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ORIGINAL ARTICLE

Hepatitis B birth vaccination, cohort study, Tunisia 2000–2017

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ABSTRACT

We aimed to compare the efficiency of the first dose of Hepatitis B (HB) vaccine: at Birth versus at 3 months and to evaluate the efficacy of HB vaccine. We conducted a cohort study in the governorate of Monastir. Vaccinated Cohort (VC) included populations receiving the first dose at 3 months (Protocol 1), and at birth (HepB-BD) (Protocol 2). First dose was followed by at least two doses. We collected, from January 2000 to December 2017, cases diagnosed by serological markers (hepatitis B surface antigen (HBsAg) and anti-HBc). We calculated Absolute Risk (AR) per 100,000 PY and the Relative risk reduction (RRR). Twenty-five cases were notified among VC and 1501 cases among not vaccinated cohort (NVC). Twenty-three cases were notified among the cohort receiving the first dose at 3 months and two cases in Protocol 2. The AR per 100,000 PY was 5.67 (CI95%: 3.36–7.99) in Protocol 1 and 0.11 (CI95%: 0.001–0.26) in Protocol 2. The RRR was 77% (95% CI: 66; 85) in Protocol 1 and 99.4% (95% CI: 97.8; 99.9) in Protocol 2. We identified 4 HB cases for children aged between 5 and 11 who benefited from protocol 1 (born between 2000 and 2006) and zero cases for children of the same age group benefiting from protocol 2 (born between 2011 and 2017). The annual number of HB has decreased from 112 in 2000 to 48 in 2017. We predicted 40 new cases of HB in 2030. HepB-BD was 99.4% effective at preventing HB. The continuity of HepB-BD worldwide would achieve WHO's goal of eliminating HB as a threat to health by 2050.

Abbreviations: AR: Absolute Risk; ARR: Absolute Risk Reduction; G1: Group1; G2: Group2; HB: Hepatitis B; HepB-BD: Hepatitis B Birth Dose; MENA: Middle East and North Africa; NNV: Number Needed to Vaccine; HIV: Human Immunodeficiency Virus; NVC: Not Vaccinated Cohort; PY: Person Year; RRR: Relative Risk Reduction; RR: Relative Risk; VC: Vaccinated Cohort; WHO: World Health Organization

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KEYWORDS
Efficiency; hepatitis B; humans; vaccination; Tunisia

1. Background

Hepatitis B (HB) infection is the seventh leading cause of mortality worldwide, responsible for 1.34 million deaths in 2015 with an estimated prevalence of 1.3% in the age under 5 [1,2]. Tunisian prevalence rate of Hepatitis B surface antigen (Ag-HBS) was 1.7% (95% CI [1.6%–1.9%]) [3]. WHO has implemented child immunizations and prevention of mother-to-child transmission to reduce the number of new cases and deaths from chronic hepatitis B.

In 2016, the first global health sector strategy on viral hepatitis was endorsed with the goal of eliminating viral hepatitis as a public health threat by 2030 [4,5]. Thus, WHO has revised the age of administration of the first dose of HB vaccine to be dispensed at birth within 24 hours (HepB-BD) instead at the age of 3 months recommended previously [6]. HB immunization was included to the Tunisian Expanded Program of Immunization (EPI) since April 1995 as Protocol 1 (G1) (first dose at 3 months). Protocol 2 (G2) (HepB-BD) started in April 2006 for babies born to positive mothers as a post-exposure prophylaxis. In 2014 protocol 2 was expanded to all newborns [7,8]. In Tunisia, a high vaccination coverage has been reported (94%) [9], particularly in Monastir governorate (98%) [10]. Similarly, the prenatal care was adequate for 82.5% in the study area (including screening of HB serological markers) [11]. In Tunisia, HB's screening is done by all physicians to achieve WHO's goal by 2030 and declaration is mandatory [12].

2. Objective

We aimed to compare the efficiency of the first dose of HB vaccine: at Birth versus at 3 months and to evaluate the efficacy of HB vaccine.

3. Methods

3.1. Study design

We performed a cohort study in the governorate of Monastir from January 2000 to December 2017.

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3.2. Study Setting

Monastir governorate is an industrial-oriented and touristic region, including 13 delegations with 580,760 inhabitants [13]. During the study period, there was no change in medical practices.

Periods of recruitment: we started data collection of HB cases in January 2000. In December 2017 we started to analyze according to vaccination status and according to both protocols. Exposure duration at endpoint varied from 11 to 22 years for G1 and from one to ten years for G2.

3.3. Study population

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3.3.1. Exposed/not exposed population

Not exposed population (NVC) were born before 1995 and exposed population to vaccination (VC) were born after this date. VC born from 1995 to 2006 benefited from Protocol 1 (G1: first dose at 3 months) and those from 2006 benefited from Protocol 2 (G2: first dose at birth). The two protocols were followed by at least two more doses. Patients living in other governorate were not included. Each vaccination is recorded on the personal immunization card.

3.3.2. Event

We studied all HB diagnosed from 1 January 2000 to 31 December 2017. Diagnosis criteria of HB is based on serological markers. Since two decades a mass screening program gets started in our country including serological markers of HB infection (hepatitis B surface antigen (HBsAg) and anti-HBc). Screening has been done in the prenuptial visit, at pregnancy, in clinically suspected cases, in blood donation, in the relatives of HB positive cases, in people living with HIV and in people living with other diagnosed sexually transmitted infections. Positive HB screening tests were associated with a spouse and family investigation. Screening program is done by all physicians to achieve WHO's goal by 2030. In Tunisia, HB's declaration is mandatory [12].

3.4. Variables

Data included demographic variables (age, sex), vaccination status, and year at diagnosis. The vaccination status was verified by an anamnestic survey and by the immunization card control. We considered incident cases the new diagnosed cases (hepatitis B surface antigen (HBsAg) and anti-HBc) during the study period.

3.5. Data collection method and measurement

HB cases were registered in a database ('epi info' software) in the Regional Directorate of Primary Health of Monastir.

3.6. Bias

Several training days on HB screening and case management were carried out for the majority of physicians and laboratory to decrease the risk of underestimation.

3.7. Statistical analysis

Data were verified and analyzed using IBM SPSS Statistics version 22.0 software (IBM Corp., Armonk, NY, USA). Chi square tests were used to compare distribution of cases according to age groups and sex. Trends and prediction were calculated using Log-linear Poisson model. A p-value of <0.05 was considered statistically significant. The Absolute Risk (AR) per 100,000 person year (PY) was calculated based on Tunisian National Institute of Statistics data [13].

AR, Absolute risk reduction (ARR); Relative risk (RR), Relative risk reduction (RRR), and Number Needed to Vaccine (NNV) were calculated using Microsoft Excel 2013.

3.8. Ethical considerations

The protocol was approved by the ethics committee of Faculty of medicine of Monastir. The study was conducted under Good Clinical Practice conditions and according to ethical standard collections. Each patient was assigned a unique identifying code and all documents were labeled accordingly to maintain anonymity. Investigations around all diagnosed cases were conducted and managed according to ethical standards.

4. Results

4.1. Effectiveness of birth-dose versus 3-month-dose (G1 vs G2)

Twenty-three incident cases were notified in G1 and two cases in G2. The RRR of HB vaccination was 77% (95%CI: 66; 85) with protocol 1 and 99.4% (95%CI: 97.8; 99.9) with protocol 2. The RR of developing HB vaccine (G2 vs G1) was 0.019 ($p < 0.001$) (Table 1). We identified 4 HB cases for children aged between 5 and 11 who benefited from protocol 1 (born between 2000 and 2006) and zero cases for children of the same age group benefiting from protocol 2 (born between 2011 and 2017).

Table 1. Effectiveness of hepatitis B vaccine according to the two protocols, Monastir, Tunisia 2000–2017.

	Cases	Population	Absolute risk per 100,000 PY (95% CI)	Absolute risk reduction per 100,000 PY	Relative risk	Relative risk reduction	Number Needed to vaccine	p
First dose at 3 months	23	405,011	5.67 (3.36;7.99)	19.73	0.22 (0.14–0.34)	0.77 (0.66–0.85)	5067 (4044–6783)	<0.0001
NVC	664	2,612,173	25.42 (23.4–27.3)					
HepB-BD	2	1,812,887	0.11 (0.001–0.26)	19.85	0.005 (0.001–0.022)	0.994 (0.978–0.999)	5037.1 (4563 – 5620.0)	<0.0001
NVC	837	4,192,827	19.96 (18.6–21.31)					
HepB-BD	2	1,812,887	0.11 (0.04–0.02)	5.56	0.019 (0.005;0.082)	0.981 (0.918;0.995)		<0.0001
First dose at 3 months	23	405,011	5.67 (3.36;7.99)					

NVC: Not Vaccinated cohort

4.2. Effectiveness of HB vaccine (VC vs NVC)

During study period 1,526 new cases of HB were diagnosed being 1,501 in NVC and 25 in VC. The AR/100,000 PY, was 22.06 (95% CI: 20.94; 23.17) in NVC and 1.11 (95% CI: 0.68; 1.55) in VC (P < 0.0001). The RRR of was 95% (95% CI: 92.5, 96.6). NNV was 4,775 (95%CI: 4,367; 5,268) (Table 2). In age group 0–22 years HB vaccine prevented 95% of HB cases (n = 217 cases) (Figure 1).

4.3. Other results

For all groups, the AR/100,000 PY was 16.85 with a significant regional disparity passing from 23.08 in urban region (Monastir city) to 7.04 in rural one (Bekalta) (Table 3). Sex ratio was 3.95 in NVC (p < 0.001) and 1.5 in VC (p = 0.317).

According to age, AR was the highest among 20–39 years age group (36.40/100,000 PY) and the lowest in 0–19 years age group.

A negative and significant trend was noted in both sex, in NVC (b = −0.052; CI95% (−0.042; −0.062); p < 0.0001)) (Figure 2) and in 20–39 years age group (b = −0.063; CI95% (−0.05; −0.07); p < 0.0001)) (Table 4). We estimated 40 the number of new cases in 2030 (CI95%: 28–63)(Figure 3).

5. Discussion

Key results: HepB-BD protocol had more effectiveness than protocol 2. AR was concordant to national rates. HB trends were significantly decreasing. A herd immunity effect was established in NVC.

5.1. Interpretations

According to WHO; HB vaccination is the most effective way to prevent HB virus infection. If given within 24 hours after birth, followed by at least two more doses, is effective at preventing perinatal HB virus infection and inducing immunity to HB virus [14].

Tunisia located in the Eastern Mediterranean Region had an intermediate prevalence of HB infection in 2009 [15] and low prevalence in 2015 [3]. It was one of the 95 countries which had included HepB-BD as a part of national immunization schedule for all children in 2014. In our study, we determinate the efficacy of HepB-BD protocol proving the prevention of mother-to-child HB virus transmission. No cases of HB aged less than 5 years were reported since 2014, confirming the reduction of perinatal HB virus transmission by positive mothers [16]. Our results were concordant with studies conducted in South-East Asia, America, and Western Pacific [17-19]. According to WHO, 90% of perinatal infections and horizontal transmission of household contacts can be prevented by HepB-BD followed by

Table 2. Effectiveness of HB vaccine (Monastir (2000–2017)).

Years		Cases	Population	Absolute risk per 100,000 PY (95% CI)	Absolute risk reduction per 100,000 PY	Relative Risk	Relative Risk reduction	number needed to treat	p
2000–2017	VC	25	2,246,551	1.11 (0.68;1.55)	20.94	0.050 (0.034,0.075)	0.95 (0.925; 0.966)	4775 (4367;5268)	< 0.0001
	NVC	1501	6,805,000	22.06 − 20.94;23.17)					
2000	VC	1	43,624	2.29 (0; 6.8)	22.08	0.094(0.01; 0.67)	0.905 (0.33; 0.99	4526 (2716; 13,564)	0.0186
	NVC	112	459,240	24.38 (1.9; 28.9)					
2001	VC	1	53,175	1.88 (1.81;5.57)	23.91	0.0729 (0.010; 0.522)	0.927 (0.478;0.990)	4181 (2675; 9797)	0.0091
	NVC	116	449,689	24.90 (20.29;29.51)					
2002	VC	0	62,726	0	24.38	0.0333(0.0021;0.5353)	0.9667 (0.4647; 0.9979)	4316 (2832;9070)	0.0164
	NVC	105	440,138	24.385 (19.72; 29.04)					
2003	VC	2	72,277	2.767 (1.0; 6.660)	21.16	0.1135 (0.028;0.459)	0.8865 (0.541;0.972)	4626 (3020;9878)	0.0023
	NVC	105	430,587	23.943 (19.35; 28.512)					
2004	VC	1	81,828	1.222 (0;3.62)	24.19	0.048 (0.006;0.344)	0.951 (0.655;0.993)	4134 (2844;7567)	0.0025
	NVC	117	421,036	25.413 (20.599;30.228)					
2005	VC	0	91,380	0	25.88	0.0267 (0.0017; 0.4296)	0.9733 (0.5704; 0.9983)	5003 (3412; 9374)	0.0106
	NVC	109	411,484	25.888 (21.029–30.7480)					
2006	VC	0	100,931	0	20.89	0.0236 (0.0015;0.3799)	0.9764 (0.6201;0.9985)	4872 (3390;8655)	0.0082
	NVC	84	401,933	20.899 (16.43; 25.36)					
2007	VC	2	110,482	1.18 (0; 4.32)	18.32	0.089 (0.022;0.366)	0.910 (0.634;0.978)	5458(3732;10,153)	0.0008
	NVC	79	392,382	20.13 (15.69; 24.57)					
2008	VC	3	120,033	2.49 (0;5.33)	30.41	0.076 (0.024;0.238)	0.92 (0.76;0.97)	3289 (2451;4994)	< 0.0001
	NVC	126	382,831	32.91 (27.16;38.65)					
2009	VC	0	129,584	0	17.68	0.217 (0.001;0.350)	0.783 (0.65;0.999)	5738 (4045;9868)	0.0069
	NVC	66	373,280	17.68 (13.41;21.94)					
2010	VC	1	139,135	0.71 (0;2.13)	18.80	0.036 (0.005;0.265)	0.964 (0.735;0.995)	5319 (3818;8767)	0.0010
	NVC	71	363,729	19.52 (14.98;24.06)					
2011	VC	1	148,686	0.675 (0;19.9)	17.39	0.037(0.005;0.268)	0.963 (0.732; 0.995)	5749 (4118;9515)	0.0011
	NVC	64	354,178	18.07 (13.64;22.49)					
2012	VC	1	158,237	0.63 (0;1.87)	21.71	0.028 (0.003;0.203)	0.972 (0.797;0.997)	4607 (3434;6995)	0.0004
	NVC	77	344,627	22.34 (17.35;27.33)					
2013	VC	0	167,788	0	19.99	0.014 (0.0009;0.239)	0.986 (0.761;0.9991)	5039 (3751;7676)	0.0030
	NVC	67	335,076	19.99 (15.20;24.78)					
2014	VC	2	177,340	1.13 (0.44;2.69)	13.00	0.079 (0.019;0.328)	0.921 (0.672;0.981)	7691 (5361;13,604)	0.0004
	NVC	46	325,524	14.13 (9.78;17.86)					
2015	VC	2	186,891	1.07 (0.41;2.55)	15.38	0.065 (0.015;0.267)	0.935 (0.733;0.985)	6500 (4692;10,572)	0.0001
	NVC	52	315,973	16.45 (11.98;20.93)					
2016	VC	5	196,442	2.54 (0.31;4.78)	15.07	0.144 (0.057;0.361)	0.856 (0.639;0.943)	6633 (4714;11,186)	<0.0001
	NVC	54	306,422	17.62 (12.92;22.32)					
2017	VC	3	205,993	1.46 (0.20;3.26)	15.65	0.085 (0.027;0.272)	0.915 (0.728;0.973)	6361 (4641;10,104)	<0.0001
	NVC	51	296,871	17.18 (12.46;21.89)					

AAR: Absolute Risk Reduction; *: per 100,000 PY; NNT: number needed to treat.

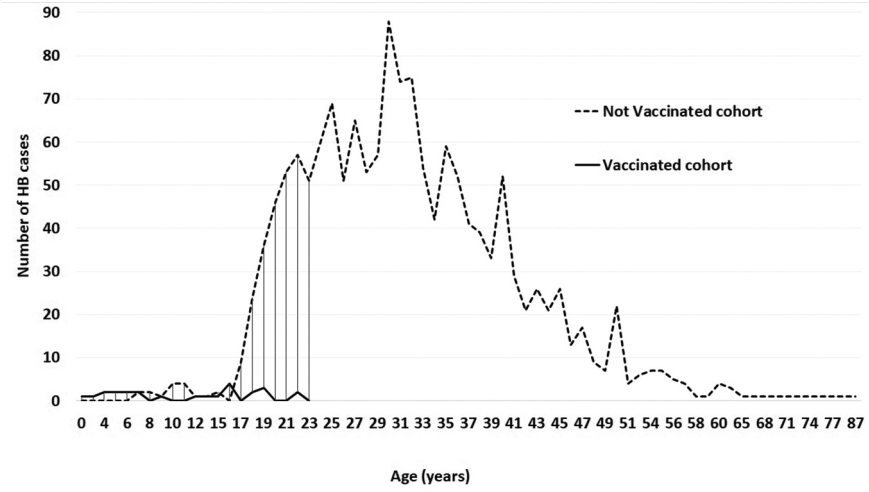

Figure 1. Age distribution of cases of hepatitis B according to immunization status (2000–2017; Monastir Tunisia).

Table 3. Absolute risk of developing HB, by delegations (Monastir; Tunisia, 2000–2017).

	Population	Cases	Absolute risk per 100,000 PY (95% CI)
Over all	502,864	1526	16.85
Delegations			
Monastir	92,914	386	23.08
Jemmal	60,346	249	22.92
Ksibet Medyouni	31,649	107	18.78
Moknine	82,581	267	17.96
Ksar hellel	44,683	142	17.66
Bembla	29,968	79	14.65
Sayada – Lamta – Bouhjar	23,918	58	13.47
Sahline	24,624	45	10.15
BniHassen	13,259	22	9.22
Zeramdine	27,840	46	9.18
Wardanine	20,333	31	8.47
Teboulba	34,319	50	8.09
Bekalta	15,772	20	7.04

at least 2 additional doses in early childhood [20]. Our results determining that 99% of cases can be preventable by HepB-BD.

The negative trend of notified new cases of HB and the low AR in younger than 20 years approved the high HB vaccine effectiveness. Our results were concordant with literature [3].

The high AR notified in the 20–39 age group may be related to prenuptial screening and to the high-risk sexual activity in this age group. The decrease of HB new cases in this age group can be explained by herd immunity effect and by couple immunization during prenuptial visit. Indeed, it is advisable for HB-negative couples to be vaccinated, while vaccination is mandatory for discordant couples [21].

The AR difference according to sex was consistent with a local study conducted at Monastir University Hospital (2002–2013, 22), in northern India [23] and in France [24]. This may be related to that men are more exposed to transfusions (road and work accident), sexual behavior, and imprisonment [25]. In addition, females have a better immune response due to the lower plasma disappearance rate for Ag-HBs in males [26–28]. In VC we determine an equivalent number of new cases according to sex.

In our study, the general trend of HB infection was decreasing, concordant with the conclusion in the eastern Mediterranean regions [29]. Iran (MENA) described increasing trends from 2008 to 2013 [30]. In 2030 forty new cases were predicted to be diagnosed in Monastir governorate. These results

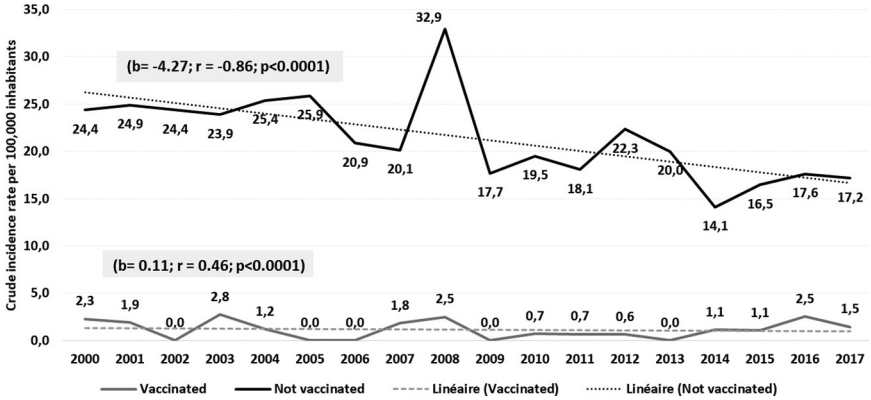

Figure 2. Trends of hepatitis B crude incidence rate/100,000 inh according to immunization status (2000–2017; Monastir Tunisia).

Table 4. Absolute risk and trends of HB, by age groups and gender (Monastir, Tunisia, 2000–2017).

	Population	Cases(%)	Absolute risk per 100,000 PY	Slope (b)	CI 95% (b)	p
Age groups (Years)						
0–19	186,890	109 (7.1)	3.24	−0.145	−0.10;-0.18	<0.0001
20–39	171,046	1121 (73.5)	36.40	−0.063	−0.05;-0.07	<0.0001
40–59	101,466	278 (18.2)	15.22	0.029	0.006–0.011	0.012
≥ 60	43,460	18 (1.2)	2.30	0.012	-	<0.785
Gender						
Men	252,757	1213 (79.5)	26.66	−0.037	−0.02;-0.04	<0.0001
Women	250,106	313 (20.5)	6.95	−0.105	−0.08; −0.12	<0.0001

Slope (b) calculated by Log-linear Poisson regression model,

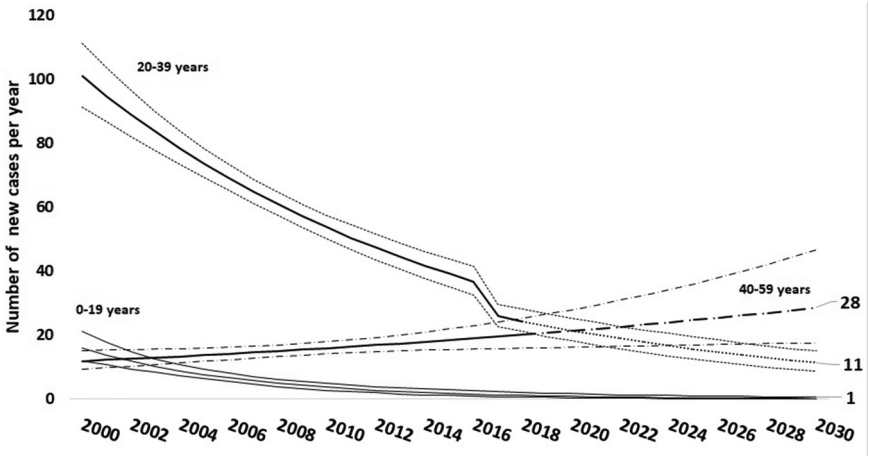

Figure 3. Prediction to 2030 of cases of hepatitis B according to age group.

demonstrate difficulties to achieve WHO's goal by 2030, we suppose that the year 2050 is more reasonable to eliminate hepatitis in our region.

6. Limitations

This study confirmed the effectiveness of WHO strategies but some limitations related to data collection which can underestimate the number of new cases. In addition, NVC could include some people who could be immunized in vaccination campaigns launched before 1995.

7. Conclusion

HepB-BD followed by at least two doses was 99.4% effective at preventing HB. The continuity of HepB-BD worldwide would achieve WHO's goal of eliminating HB as a threat to health by 2050.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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The study was approved by the Institutional Ethics Committee of the Medical Faculty of Monastir, Tunisia under number IORG0009738N°25/OMB0990-0279.

Ethics approval and consent to participate

The data were obtained from a passive surveillance system focused on reportable diseases and conducted under the approval of the Regional Directorate of Primary Health according to ethical standards with the maintenance of anonymity of each patient. Thus, according to the Tunisian National Committee on Medical Ethics (http://www.comiteethique.rns.tn/index.php), it was not necessary to obtain the personal consent of the study participants.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests No Competing interests for all authors.

Authors' contributions

WD: Conceptualization, Formal analysis, Methodology, Writing - original draft.

ASB: design of the work Formal analysis, Methodology, , and substantively revised the draft.

MK, CBN, MBF, HA, IZ, and SC: Formal analysis, interpretation of data, and draft revision. IM and SG: data collection and verification.

All authors agreed to be personally accountable for the author's own contributions, have read and approved the manuscript.

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