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CASE SERIES Open Access

A Case Series of T Cell and Cytokine Immune Responses in Six Health Care Workers Vaccinated with a Recombinant Hepatitis B DNA Vaccine

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Abstract

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Background:
The vaccination coverage among health care workers (HCWs) in Zambia is low. Most vaccinated HCWs do not know how they responded because they self-vaccinate and/or do not receive all recommended doses. Hence, we aimed to assess T cell and cytokine responses, hepatitis B surface antigen (HBsAg) antibodies (anti-HBs) in HCWs in Kalulushi, Zambia after vaccination with a recombinant hepatitis B vaccine from the serum Institute of India.

Methods and Materials:
Peripheral blood mononuclear cells (PBMCs) collected from 6 vaccinated HCWs (cases) who had received at least 2 doses of the vaccine were stimulated with the HBsAg. Using flow cytometry, the concentrations of tumor necrosis factor, interleukin 10, interleukin 6, and interleukin 2 were measured in the supernatant while HBsAg-specific $CD4^+$ and $CD8^+$ effector and memory were measured using the cell pellet. Using plasma, anti-HBs, HBsAg, the Hepatitis B core antigen (HBcAg) and antibodies against the HBcAg (Anti-HBc) were tested using the enzyme-linked immunosorbent assays and data were summarised descriptively.

Results:
Four of our cases were male, all had a median age and BMI of 32 [IQR 29-44] years and 23.1 [IQR 21.1-27.6] kg/m2 respectively. The anti-HBs in all 6 cases increased after each dose and in 5 of the cases, either the HBsAg-specific effector $CD4^+$ or effector $CD8^+$, or memory $CD4^+$, and/or memory $CD8^+$ responses after doses 1, 2 and 3 were detectable. Despite having anti-HBs of 0IU/mL at baseline, participant 2 had 18.6% and 45.5% $CD4^+$ and $CD8^+$ memory after dose 1 respectively. Case 1 had the highest HBsAg-specific TNF (244.81pg/mL) after dose 2 while case 3 also had the highest HBsAg-specific IL-6 (69.91pg/mL) after dose 2 and were both HIV^+. Additionally, only the 3 participants who were HIV^+ had HBsAg-specific effector and memory $CD8^+$ cells after vaccination.

Conclusion: From our case series, we demonstrate that HBV vaccines are immunogenic in HCWs in Zambia. They elicit at least one HBsAg-specific immune response after one dose. We recommend vaccinating all HCWs and more similar studies to help understand HBV-specific immune responses in vaccinees better.

Keywords: *Health care workers, Hepatitis B, Vaccination, HBsAg-specific T cells, Cytokines, antibodies*

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INTRODUCTION

The burden of hepatitis B virus (HBV) is estimated to be around 3.9% globally (1) and 6.1% in Africa (2). According to the population-based HIV impact assessment report of 2016, the prevalence of HBV in Zambia is around 5.6% in the general population (3) and maybe 4 times higher in health care workers (HCWs) (4). In 1983, the prevalence of HBV in HCWs in Zambia was estimated to be around 3.1% (5) while preliminary results from our recent study reported a prevalence of 4.7% in HCWs in the Kalulushi district (under review).

Hepatitis B virus causes liver complications including hepatocellular carcinoma (HCC) and may lead to death (6). It is transmitted perinatally from an infected mother to her infant, through unsafe sexual practices, and also through contact with infected body fluids such as blood (7). This high transmissibility coupled with the frequent exposure of HCWs to various infectious materials during routine work greatly increases the risk of HBV infection acquisition. It is for this reason that HCWs are identified as a high-risk population (8–10) that needs to be vaccinated against HBV (11).

Immunological responses to these vaccines are measured through the quantification of hepatitis B surface antigen (HBsAg) specific antibodies (anti-HBs) after complete vaccination. The attainment of anti-HBs ≥10IU/mL is used as the correlate of the protection (CoP) (12). Individuals with anti-HBs <10IU/mL after complete vaccination are considered non-responders while those with anti-HBs titers are ≥1000IU/mL as good responders (13).

Studies have reported detectable HBsAg-specific T cells in poor responders despite their inability to mount the recommended anti-HBs titer (≥10IU/mL) (14). However, high anti-HBs titers have also been associated with elevated levels of CD45RA$^-$chemokine (C-C motif) receptor 7 (CCR7)$^+$ central memory T cells, effector memory T cells (CD45RA$^-$CCR7$^-$), circulating T follicular helper (T_fh) cells, and a lower naïve B and T cell expression (15). Anti-HBs are also associated with elevated interleukin-2 (IL-2), tumour necrosis factor-alpha (TNF-α), and interferon-gamma (INF-γ)(16). In participants whose anti-HBs were >10,000IU/mL, tumour necrosis factor-beta (TNF-β), IL 4, and IL-10, and interferon-gamma (IFN-γ) were detectable but not in non-responders (<10IU/mL)(14).

Most studies that have been done to assess responses to HBV vaccines have been conducted in individuals with underlying health conditions with very few being done in Africa (16–21). Those conducted in HCWs have mainly focused on HBV prevalence, knowledge, vaccination coverage, and vaccine responsiveness using anti-HBs with few studies looking at T cells and cytokines after HBV vaccination. It is for this reason that this case series aimed to report HBsAg-specific CD4$^+$ and CD8$^+$ effector and memory responses, anti-HBs as well as cytokines after vaccination with a recombinant HBV vaccine (rHBV) using Peripheral Blood Mononuclear cells (PBMCs).

METHODS AND MATERIALS

Study Design and Setting

We included 6 HCWs (cases) from a large interventional study in the Kalulushi district on the Copperbelt that had received a rDNA vaccine from the Serum Institute of India. The vaccine was administered at 0,1 months, and 6 months as per recommended vaccination schedule. These 6 cases had PBMC samples collected after each dose and these PBMCs were stimulated with the HBsAg at a concentration of 10µg/mL with the negative control for each being unstimulated. These PBMCs were used to measure HBsAg-specific effector and memory CD4$^+$ and CD8$^+$ T cells while the supernatant was used to quantify tumour necrosis (TNF), interleukin 2, 6, and 10 using Flow cytometry. All T cell data was analysed using flowJo and gated. HBsAg-specific T cell responses were obtained by converting the difference between HBsAg-stimulated and unstimulated into a proportion. The difference was considered specific if the difference was ≥10 cells. The anti-HBs (baseline and after each dose) and anti-HBc (baseline) were measured in plasma using the enzyme-linked immunosorbent assay. The difference between the stimulated and unstimulated cytokine concentrations was regarded as HBsAg-specific while HBsAg non-specific cytokine responses were taken as measured.

RESULTS

Baseline characteristics of the cases

At baseline, 4 of our cases were male, 3 were HIV$^+$ and 3 were anti-HBc reactive with median age and BMI of 32 [IQR 29-44] and [IQR 21.1-27.6] respectively (Table 1).

Table 1: Baseline characteristics of the cases

Case	Sex	Age 32 [IQR 29-44]	HIV status	CD4 count [cells/ mm^3]	BMI 23.1 [IQR 21.1-27.6]	Anti-HBs	Anti-HBc
1	Male	54	Positive	707	19.8	0	Reactive
2	Male	44	Positive	437	21.1	0	Reactive
3	Female	31	Positive	698	22.3	0	Non-reactive
4	Female	29	Negative	n/a	27.6	0	Non-reactive
5	Male	28	Negative	n/a	23.8	0	Non-reactive
6	Male	33	Negative	n/a	28.6	0	Reactive

Case 1: This was an HIV$^+$ male aged 54 years old with a CD4 count of 707 cells/mm^3 and a BMI of 19.8kg/m^2. He was anti-HBc reactive with an anti-HBs titer of 0IU/mL at baseline. He received all 3 doses and had PBMCs collected at all 3-time points. The anti-HBs increased after each dose, they increased from 3IU/mL to 436IU/mL after dose 2 and 6818IU/mL after dose 3. After dose 1, no HBsAg-specific T cell responses were elicited. However, after dose 2, 100% HBsAg-specific CD4$^+$ effector, 100% HBsAg-specific CD4$^+$ memory, 100% HBsAg-specific CD8$^+$ effector, and 100% HBsAg-specific CD8$^+$ memory were elicited. After dose 3, 73.1% CD4$^+$ effector T cells were the only population that was detected (shown in Table 2). All his HBsAg-specific cytokine concentrations were low except TNF (244.81pg/mL) which was highest after dose 2 (shown in Tables 3 and 4).

Case 2: This was a 44-year-old man with a BMI of 21.1 kg/m^2, a reactive anti-HBc, HIV$^+$ status with a CD4$^+$ count of 437 cells/ mm^3. He received all 3 doses of the vaccine but only had PBMCs collected after doses 1 and 2. After dose 1, he had anti-HBs of 0IU/mL, 151IU/mL after dose 2, and 3923IU/mL after dose 3. On the other hand, after dose 1, 26.1% HBsAg-specific CD4$^+$ effector, 8.6% HBsAg-specific CD4$^+$ memory, 32% HBsAg-specific CD8$^+$ effector, and 17% HBsAg-specific CD8$^+$ memory were detected and increased to 45%, 64.6%, 70.5%, and 53.8% respectively after dose 2 (shown in tables 2). Both his HBsAg-specific and non-specific cytokine concentrations were broadly similar with IL-6 being higher after dose 2 (9.81pg/mL) (shown in tables 3 and 4).

Case 3: This was a 31-year-old female with a BMI of 22.3kg/m^2, a non-reactive anti-HBc, and an HIV$^+$ status with a CD4 cell count of 698 cells/m^3. She had received 3 doses of the rHBV vaccine but only had PBMCs collected after doses 1 and 2. She had a baseline titer of 0IU/mL which increased to 8IU/mL after dose 1, 224IU/mL after dose 2, and 9013IU/mL after dose 3. After dose 1, 30.8% HBsAg-specific CD4$^+$ effector, and 4.7% HBsAg-specific CD4$^+$ memory were detected with no HBsAg-specific CD8$^+$ effector and memory. These populations however increased after dose 2 to 96.1%, 96.1%, 94.7%, and 95.4% respectively (shown in Table 2). Her HBsAg-specific TNF and IL-6 concentrations were higher after dose 2 (16.15 and 69.91pg/mL respectively). Her HBsAg-non-specific IL-6 concentration after dose 1 was 11.92pg/mL after dose 1 but no HBsAg-specific IL-6 was detected after dose 1 (shown in tables 3 and 4).

Case 4: This was a 29-year-old female with a BMI of 27.6 kg/m^2 with a non-reactive anti-HBc and HIV$^-$ status. She received 2 doses of the vaccine and had PBMCs collected after both doses. At baseline, she had an anti-HBs titer of 0IU/mL that increased to 1IU/mL after dose 1, and 143IU/mL after dose 2. She had no detectable HBsAg-specific T cells after both doses (shown in Table 2). Despite her non-HBsAg-specific TNF being 13.84pg/mL, her HBsAg-specific TNF after dose 1 was 4.37pg/mL. No HBsAg-specific IL-2 and IL-6 were detected after doses 1 and 2 but HBsAg non-specific IL-2 and IL-6 concentrations were low and similar between the 2 doses (shown in tables 3 and 4).

Case 5: This was a 28-year-old male with a BMI of 23.8kg/m^2, a non-reactive anti-HBc and HIV$^-$ status. He received all 3 doses of the vaccine and PBMCs were collected after each dose. His baseline anti-HBs was 0IU/mL which increased to 224IU/mL after dose 1, 942IU/mL after dose 2 and 15787IU/mL after dose 3. However, the only HBsAg-specific T cell response observed after dose 1 was the CD4$^+$ memory (49.1%) but were all undetectable after dose 2. Interestingly, 100% of the detected HBsAg-specific T cells after dose 3 were CD4$^+$ memory with no HBsAg-specific

$CD4^+$ effector, $CD8^+$ effector and $CD8^+$ memory (shown in tables (shown in table 2). All his HBsAg-specific cytokine concentrations were very low except TNF concentration after dose 3 (5.04pg/mL) (shown in tables 3 and 4).

Case 6: This was a 33-year-old male with a BMI of 28.6kg/m^2, a reactive anti-HBc, and an HIV^- status. He received all 3 doses of the vaccine but only had PBMCs after doses 2 and 3. His baseline titer was 0 IU/mL which increased to 7 IU/mL after dose 1, 940 IU/mL after dose 2 and 1056I U/mL after dose 3. After dose 2, he had 100% HBsAg-specific $CD4^+$ memory with no $CD4^+$ effector, $CD8^+$ effector or $CD8^+$ memory. After dose 3, no HBsAg-specific $CD4^+$ effector, $CD4^+$ memory, $CD8^+$ effector or $CD8^+$ memory was detected (shown in tables (shown in tables 2). Both his HBsAg-specific and non-specific cytokine concentrations were low ranging between 0 and 1.32 pg/mL. However, his HBsAg-specific TNF after dose 3 was 3.38 pg/mL (shown in Tables 3 and 4).

Table 2: HBsAg-specific antibodies and T cells after HBV vaccination

CN	After dose 1			After dose 2			After dose 3		
	Anti-HBs	T cell populations	%	Anti-HBs	T cell populations	%	Anti-HBs	T cell populations	%
1	3	No HBsAg-specific T cells	-	436	CD4+ effector	100%	6818	CD4+ effector	73.1%
			-		CD4+ memory	100%		CD8+ memory	71.2%
			-		CD8+ effector	100%		-	-
					CD8+ memory	99.9%		-	-
2	0	CD4+ effector	26.1%	151	CD4+ effector	45%	3923	*	-
		CD4+ memory	8.6%		CD4+ memory	64.6%		*	-
		CD8+ effector	32%		CD8+ effector	70.5%		*	-
		CD8+ memory	17%		CD8+ memory	53.8%		*	-
3	8	CD4+ memory	30.8%	224	CD4+ effector	96.1%	9013	*	-
		CD8+ memory	4.7%		CD4+ memory	96.1%		*	-
			-		CD8+ effector	94.7%		*	-
			-		CD8+ memory	95.4%		*	-
4	1	No HBsAg-specific T cells	-	143	No HBsAg-specific T cells	-	*	*	-
5	224	CD4+ memory	49.1%	942	No HBsAg-specific T cells	-	15787	CD4+ memory	100%
6	7	*	*	940	CD4+ memory	100%	1056	No HBsAg-specific T cells	

CN-Case number*no sample collected

Table 3: HBsAg non-specific TNF, IL-10, IL-6, and IL-2 cytokine concentrations after HBV vaccination

Case	TNF After dose 1	TNF After dose 2	TNF After dose 3	IL-10 After dose 1	IL-10 After dose 2	IL-10 After dose 3	IL-6 After dose 1	IL-6 After dose 2	IL-6 After dose 3	IL-2 After dose 1	IL-2 After dose 1	IL-2 After dose 3
1	1.35	733.85	1.12	7.23	9.5	2.13	4.51	127.25	0.78	0.69	1	0.85
2	1.12	2.79	*	4.37	1.68	*	2.74	10.88	*	1.36	0.55	*
3	15.35	33	*	4.02	5.63	*	11.92	84.55	*	1.81	1.29	*
4	13.84	0	*	3.64	4.82	*	4.67	1.03	*	0.6	0.93	*
5	16.04	1.77	17.24	2.98	0	2	9.49	0	2.9	0	0.85	0
6		0	7.94		0	1.32		0	0.37		0.89	1.32

Table 4: HBsAg-specific TNF, IL-10, IL-6, and IL-2 cytokine concentration after HBV vaccination

Case	TNF After dose 1	TNF After dose 2	TNF After dose 3	IL-10 After dose 1	IL-10 After dose 2	IL-10 After dose 3	IL-6 After dose 1	IL-6 After dose 2	IL-6 After dose 3	IL-2 After dose 1	IL-2 After dose 2	IL-2 After dose 3
1	1.38	244.81	0	4.56	0	0	3.48	0	0	0	0	0
2	0	2.79	*	2.06	0	*	0	9.81	*	0.54	0	*
3	0	16.15	*	0	0	*	0	69.91	*	0	0	*
4	4.37	0	*	0.23	0.4	*	0	0	*	0	0	*
5	0	0	5.04	0	0	0	0	0	0	0	0.85	0
6		0	3.38		0	0		0	0.37		0.89	0.83

DISCUSSION

We aimed to assess the expression of HBsAg-specific $CD4^+$ and $CD8^+$ effector and memory T cell responses, HBsAg-specific and non-specific IL-4, IL-10, IL-2, TNF, and anti-HBs after each dose of the rHBV vaccine in the 6 cases. Hence, for the first time in Zambia, we here present a case series on, T cell, cytokine and anti-HBs responses to a rHBV vaccine. We found that the rHBV vaccine-induced effector and memory T cell responses in the vaccinees as reported elsewhere (19). We also found that HBsAg-specific T cell responses were highest after dose 2 and reduced

after dose 3, which may be due to germinal center reactions formed 3 to 6 weeks after vaccination before they self-terminate (17,18). This pattern is consistent with the anti-HBs fold-rise change highest after dose 2 (i.e., after dose 1= 6 IU/mL [2-82] IU/mL, after dose 2= 90.6 IU/mL [4.2-117.6 IU/mL] and after dose 3= 16.2 IU/mL [1.1-25.8IU/mL] data not shown). HBsAg-specific $CD8^+$ effector and memory responses were only detectable in HIV+ cases (1, 2, and 3). Our findings do not agree with Joshi *et. al.*, and Friedrich *et. al.*, who explained that no HBsAg-specific $CD8^+$ responses are expected because recombinant vaccines are processed and presented by MHC II and not MHC I (16). However, a study conducted by Giacomet *et al.*, in HIV^+ children reported high expression of HBsAg-specific $CD8^+$ cells in these children which may suggest antigen cross-presentation by the MHC II (16). We also found that $CD4^+$ T cell memory may be elicited in some vaccinees even just after one dose of the rHBV vaccine. This was seen in participants 2, 3, and 5 whose anti-HBs were 0IU/mL, 81.3IU/mL, and 224 IU/mL respectively just after the first dose. A study by Larsen *et. al.*, assessed HBsAg-specific proliferation and described participants with anti-HBs between 30 and 80000IU/mL as intermediate responders. These participants showed no correlation between anti-HBs and the HBsAg-specific stimulation index leading to them describing HBsAg responsiveness as either total non-response (i.e., undetectable anti-HBs and all cellular compartments) or partial-response (i.e., weak anti-HBs and/or T cell responses) or strong response (i.e., strong anti-HBs and all cellular compartments) (14). This may also explain why some participants did not elicit any HBsAg-specific CD4+ and/or CD8+ cells despite having anti-HBs greater than the CoP. Though current data suggests that an anti-HBs titer ≥100IU/mL after complete vaccination may be associated with the persistence (shown by memory T cell expression) of protection (22–24), participant 2 had detectable HBsAg-specific memory despite being an anti-HBs non-responder. However, this may be attributed to previous exposure (Anti-HBc+). The highest TNF and IL-6 concentrations after dose 2 were seen in Participant 1 who was also HIV+ and 54 years old. This may be because older age and HIV+ status are associated with elevated pro-inflammatory cytokines (25). Although IL-2 concentrations were almost constant and almost undetectable in all participants, recent studies have reported IL-2 as a reliable marker for testing HBsAg-specific responsiveness (16) but not in this case. It is however important to highlight that many immunological factors may be responsible for these cytokine differences observed here and elsewhere (14). In all our 6 cases, Schillie *et. al.*, reports that the first dose can elicit anti-HBs ≥10IU/mL in 30-55% of the vaccinees and 75% after the second dose (20) and we found that anti-HBs increased after each dose i.e., 2 participants after dose 1 had anti-HBs >10IU/mL, and all participants after doses 2 and 3 had anti-HBs >100IU/mL, and >1000IU/mL respectively. A recent study by Silvia *et. al.*, showed that primary anti-HBs of 100IU/mL can persist for up to 30 years in exposed HCWs (22). Therefore, all 6 participants may be protected for the next 30 years.

CONCLUSION

Despite this being a case series, we show that rHBV vaccines are immunogenic in HCWs. They elicit anti-HBs as high as 100IU/mL after dose 2 and at least one HBsAg-specific $CD4^+$ or $CD8^+$ response after dose 1. Therefore, as reported by Larsen *et. al.*, we also conclude that non-responsiveness is the total absence of HBsAg-specific antibodies, cytokines and T cells and recommend that all HCWs should be vaccinated with at least 2 doses. Even with this, we still suggest repeating this study with at least 94 participants (a sample size calculated using an immune response rate of 94% with an attrition rate of 10%) to help validate our findings.

DECLARATION

Competing interests There were no competing interests from all authors in this study.

Author contributions All co-authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved. TNP and SM conceptualized this study. TNP drafted the first draft which was shared with all co-authors. CC, MS[1], KM, LH, RC, ON, SM and MS[3] contributed to the data acquisition, analysis and interpretation. All co-authors reviewed the draft and gave their critical input leading to a revised final draft that was approved by all.

Ethics approval and consent to participate The parent study was approved by the University of Zambia Biomedical Research Ethics Committee (UNZABREC) under the reference number 003-01-19 and registered on ClinicalTrials.gov, under the identifier number, NCT04072211. The current study was approved by UNZABREC under reference number 746-2020 and by the National Health Research Authorities (NHRA). A waiver of consent from UNZABREC to use these samples as well as participant information was obtained.

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