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Longitudinal assessment of an Ebola vaccine trial understanding among healthcare providers in the Democratic Republic of the Congo

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ABSTRACT

Background: The long-term retention of information disclosed during the informed consent in clinical trials lasting over a year cannot be guaranteed for all volunteers. This study aimed to assess the level of participants' retention and understanding of the trial information after two years of participation in a vaccine trial.

Methods: In total, 699 health care providers (HCPs) and frontline workers were enrolled in the EBL2007 vaccine trial conducted between February 2019 and September 2022 in the Health District of Boende, Democratic Republic of the Congo (DRC). Individual scores obtained from a questionnaire (test of understanding, TOU), specifically designed to assess the understanding of the consent at baseline, were collected before the clinical trial started and at one-year and two-year intervals.

Results: TOU scores were high in the beginning of the trial (median TOU = 10/10), but significantly decreased in both the first and second years following (median TOU = 8/10 in year 1 and median TOU = 9/10 in year 2, p-value < 0.0001). The decrease in scores was significantly higher among individuals with occupations requiring shorter education such as midwives (median TOU = 7/10 in year 1 and 8/10 in year 2, pvalue = 0.025). Furthermore, older participants exhibited poorer retention of information compared to younger individuals (median TOU = 8/10 vs 9/10, p-value = 0.007).

Conclusion: We observed a significant decline in the informational knowledge of informed consent, specifically in terms of basic knowledge on the study vaccine and trial procedures. As participant safety and understanding is a paramount ethical concern for researchers, it is crucial for participants to fully comprehend the study's objectives and potential risks. Therefore, our findings suggest the need for clinical researchers to re-explain participants to optimize the protection of their rights and wellbeing during the research.

1. Background

Prior to being recruited in a clinical trial, potential volunteers are informed of the trial aims, methods, reasonably anticipated benefits, potential risks or discomfort and general study requirements. By providing key study aspects, the informed consent allows for potential participants to decide which risks, benefits, and procedures are acceptable to them in the study, making it possible to adequately decide to continue with the trial [1]. A series of regulatory and ethical guidelines (e.g., The Council for International Organizations of Medical Sciences guidelines) highlight the need for potential trial participants to understand the information provided during the informed consent [1–4]. Both informed consent and understanding are core ethical imperatives for entering a clinical trial. Unfortunately, it has been reported that some volunteers in clinical trials limit their consent to a document designed to protect the investigators in the event of an intervention-

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related complication, completely ignoring their autonomy and their right to be protected from harm [5,6].

Evidence in the literature repeatedly indicates that research participants and patients undergoing medical procedures do not always correctly understand the research protocol involved [7–11]. Besides, most of the research participants may be illiterate and unfamiliar with medical research, especially for trials conducted in low-income countries [12]. Furthermore, in long-term studies involving extended participant follow-up periods [13–15], decreased ability to retain information studied over time is an additional barrier to to a complete understanding of the risks and benefits of the research [16,17]. This issue is especially pertinent in vaccine trials, as participants need to maintain their understanding and consent form over extended periods, spanning months or years[11,15].

Despite the fact that international research ethics guidelines emphasize the continuing nature of informed consent, a limited amount of investigators have published results related to assessments of participants' level of understanding of the clinical trial prior to enrolling and during the clinical trial [1,10,18–20]. In addition, there are few practical guidelines on how to optimize the safety of volunteers to guarantee understanding of the consent form, which should be seen as a continuous dynamic process rather than an isolated event during the clinical study [21]. Therefore, it is essential to incorporate periodic reassessments of consent understanding during the follow-up phase [11]. This approach may help to enhance the optimization of participants' comprehension and retention of informed consent content-related information in vaccine trials. The challenges of ensuring proper understanding of study information have led some researchers to recommend that participants' understanding be assessed after the consent discussion [22–25].

In Boende, the Democratic Republic of the Congo (DRC), we conducted an Ebola vaccine trial (EBL2007) which included registered healthcare providers (HCPs) and frontline workers. This randomized, open-label, phase 2 study aimed to assess the safety and immunogenicity of a heterologous prophylactic vaccine regimen followed by a booster dose one or two years after the initial dose [26]. One of the eligibility criteria for participation in the trial was the ability to successfully answer at least 9/10 questions of the Test of Understanding (TOU, Supplement 1). This TOU consisted of a true/false questionnaire to assess the understanding of trial consent among participants at baseline and when the trial was ongoing one and two years later. This sub-study collected the answers and scores of participants on the TOU and assessed whether participants understanding of the consent/EBL2007 vaccine protocol waned over time, in a trial that was two years and half in duration.

2. Methodology

2.1. EBL2007 vaccine trial and TOU assessment

EBL2007 vaccine trial screening and enrolment procedures started in December 2019 and were completed in February 2020. Forthcoming trial participants were invited to attend an introductory workshop where the study protocol and activities were explained. They were also provided with a copy of the consent form to review at their leisure. If they expressed interest in participating, they were requested to return on the following day for screening and formal consent (Day 1).

Alongside the screening process on Day 1, a pretested and structured TOU was foreseen for potential participants following the informed consent discussion/dialogue and prior to signing the consent form.

The TOU helped the investigators to determine to which extent potential participants had basic knowledge of the study vaccines, trial procedures, purpose of the trial, acceptable risks, and volunteerism in the trial. The TOU questionnaire was translated from English to French, and afterwards, it was translated from French into Lingala by an experienced translator. To ensure translation accuracy, a back-translation process was applied at each stage. This involved translating the text from Lingala to French, and subsequently, from French back to English, each step performed by a different translator than the original.

Participants eligible for enrolment in the trial had to be able to correctly answer at least nine of the ten test questions ($\geq$9/10) across three attempts in the preferred language. If the participant failed the first attempt, he/she was retested. Two repetitions were allowed, and the study nurses provided additional information regarding the protocol before and between each attempt. If participants failed the third attempt, they were not allowed to join the EBL2007 vaccine trial.

To measure their understanding over time, starting from late November/early December 2020, the EBL2007 vaccine trial protocol was amended so that the TOU could be repeated (one attempt) among enrolled participants approximately one- and two-years following inclusion, without impacting their continuation in the trial. When a participant failed, he/she was reminded of the key information related to the informed consent such as knowledges on the study vaccine, voluntary participation, benefits, risks and trial procedures. Participants scoring below 9/10 in first and second-year assessments had only one TOU attempt.

2.2. Data collection

The data for this study consisted of EBL2007 vaccine trial participants' demographics and TOU scores obtained at baseline and then approximately 1 and 2 years later]. Scores were extracted from paper TOU at the end of enrollment (March-April 2020) and at the end of the Year 1 follow up visit (March-April 2021) and the Year 2 (March-April 2022) follow-up visits. Two study staff members entered (double data entry) these data into a purpose-built Redcap database using tablets. The original paper questionnaires contained non-identifying information of the participants in the EBL2007 clinical trial. The extracted data included the following variables: participant ID; day of the visit; month of the visit; year of the questionnaire administration; signature of the person who administered the questionnaire; answers given by the participant to each of the 10 true/false (Supplement 1).

2.3. Quality assurance

An independent person performed quality assurance by checking the consistency of the data entered in the two Redcap databases. Any inconsistencies found were corrected by comparing them to the original paper TOU. Additional data, including demographic variables of the study participants, were obtained from the EBL2007 study database, and linked to the survey data.

2.4. Data analyses

To check the change in TOU (as proxy for information retention) over time and to see if it differed between participants, we performed a beta regression analysis. This technique is recommended when the dependent variable (TOU) represents proportional data derived from counts of "successes" (correctly answered questions) and "failures" (wrongly answered questions)[27]. Different models were developed with the TOU score as dependent variable and study year, age, sex, and occupation as explanatory variables. To test if the TOU decreased over time in particular participant categories, we considered a combination of the study year with the other explanatory variables (year*age and year*occupation). Because the sample size for some occupations was too low (<10 participants), we grouped caregivers, laboratory technicians, pharmacy assistant, facility maintenance worker, under the category 'others'. We also divided the ten questions of the TOU (Supplement 2) according to five different categories: 1) 'Basic knowledge on the study vaccine' grouping questions 1 and, 3 3) 'Study procedures' for question 2, 3) 'Purpose of the trail' for question 4, 4) question 5 and 7 as 'Voluntarily participation' and 5) questions 6,8,9, and 10 were grouped

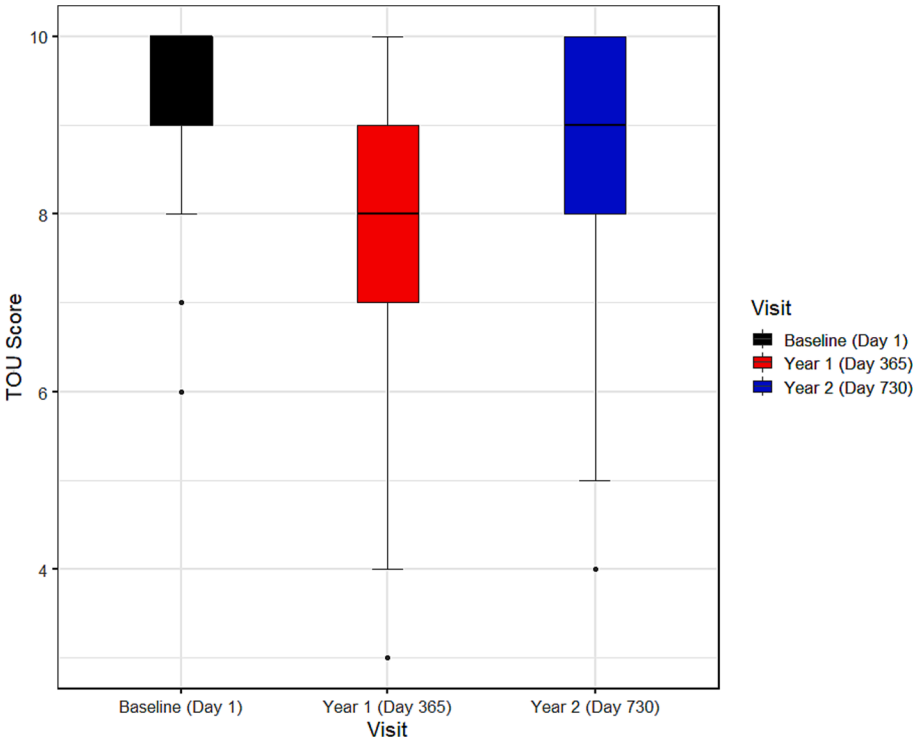

Fig. 1. Ability of healthcare providers and frontline workers to provide correct answers to the TOU over time.

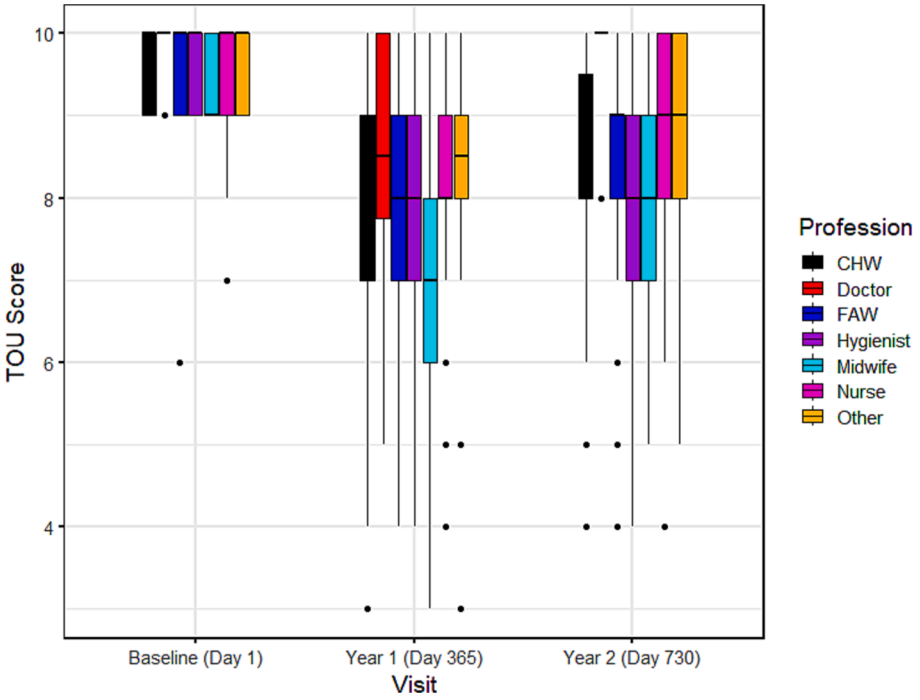

Fig. 2. Ability of healthcare providers and frontline workers to provide correct answers to the TOU over time and profession. At baseline and in year two, the minimum and maximum scores obtained by all the Doctors are equal.

as 'Safety risks (Supplement 2). To test for difference between years for each question category, we performed a generalized linear model with binomial distribution. Different models were developed for each question with "questions correctly answered" as binary response variable and time (year 0–2) as response variable. Similarly, we investigated if the "occupation" and age could also significantly affect the correctness to the answer. Analyses were performed using -the R-packages" betareg" and"emmeans", "lmer" and boxplots were created with "ggplot2".

2.5. Ethical review

The National Ethics Committee of the DRC Ministry of Health (approval reference n ° 211/CNES/BN/PMMF/2020) approved the current sub-study nested in the amended EBL2007 study protocol. The

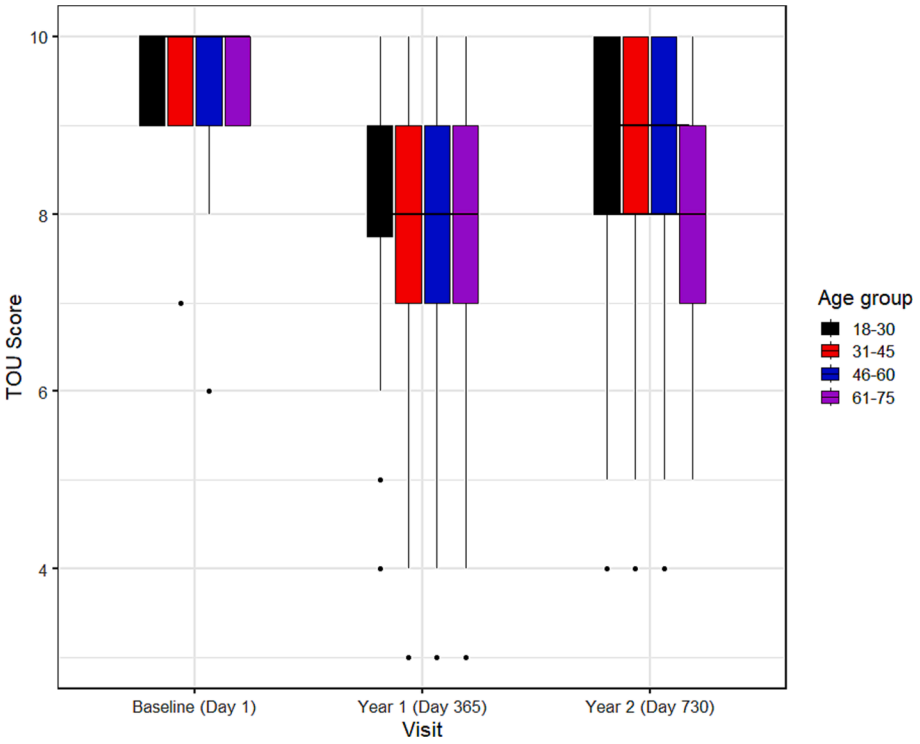

Fig. 3. Ability of healthcare providers and frontline workers to provide correct answers to the TOU over time and per age category.

Table 1
Effect of time (years) and occupations on % of correctly answered questions since the trial started for different categories of questions.

	Questions	df	Chi^2	p-value
Effect of Time (years)	Q1,3: Basic knowledges on the study vaccine	2	27.481	**< 0.0001**
	Q2: Study procedures	2	77.922	**< 0.0001**
	Q4: Purpose of the trial	2	6.136	0.05
	Q5,6,8,9,10: Safety risks	2	8.1034	0.02
	Q7: Voluntarily participation	2	2.1003	0.35
Effect of occupation	Q1,3: Basic knowledge on the study vaccine	6	29.578	**< 0.0001**
	Q2: Study procedures	6	6.8894	0.33
	Q4: Purpose of the trial	6	4.7456	0.58
	Q5,6,8,9,10: Safety risks	6	5.2794	0.51
	Q7: Voluntarily participation	6	12.723	0.05

EBL2007 vaccine trial was registered at clinicaltrials.gov (NCT04186000).

3. Results

3.1. Baseline characteristics of participants of EBL2007 vaccine trial

A total of 720 HCPs and frontline workers participants were screened for inclusion in the EBL2007 vaccine trial, of which 699 (97.08 %) were eligible at baseline (Day 1). Out of the 21 individuals who did not successfully pass the screening process, four of them had not attained the stipulated score (≥9/10) on the comprehension test after three attempts, and the other trial inclusion criteria were not met by the remaining 17. Approximately one year following the baseline, 671 participants returned and underwent re-administration of the TOU, whereas after two years, 651 participants returned. The demographic characteristics of the study population are summarized. The scores of the TOU ≥ 9/10 at baseline were available for 698 (99.9 %) participants. The study population was predominantly male (76.5 %). The EBL2007 vaccine trial had a retention rate of 93.1 % from Day 1 to Day 730.

3.2. TOU scores at baseline, year 1 and year 2

TOU scores dropped from a minimum score of 9/10 and a median of 10/10 to a median of 8/10 one year after inclusion (p-value < 0.0001) and a median of 9/10 in year 2 (p-value < 0.0001) (Fig. 1).

The decrease in TOU score over time differed between occupations (df = 12, p-value < 0.0001). Midwifes scored lower on the test at subsequent years compared to the other occupations. The drop was significant at year 1 (with a median TOU score = 7/10, p-value = 0.025), and not significant at year 2 (with a median TOU score = 8/10; p-value = 0.062). Doctors showed the lowest decrease in TOU score over time (TOU score = 8.5/10 at year 2 and 10/10 at baseline, p-value = 0.34 (Fig. 2).

The analysis across different age groups revealed similar performance in all categories, with a notable exception observed in year two for the oldest age category (61–75 years old). In this group, there was a decrease in scores compared to the younger categories, particularly the 18–30 years old group (median TOU = 8/10 for 61–75 years old vs 9/10 for 18–30 years old, df = 6, p-value = 0.007). This indicates that while the performance was generally consistent across most age groups, the 61–75 year old group demonstrated a distinct deviation at year 2 (Fig. 3).

Table 1 and Fig. 4 describe the observed differences among participants according to the TOU question categories. The strongest differences were observed for "Basic knowledge on the study vaccine" and "study procedure" questions (pvalue < 0.0001) for which a clear decrease in proportion of correctly answered questions was observed one year after the start of the study (Table 1). Although a decrease in proportion of correctly answered questions was also observed for the other questions groups such as purpose of the trial (pvalue = 0.05), safety risks (pvalue = 0.02) and voluntarily participation (pvalue = 0.35), they were answered more correctly overall (Fig. 4).

Furthermore, we observed that the questions related to" Basic knowledge on the study vaccine" were answered more incorrectly by certain occupations (p-value < 0.0001). Indeed, 50 % of participants among occupations like community health care workers, doctors,

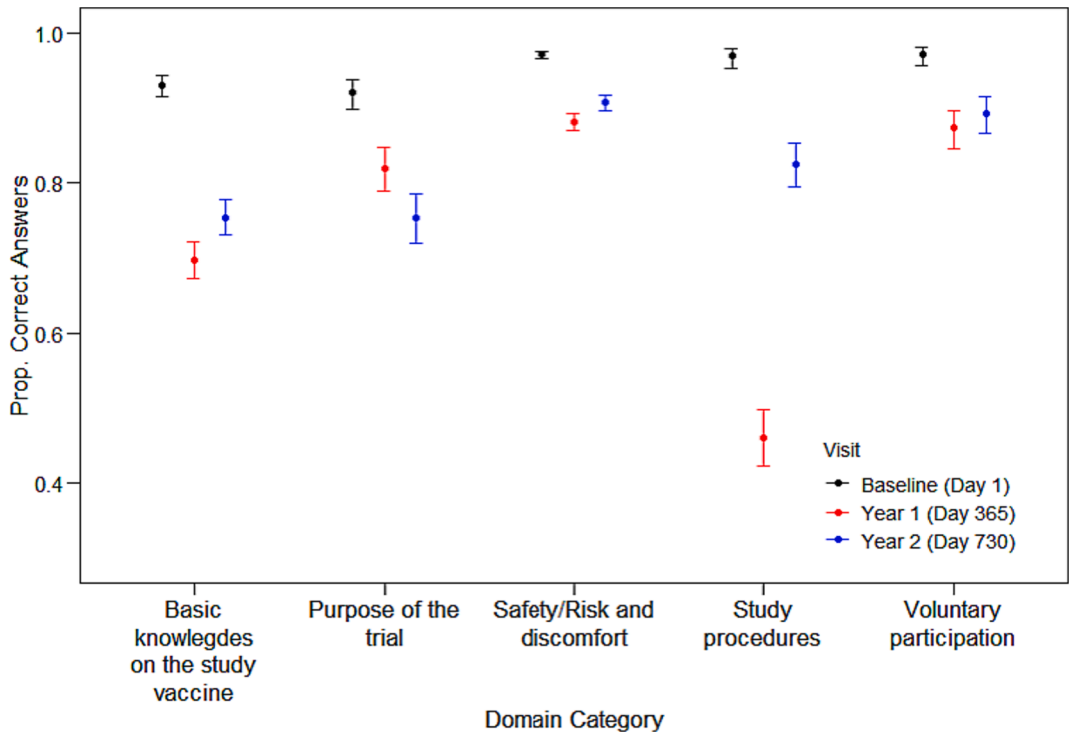

Fig. 4. Effect of time on the Proportion of questions that were answered correctly during the EBL2007 vaccine trial separated for different categories of questions (Basic knowledge on the study vaccine, study procedures, Purpose of the trail, Safety risks and Voluntarily participation). Different colors represent different years. Error bars represent 95% binomial confidence intervals.

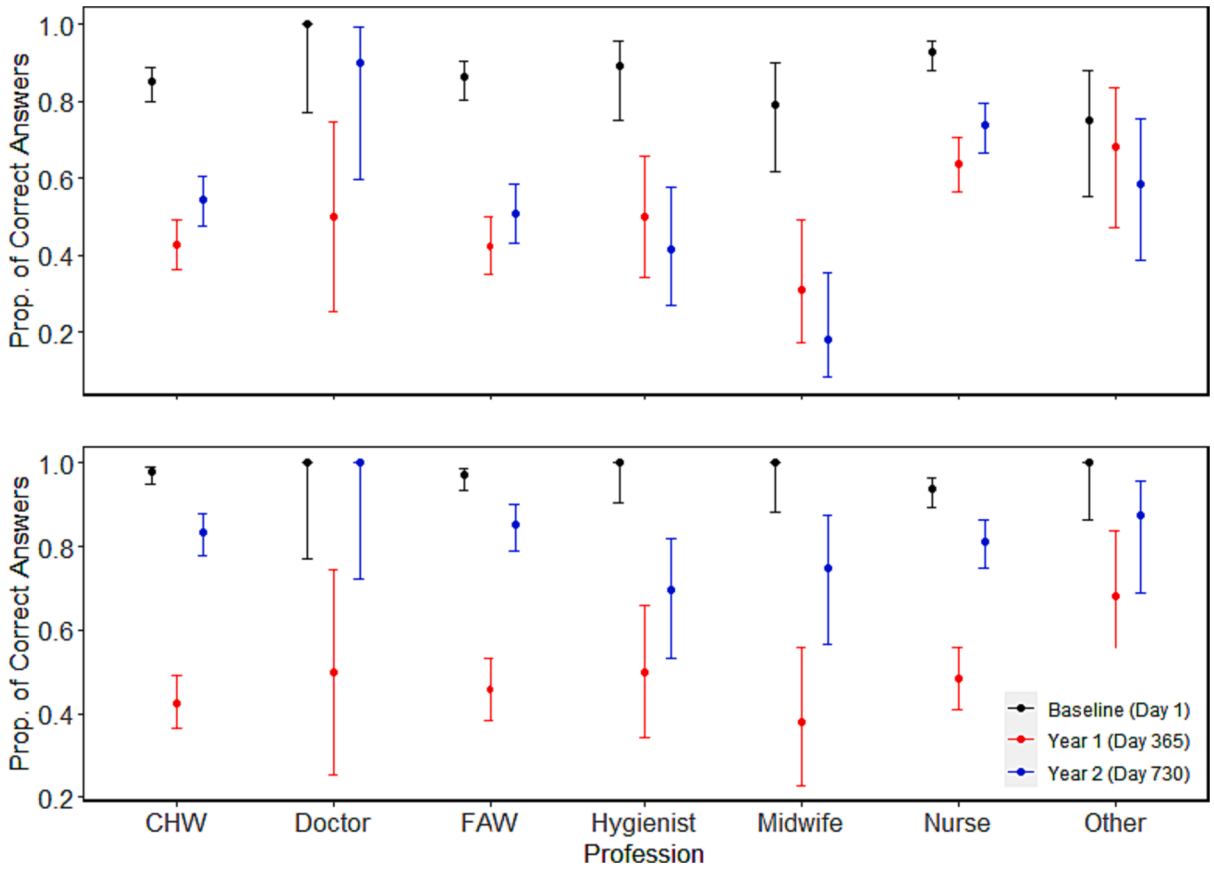

Fig. 5. Effect of occupation on the proportion of questions that were answered correctly during the vaccine trial separated for different years. ***Above*** correctly answered questions related to "Basic knowledge on the study vaccine". ***Below*** correctly answered questions related to "study procedures". Different colors represent different years. Error bars represent 95% binomial confidence intervals. CHW (Community health care workers) and FAW (First aid worker).

Appendix 1
Baseline characteristics of participants in the EBL2007 vaccine trial.

		Mean (SD) Min Max
Age (year)	N = 698	45.0 (12.0) 19 75
18 – 30, n (%)	102(14.6 %)	
31–45, n (%)	231 (33.2 %)	
46–60, n (%)	297(42.5 %)	
61–75, n (%)	68(9.7 %)	
Sex, n (%)		
Female	164(23.5 %)	
Male	534(76.5 %)	
Occupation, n (%)		
Community Health Worker	236(33.8 %)	
Nurse	181(25.9 %)	
First Aid Worker	177(25.4 %)	
Hygienist	37(5.3 %)	
Midwife	30(4.3 %)	
Medical Doctor	13(1.9 %)	
Health Facility Cleaner	10(1.4 %)	
Care Giver	7(1 %)	
Other	3(0.4 %)	
Laboratory Technician	2(0.3 %)	
Pharmacist Assistant	2(0.3 %)	

midwifes and nurses answered these questions incorrectly. Although doctors and community health care workers had more correct answers at year 1, nurses and midwifes made more mistakes in year 2 (Fig. 5). In contrast, the questions related to "Study Procedures" were answered equally incorrect by all occupations in year 1 and equally better in year 2 (p-value = 0.3312) (Fig. 5). The other question categories were not answered significantly different by the different occupations over the years (Table 1).

4. Discussion

This study assessed comprehension of a vaccine trial among 699 HCP and frontline worker participants over two years.

A substantial reduction in the overall TOU score was observed during planned visits in the first and second years after inclusion, suggesting that consent should be repeated in longitudinal studies that span over time N[15,28]. The TOU score at screening might merely be a literal reminder prior to signing the consent form, becoming vague afterward [11]. Recall of informed consent declined, especially regarding basic vaccine knowledge and trial procedures. The inability to remember the topic in regards with basic knowledges about the investigational product in a trial, has been reported in previous studies [11,29–32]. These studies indicate a complete lack of retention of basic details about the investigational product or study vaccine among participants enrolled in a long-term clinical trial ranging from one to five years. Similarly, challenges in recalling study procedures among trial participants were reported in previous studies conducted in both high and low-income countries [11,15,29]. In these studies, some respondents were unable to correctly recall or explain certain procedures/concepts used during the consent process, such as randomization, placebo, blinding [31–34].

The decline in retention of the consent form content was less pronounced two year after the commencement of the trial. Noteworthy that individual sessions to clarify the content of the informed consent followed each trial participant, mostly in the event of weak TOU performance. Furthermore, the recapitulation of the same TOU questionnaire in the trial (Day 1, Year 1, and Year 2) likely contributed to a slight improvement in the overall score in Year 2 compared to Year 1. Similar findings were reported by Chaisson et al., who conducted the same comprehension questionnaire at enrollment and during follow-up [10]. The results indicated that participants exhibited an improved understanding of the key study information [35].

Several reasons may have helped participants achieve the baseline TOU score, including the use of printed trial information sheets, concise consent and its translation into the local language, workshops explaining the protocol with multimedia and video during the screening process.

The decline in the TOU score over time differs across occupations. Similar findings were reported in other studies conducted in Africa showing that more years of education was associated with a deeper level of understanding in medical research [22,36,37]. Some professional categories, such as doctors and midwives, were underrepresented in the trial. This is likely to be related to the scarcity of specific occupations among HCPs in remote health districts of the DRC, such as Boende, where most of HCPs likely head for the cities, which offer better infrastructure and financial incentives[38].

Likewise, the understanding level of the informed consent decreased in older participants. A similar situation was apparent in the age category in studies conducted elsewhere where the decrease in understanding was more pronounced over time for older than for younger people [32,37,39]. Compared to younger people, older people may feel less comfortable and confident asking questions or expressing concerns during the informed consent process. The motivation to participate may be different from that of younger people as well. For example, older people may be more motivated by the potential benefits of research participation for their health needs than by the aspects of informed consent.

Importantly, it was not possible to check the effect of sex and the TOU score over the years, as it was confounded with occupation (Supplement 3). Moreover, our analysis revealed that certain professions within our participant pool were sex-specific, which limited the scope for investigating gender differences in these categories. However, in mixed-sex professions, statistical tests such as the Welch Two Sample *t*-test showed no significant gender-based differences in TOU scores, except in specific cases like First-Aid Workers (FAW: t = -3.202, df = 180.92, p-value = 0.001613) where a significant sex difference was observed, sex did not generally have a statistically significant impact on TOU scores across most professions in our study. The distribution of males and females in the FAW is 134 males and 43 females. The negative t-value of −3.202 indicates that females have a lower mean score compared to males.

The use of true/false questions was a limitation of this survey. The used TOU may have led to an overestimation of the participant comprehension at baseline or in how participants incorrectly responded at one and two years after the trial initiation. The use open-ended or multiple-choice questions might better reflect the actual level of understanding of the participants. Furthermore, as the order of questions in the TOU questionnaire used in Year 2 did not change from the baseline, the slight improvement observed in Year 2 compared to Year 1 could be the result of recalling correct answers as clarified in Year 1, rather than an indication of improved understanding of the trial due to further explanations about the study provided in year 1.

Another limitation to our findings is that our population group of HCP and frontline workers, with a typically higher educational level than the general population, may have maintained a better level of the study comprehension than with other population groups.

Nevertheless, the greatest strength of this survey resides within the extent to which it has brought together data on the understanding of consent in a longitudinal manner. The results generated are further evidence of the need to consider consent as an ongoing and not an isolated process in long-term studies like vaccine trials.

To enhance participants' understanding, engagement, and autonomy in long-term clinical trials like vaccine trials, we propose following recommendations: 1. Regular and periodic rehearsal of the informed consent throughout the duration of the vaccine trial; 2. Periodic recapitulation of a TOU with open-ended questions, allowing participants to explain in their own words what they have retained from their consent to the trial, or multiple choice questions; 3. The use of tailored wording for the TOU that considers participants' age, level of education, and health literacy proficiency; 4. A periodic reconsent of participants failing the TOU; and 5. Paying specific attention to more vulnerable

participants (low education and older age).

5. Conclusion

We conclude that participants of clinical trial can forget crucial information on the study over time. Therefore, we recommend assessing the understanding of consent as a prerequisite to each study visit, as this may safeguard the autonomy, respect and beneficence of participants in volunteering studies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Potential conflicts of interest

All authors attest they meet the ICMJE criteria for authorship.

Appendix 1

(See Appendix 1).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.12.076.

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