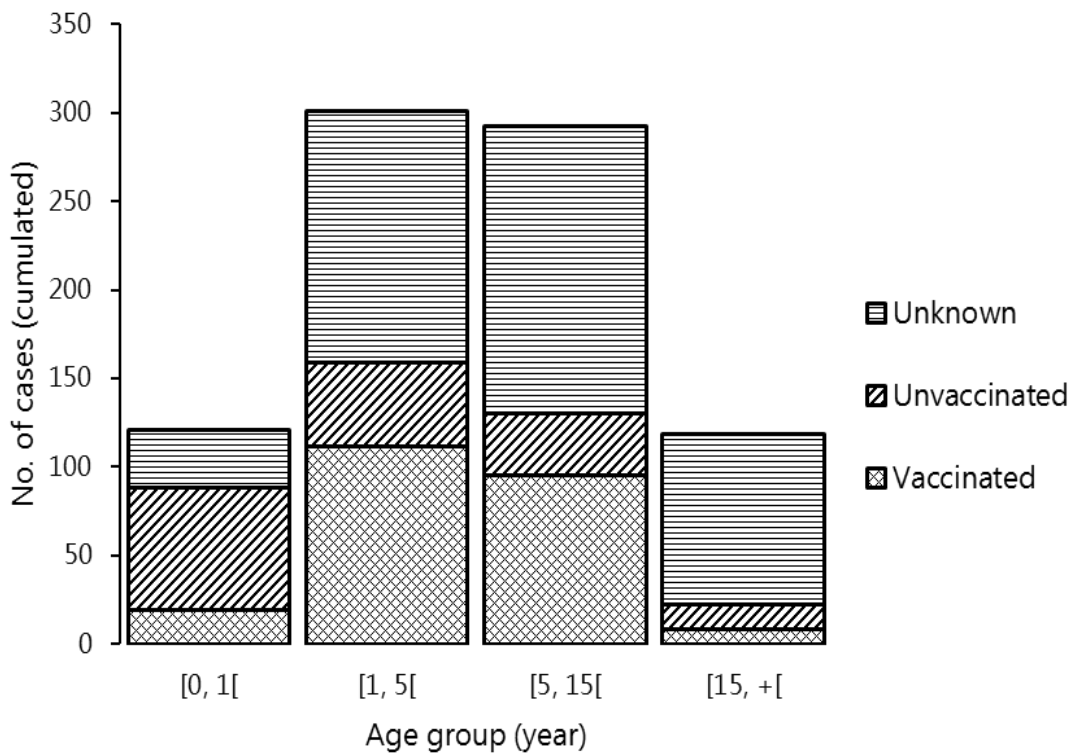


Figure 3. Number of confirmed measles cases (IgM+) according to vaccination status, by age group from 2015 to 2019 in Côte d'Ivoire ($n = 832$).
Source: Surveillance Data and Laboratory Data (Côte d'Ivoire, from 2015-2019)

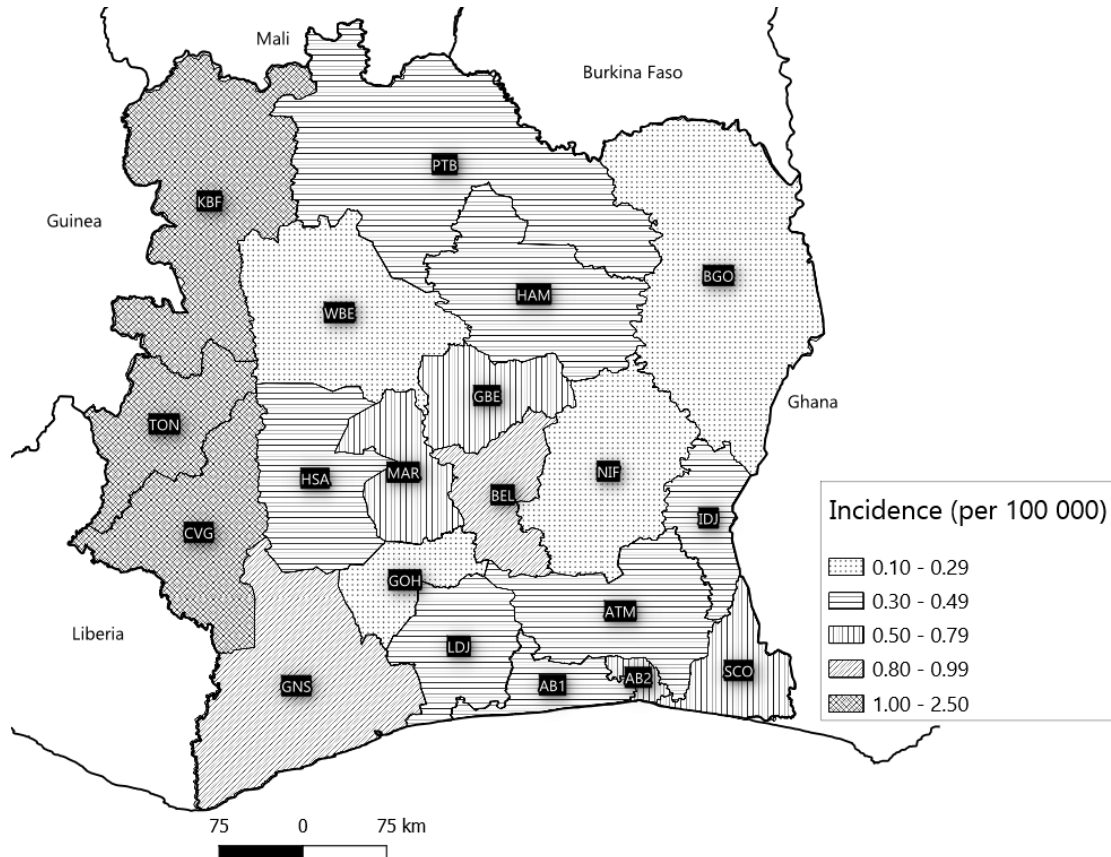


Figure 4. Cumulative incidence of measles by health region from 2015 to 2019 in Côte d'Ivoire ($n = 832$). Abidjan 1 Grands Ponts (AB1), Abidjan 2 (AB2), Agnéby-Tiassa-Mé (ATM), Bélier (BEL), Bounkani-Gontougo (BGO), Cavally-Guémon (CVG), Gbèkè (GBE), Gbôklè-Nawa-San Pédro (GNS), Goh (GOH), Hambol (HAM), Haut Sassandra (HSA), Indénié-Djuablin (IDJ), Kabadougou-Bafing-Folon (KBF), Loh-Djiboua (LDJ), Marahoué (MAR), N'Zi-Iffou (NIF), Poro-tchologo-Bagoué (PTB), Sud-Comoé (SCO), Tonkpi (TON), Worodougou-Béré (WBE). Source: Surveillance Data and Laboratory Data (Côte d'Ivoire, from 2015-2019).

the south (Table 1).

DISCUSSION

The study showed a median measles-specific IgM+ proportion of 8.09% in suspected measles cases. This rate increased each year even though the laboratory was often confronted with reagent breakdowns. Our rates are higher than those of Doshi et al. (2015) who reported 3.70% in the Democratic Republic of Congo. The present results could be credited with strengthening the diagnostic capacity of the National Measles Reference Laboratory and player training at the peripheral level in detection and case reporting. In our study, 19.95% of IgM+ cases were unvaccinated - a different result from that of Watanabe et al. (2019) whose study indicated 50% unvaccinated subjects among confirmed measles cases in Japan. This difference could be explained by the proportion of cases with unknown status (52.04%) in our study. In the present study, vaccination coverage was

variable according to health status and geographic distribution but remained below the elimination targets ($\geq 95\%$). Doshi et al. (2015) reported a rate of 73% in the Democratic Republic of Congo.

The results indicate a high risk of measles infection among unvaccinated IgM+ cases ($P < 0.0001$). The study by Doshi et al. (2015) showed that measles vaccination was protective in children aged 12 to 59 months with a vaccine efficacy of 80%. Moreover, the risk increases with age and certain regions of residence. A study in China reported that "the proportion of measles cases among those aged 15 years and older increased from 52.99% in 2006 to 67.64% in 2013 since vaccination coverage of measles increased" (Ma et al., 2019).

In the study, given that the risk of measles infection increased with age in addition to the need to include a second dose of measles vaccine in the routine programme as recommended by WHO, studies must be undertaken to understand vaccine hesitancy and identify the reasons for vaccine insufficiency in order to improve vaccination coverage for the first (MCV1) and second

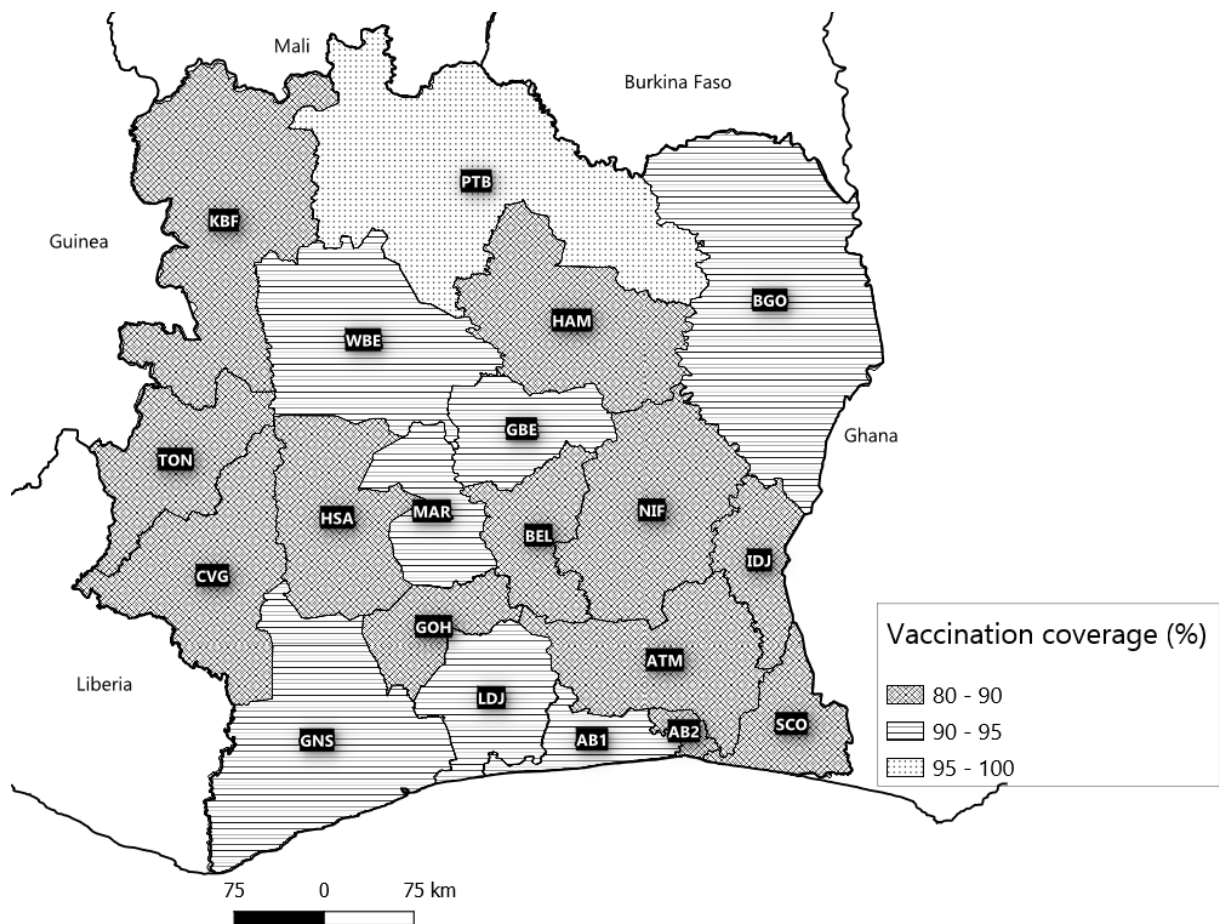


Figure 5. Measles vaccine coverage (average) of the health regions from 2015 to 2019 in Côte d'Ivoire. Abidjan 1 Grands Ponts (AB1), Abidjan 2 (AB2), Agnèby-Tiassa-Mé (ATM), Bélièr (BEL), Bounkani-Gontougo (BGO), Cavally-Guémon (CVG), Gbèkè (GBE), Gbôklè-Nawa-San Pédro (GNS), Goh (GOH), Hambol (HAM), Haut Sassandra (HSA), Indénié-Djuablin (IDJ), Kabadougou-Bafing-Folon (KBF), Loh-Djiboua (LDJ), Marahoué (MAR), N'Zi-Iffou (NIF), Poro-tchologo-Bagoué (PTB), Sud-Comoé (SC0), Tonkpi (TON), Worodougou-Béré (WBE).

Source: Vaccination data.

Source: Expanded Programme Immunization of Côte d'Ivoire (2015-2019).

(MCV2) doses of measles. It would also be appropriate to extend catch-up campaigns to older children and young adults. Insufficient vaccination coverage (less than 95%) results in a yearly increase in the number of susceptible subjects. These susceptible subjects are also increasing in older populations, leading to higher measles infection ages in the absence of immunization catch-up programmes (Baudon et al., 2011).

As for factors associated with place of residence, the present study showed a high risk of measles infection in five health regions located in the western part of the country compared with one of the health regions of the economic capital (Abidjan) located in the south. These observations could be explained by the fact that the western and north-western regions of Côte d'Ivoire share borders with three countries (Guinea, Liberia and Mali). These three countries present high measles incidence and have insufficient vaccination coverage according to

WHO estimates. The average MCV1 coverage from 2015 to 2018 for these countries was 48, 80.50 and 66.25%, respectively (WHO, 2020). It should be noted that these three countries have healthcare systems that could be affected by military and political conflicts and also strongly affected by the Ebola epidemic for Guinea and Liberia (Fanny, 2014; WHO, 2016). Moreover, these countries as well as Côte d'Ivoire have not yet included the second dose of measles vaccine (MCV2) in their routine vaccination programme – unlike Ghana (Masresha et al, 2018) and Burkina Faso (Zoma et al., 2019). However, vaccination coverage in those countries remains below the measles elimination target ($\geq 95\%$) (Plans-Rubió, 2012). The second dose is intended to boost the immunity of vaccinated children who have not seroconverted after the first dose and also catch up with those who missed the vaccination. Several studies have reported that the effectiveness of a single dose of

Table 1. Logistic regression of factors associated with measles IgM-positive from 2015 to 2019 in Côte d'Ivoire ($n = 8295$).

Variable	Parameter	No. of cases (%)		Univariate analysis			Multivariate analysis		
		IgM+	IgM-	Crude OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Vaccination status	Vaccinated	233 (28.00)	2,732 (36.61)	1(Ref)		0.0000	1(Ref)		
	Unvaccinated	166 (19.95)	1012 (13.56)	1.92	[1.56-2.38]		2.82	[2.19-3.64]	0.0000
	Unknown	433 (52.05)	3719 (49.83)	1.37	[1.56-1.61]		1.20	[1.00-1.44]	0.0472
Registration year	2015	32 (3.85)	598 (08.01)	1(Ref)		0.0000	1(Ref)		
	2016	48 (5.77)	1142 (15.30)	0.79	[0.50-1.24]		0.83	[0.52-1.32]	0.4351
	2017	157 (18.87)	1784 (23.90)	1.64	[1.11-2.43]		1.53	[1.03-2.28]	0.0373
	2018	277 (33.29)	1711 (22.93)	3.02	[2.07-4.41]		3.16	[2.14-4.66]	0.0000
	2019	318 (38.22)	2228 (29.85)	2.67	[1.83-3.88]		2.50	[1.70-3.67]	0.0000
Gender	Male	422 (50.72)	4010 (53.73)	1(Ref)		0.0987	1(Ref)		
	Female	410 (49.28)	3453 (46.27)	1.13	[0.98-1.30]		1.14	[0.98-1.32]	0.0823
Age Group (year)	Age characteristics		IgM+		IgM-		IgM (Total test)		
	Average age (SD) (Year)		7.73 (\pm 9.46)		6.93 (\pm 8.70)		7.00 (\pm 8.78)		
	Median age [IQR] (Year)		4.38 [1.58-9.29]		4.00 [1.42-8.58]		4.00 [1.50-9.00]		
	[0-1]	121 (14.54)	1054 (14.12)	1(Ref)			1(Ref)		
	[1-5]	301 (36.18)	2991 (40.08)	0.88	[0.70-1.09]	0.0427	1.37	[1.06-1.78]	0.0167
	[5-15]	292 (35.10)	2570 (34.44)	0.99	[0.79-1.24]		1.54	[1.18-2.00]	0.0015
[15 +]	118 (14.18)	848 (11.36)	1.21	[0.93-1.59]		1.56	[1.14-2.12]	0.0049	
Residential Health Region	Abidjan 1 Grands Ponts	44 (5.29)	522 (6.99)	1(Ref)		0.0000	1(Ref)		
	Abidjan 2	103 (12.38)	2001 (26.81)	0,61	[0.42-0.88]		0.65	[0.45-0.94]	0.0236
	Agnéby-Tiassa-Mé	20 (2.40)	181 (2.43)	1,31	[0.75-2.28]		1.25	[0.71-2.20]	0.4352
	Bélier	32 (3.85)	285 (3.82)	1,33	[0.83-2.15]		1.31	[0.80-2.12]	0.2797
	Boukani-Gontougo	12 (1.44)	83 (1.11)	1,72	[0.87-3.38]		1.76	[0.88-3.50]	0.1094
	Cavally-Guémon	139 (16.71)	850 (11.39)	1,94	[1.36-2.77]		1.90	[1.32-2.72]	0.0005
	Gbèkè	32 (3.85)	262 (3.51)	1,45	[0.90-2.34]		1.37	[0.85-2.23]	0.1994
	Gbôklè-Nawa-San Pédro	105 (12.62)	529 (7.09)	2,35	[1.62-3.42]		1.93	[1.32-2.82]	0.0006
	Goh	13 (1.56)	106 (1.42)	1,46	[0.76-2.80]		1.49	[0.77-2.88]	0.2408
	Hambol	12 (1.44)	95 (1.27)	1,50	[0.76-2.94]		1.38	[0.70-2.74]	0.3528
	Haut Sassandra	30 (3.61)	211 (2.83)	1,69	[1.03-2.76]		1.68	[1.02-2.77]	0.0402
	Indénié-Djuablin	14 (1.68)	174 (2.33)	0,95	[0.51-1.78]		0.95	[0.50-1.79]	0.8688
	Kabadougou-Bafing-Folon	36 (4.33)	481 (6.45)	0,89	[0.56-1.40]		0.89	[0.56-1.41]	0.6095
	Loh-Djiboua	18 (2.16)	145 (1.94)	1,47	[0.83-2.63]		1.48	[0.82-2.66]	0.1895
Marahoué	29 (3.49)	128 (1.72)	2,69	[1.62-4.46]		2.87	[1.71-4.81]	0.0001	
N'Zi-Iffou	10 (1.20)	198 (2.65)	0,60	[0.30-1.21]		0.71	[0.35-1.46]	0.3537	

Table 1. Cont.

Porotchologo-Bagoué	29 (3.49)	296 (3.97)	1,16	[0.71-1.90]	1.34	[0.82-2.21]	0.2445
Sud-Comoé	18 (2.16)	241 (3.23)	0,89	[0.50-1.57]	1.04	[0.58-1.84]	0.9050
Tonkpi	130 (15.63)	644 (8.63)	2,39	[1.67-3.44]	2.14	[1.48-3.09]	0.0000
Worodougou-Béré	6 (0.72)	31 (0.42)	2,30	[0.91-5.80]	2.09	[0.81-5.37]	0.1265

Regression logistic model characteristic (multivariate analysis); Cases included: 8295; Final 2 x Log likelihood: 5056.5231; Chi-square = 331.63; df = 29 *P*-value < 0.0001.

Source: Surveillance Data and Laboratory Data (Côte d'Ivoire, from 2015-2019)

measles vaccine given at age 12 to 15 months ranges from 85 to 95% while efficacy is close to 100% after the second dose (Pebody et al., 2002; Saffar et al., 2011; Rafiei Tabatabaei et al., 2013)

There are some limitations to be considered in the study. The investigation data of measles outbreaks were not considered in the study. A confirmed case of measles is defined either by laboratory confirmation when measles-specific IgM positive is present or by the epidemiological link to a laboratory-confirmed case or by clinician confirmation during an outbreak or epidemic (WHO, 2015). This sampling bias could lead to an underestimation of the measures of association if these subjects represented a significant proportion. In current practice, it is challenging to have evidence that a population has been vaccinated. Vaccination status is sometimes documented and sometimes reported by the accompanying persons. The vaccine coverage used in the study are administrative coverage which correspond to the number of vaccine doses administered to individuals in the target age group (children aged less than one year), divided by the estimated size of this population. A rate that does not cover the entire population at risk.

Conclusion

Côte d'Ivoire must strengthen its surveillance,

through rapid and good investigations and respond effectively to epidemics to meet the requirements of measles elimination. Pooling our actions by organizing synchronized vaccination campaigns with neighbouring countries is also essential.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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