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Persistence of Immunogenicity of a Purified Inactivated Zika Virus Vaccine Candidate in Healthy Adults: 2 Years of Follow-up Compared With Natural Infection

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Background. We report 2-year persistence of immune response to Takeda's prophylactic purified formalin-inactivated whole Zika virus vaccine candidate (TAK-426) compared with that observed after natural infection.

Methods. A randomized, observer-blind, placebo-controlled, dose-selection, phase 1 trial was conducted in 18–49-year-old adults at 9 centers (7 in the United States, 2 in Puerto Rico) from 13 November 2017 to 24 November 2020. Primary objectives were safety, tolerability, and immunogenicity of 3 increasing doses of TAK-426 administered as 2 doses 28 days apart to flavivirus (FV)–naive and FV-primed adults. Here, we report on safety and persistence of immunity up to 2 years after primary vaccination with 10-µg TAK-426, the highest dose, and compare neutralizing antibody responses with those observed after natural infection.

Results. TAK-426 at 10-µg had an acceptable safety profile in FV-naive and FV-primed adults up to 24 months after dose 2. Seropositivity for neutralizing antibodies was 100% at 1 year, and 93.8% and 76.2% at 2 years in FV-naive and FV-primed groups, respectively. TAK-426 responses were comparable in magnitude and kinetics with those elicited by natural Zika virus infection.

Conclusions. These results support the further clinical development of TAK-426 for both FV-naive and FV-primed populations.

Clinical Trials Registration. NCT03343626

Keywords. Zika virus; natural infection; neutralizing antibody response; persistence; safety; vaccine.

Zika virus (ZIKV) is a mosquito and sexually transmitted flavivirus (FV) first identified in Uganda in 1947; it has since been responsible for sporadic outbreaks of self-limited illness in Africa, Asia, and French Polynesia [1–4]. ZIKV spread to South and Central America, and circulation has occurred in other regions, including the United States and Europe [5, 6]. The incidence of ZIKV infections has since declined, but low sustained circulation occurs in Thailand [7], India [8], and South America [9]. Global awareness of ZIKV increased in 2015 when clusters of Guillain-Barré syndrome in adults and neurological disorders and congenital anomalies in newborns, including microcephaly, were temporally associated with a large ZIKV outbreak in Northeast Brazil [10] that subsequently spread to several countries in the Americas [11]. The World Health Organization declared ZIKV a public health emergency of international concern in February 2016 [12] and has included it as one of the priority diseases listed in its 2018 research and development blueprint [13]. Therefore, the threat of disease caused by ZIKV infection exists not only for human populations living in and traveling to currently endemic countries but also for those living in nonendemic countries where transmission of disease could occur in the future owing to the presence of the mosquito vector.

Because there is no effective therapy, a ZIKV vaccine is an important unmet medical need both for inhabitants of affected regions and for travelers to those countries. Takeda Vaccines is developing TAK-426, a purified formalin-inactivated whole ZIKV vaccine (PIZV) based on a plaque-purified subisolate

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of ZIKV strain PRVABC59 (originally obtained from the US Centers for Disease Control and Prevention [CDC]) [14]. In preclinical testing, TAK-426 was safe and well tolerated, elicited robust immune responses, and protected mice and Indian rhesus macaques in a ZIKV challenge model [14, 15]. Our group previously reported the first in-human assessment of TAK-426 in healthy FV-naive and FV-primed adults to evaluate safety and immunogenicity and to select a dosage for further clinical development [16]. We now present extended safety follow-up and persistence of the neutralizing antibody (NAb) responses from that study through 6 months after vaccination with the low (2 μg) and medium (5 μg) PIZV doses and through 2 years after vaccination with the high dose (10 μg) selected for further clinical development. We also compare the PIZV-induced NAb response with that observed after natural infection in 2 cohorts of adults with confirmed ZIKV infection.

METHODS

Study Design and Participants

This 2-part, multicenter, randomized, observer-blind, dose-selection, placebo-controlled phase 1 trial of 2 doses of TAK-426 administered 28 days apart in adults with or without prior exposure to FVs was performed in 7 centers in the United States and 2 in Puerto Rico from 13 November 2017 to 24 November 2020 [16]. The protocol (ZIK-101) was approved by the local ethical committee or institutional review board of each study center, registered on ClinicalTrials.gov (NCT03343626), and implemented in accordance with International Council for Harmonisation and Good Clinical Practice guidelines and applicable local regulatory requirements. The primary objectives were to determine the safety, tolerability, and immunogenicity of 3 increasing dosages of PIZV (TAK-426). The objectives reported here are assessments of safety and persistence of immune responses up to 2 years after completion of the primary vaccination series. Additional data, not foreseen in the protocol, are presented in response to a regulatory authority request for comparator data observed about the natural history of ZIKV infection.

Eligible participants were healthy 18–49-year-old men and nonpregnant women who provided signed informed consent and were available for the study duration. Sexually active women of childbearing potential were required to have a negative pregnancy test at screening and before the second vaccination and to practice a protocol-approved form of contraception from 2 months before screening to 2 months after the last vaccination. Other inclusion/exclusion criteria were reported elsewhere [16].

NAb titers from 2 cohorts of participants with confirmed ZIKV infection were used to compare the NAb response induced by PIZV with that induced by natural infection. Cohort A consisted of 18–69-year-old adults living in the United States who were recruited at Baylor College of Medicine, Houston, Texas, and Emory University, Atlanta, Georgia, using passive referrals and active case finding from healthcare facilities and laboratory-based screening [17]. A participant was suspected of having ZIKV infection based on clinical presentation and a history of potential ZIKV exposure. ZIKV infection was confirmed by detection of ZIKV RNA in a body fluid specimen or a positive result for ZIKV immunoglobulin (Ig) M and NAbs in serum samples with lower NAb levels or no NAbs against dengue virus (DENV) 1–4. ZIKV RNA was detected in samples by means of reverse-transcription polymerase chain reaction (RT-PCR), using TaqMan Fast Virus 1-Step Master Mix on a ViiA 7 RT-PCR System (ThermoFisher Scientific) with a primers/probe set described elsewhere [18].

ZIKV cases were further defined as DENV naive or DENV experienced according to baseline DENV-specific NAb titers (<250 for naive participants and ≥250 for primed participants). Serum NAbs against ZIKV or DENV1–4 were measured with a modified focus reduction neutralization test (FRNT), the details of which have been described elsewhere [17, 19]. Foci were imaged and counted using a CTL-Immunospot S6 Micro Analyzer (Immunospot). FRNT 50% neutralizing antibody titres ($FRNT_{50}$) were determined using GraphPad Prism software (version 10). Serum anti-ZIKV IgM antibodies were detected with the CDC Zika IgM antibody capture enzyme-linked immunosorbent assay (Zika MAC-ELISA) [20, 21]. The sensitivity and specificity of this assay stratified by days after onset of symptoms used in this analysis have been reported elsewhere [22]. Because the majority of participants blood samples in our analysis were collected within 7–166 days after symptom onset, the time frame published by Porthilo et al [22], the assay sensitivity was anticipated at >75%. The specificity for acute- and convalescent-phase samples relative to RT-PCR–confirmed DENV cases was 100% and 93.2%, respectively. All recruited participants were followed up for up to 12 months, depending on the elapsed time between disease onset and enrollment. Medical, sexual, and travel histories were obtained, a physical examination was performed, and blood, urine, and saliva samples were collected.

The second cohort, cohort B, included 109 serum or plasma samples obtained by commercial, academic, and government sources from individuals residing in Puerto Rico, Ecuador, New York, or the Caribbean who had confirmed natural infection, again, based on the detection of ZIKV RNA in a body fluid specimen or a positive result for ZIKV IgM or NAb in serum samples. Serum samples were obtained from 7 days to 4 months after infection: 30 samples from BOCA Biolistics (Florida), 10 received in 2019 and 20 received in 2016; 13 plasma samples from blood banks collected before 2016; 7 plasma samples from blood banks collected after 2016; 19 samples from Ecuador (2016–2017); and 40 samples from the CDC

(2016–2017). Samples identified and selected for assessment in cohort B were tested by vendors using the indicated assays. The laboratory assays used are either described above or were performed using commercially available kits for ZIKV. The results from these assays were used only to identify potential samples from vendors. These samples were subsequently tested at Takeda Cambridge Laboratory to confirm that the samples obtained were reactive to ZIKV or DENV with Takeda assays before use in this study.

Procedures

In the original study, ZIK-101, after serological screening for previous FV exposure at Q2 Solutions in Marietta, Georgia, using a fit-for-purpose FV screening Multiplex Luminex IgG enzyme-linked immunosorbent assay (Luminex) [16], volunteers were enrolled in FV-naive and FV-primed cohorts and randomized (1:1:1:1) to 1 of 4 groups, with approximately equal numbers of FV-naive and FV-primed participants per group. Three lots of TAK-426 were used in this study (Z426-001, Z426-002, and Z426-003), containing 2-, 5-, or 10-μg antigen content (low, medium, and high dose, respectively) adjuvanted with 200-μg aluminum hydroxide per dose. The placebo was sterile saline (West Ward Pharmaceuticals). Doses of placebo or TAK-426 were administered by intramuscular injection in the deltoid, with a second injection administered 28 days later.

Safety Assessments

Following the previously reported solicited local and systemic reactogenicity for 7 days after each vaccination, as well as unsolicited adverse events (AEs) for 28 days after each vaccination [16], safety surveillance continued throughout the 2-year follow-up, reported here for serious AEs (SAEs) and for new medical conditions, including neurological and neuroinflammatory disorders.

Immunogenicity Assessments

In ZIK-101, serum samples were obtained from all participants at baseline (day 1) and 1, 2, and 8 months and at 14 and 26 months from those in the placebo and 10-μg PIZV groups to measure postvaccination immune responses. Anti-ZIKV NAb levels were measured using a qualified plaque reduction neutralization test (PRNT) performed at Q2 Solutions (San Juan Capistrano, California). The PRNT limit of detection was 1:10 dilution, and the lower limit of quantitation was 26 (reciprocal dilution). PRNT seropositivity was defined as a titer of ≥10. Seronegative samples were assigned a titer of 5, half of the limit of detection, for calculation of geometric mean titers (GMTs) with 95% confidence intervals (CIs), using the exact Clopper-Pearson method for each group and time point. Seroconversion was defined as seronegative participants at baseline who became seropositive after vaccination or initially seropositive participants who demonstrated ≥4-fold increases in titer after vaccination. PIZV-induced PRNT results were compared with those elicited by ZIKV infection in the US cohort study (cohort A), as measured using a modified FRNT [19] at the Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas.

ZIK-101 serum ZIKV NAb levels were also measured using a fit-for-purpose ZIKV reporter virus particle (RVP) assay [23], developed and performed in the Takeda Laboratory in Cambridge, Massachusetts, with a lower limit of quantitation of 105, which was used as the threshold to define seropositivity or seronegativity. PIZV-induced RVP results were compared with those elicited by ZIKV infection in cohort B samples, which were measured concomitantly with those from PIZV-vaccinated study participants in the RVP assay.

Statistical Analysis

The ZIK-101 sample size was not based on any formal statistical hypothesis: 60 participants per group were considered adequate to select 1 of the 3 dose sizes based on the ratios of GMTs between dosage groups. Safety assessments were performed on all randomized participants who received ≥1 dose of vaccine or placebo (safety set), and immunogenicity assessments were based on the per-protocol set, comprising all participants with no major protocol violations who received ≥1 dose of the investigational vaccine or placebo and provided valid baseline serology and ≥1 postvaccination time point.

RESULTS

We previously reported that 894 volunteers were screened and 271 were enrolled in 2 cohorts (125 FV naive and 146 FV primed) and randomized to receive 2 injections of either placebo or 1 of the 3 dosages (low [2 μg], medium [5 μg], or high [10 μg] antigen concentrations) of PIZV (Figure 1) [16]. All 125 FV-naive participants were recruited from sites on mainland United States, as were 84 of the 146 (57.5%) FV-primed participants; the remaining 62 FV-primed participants were recruited from Puerto Rico. As previously reported [16], the demographics of the study groups in the safety set were consistent. Overall, participants had a mean age (standard deviation) of 35.5 years (8.7) years, with 28.0% aged 18–29 and 72.0% aged 30–49 years; 58% were female. Demographics in the per-protocol set used for immunogenicity analyses were similar. Table 1 shows the main characteristics of the PIZV high dose–vaccinated and the US ZIKV-infected observational study populations (cohort A).

Immunogenicity: NAbs

The present report on the phase 1 study describes the cumulative data available at database lock at month 26, which was 24 months after the second vaccination. As reported elsewhere [16], at month 2 (4 weeks after the second dose of PIZV),

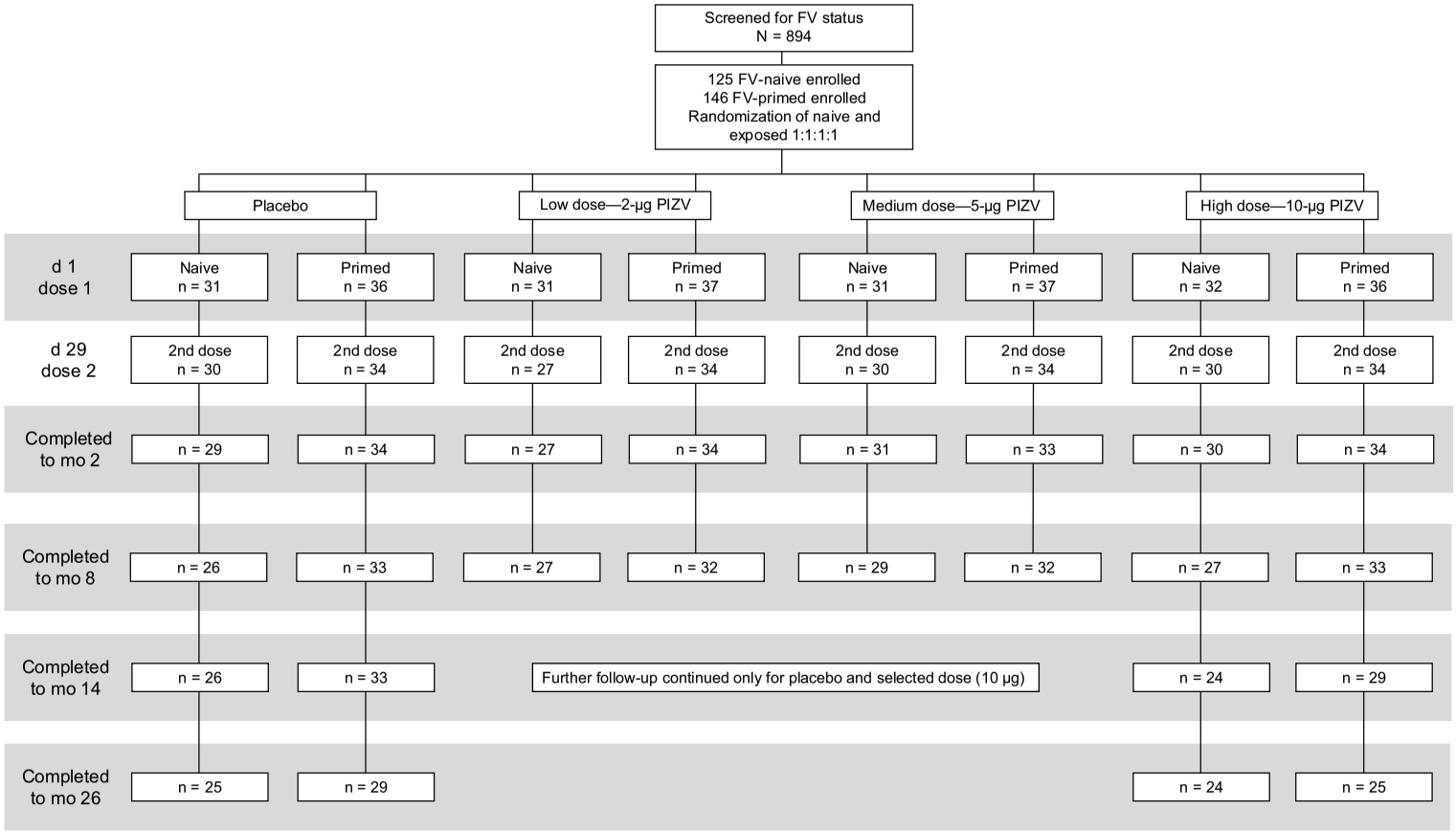

Figure 1. Study flow chart.

Table 1. Characteristics of the Population Receiving Purified Formalin-Inactivated Whole Zika Virus Vaccine (PIZV) and US ZIKV-naturally Infected Study Population (Cohort A)

Characteristic	Study Participants, No. (%)[a]	
	Phase 1 Study of 10-µg PIZV (n = 68)	Observational Cohort A (n = 45)
Female sex	36 (52.9)	31 (68.9)
Age, median (range), y	35 (20–49)	44 (18–68)
Ethnicity		
Hispanic or Latino	36 (52.9)	13 (28.9)
Not Hispanic or Latino	32 (47.1)	32 (71.1)
Race		
Black/African American	14 (20.6)	3 (6.7)
White	52 (76.5)	33 (73.3)
Multiracial	2 (2.9)	9 (20.0)
Unknown/other	0	5 (11.1)
BMI, mean (SD)[b]	27.9 (4.2)	27.4 (3.5)
FV vaccination		
Yellow fever	…	12 (26.7)
Japanese encephalitis	…	1 (2.2)
Tick-borne encephalitis	…	1 (2.2)
Serological evidence of prior DENV infection		13 (28.9)
FV naive	32 (47.1)	…
FV primed	36 (52.9)	…

Abbreviations: BMI, body mass index; DENV, dengue virus; FV, flavivirus; PIZV, purified formalin-inactivated whole Zika virus vaccine; SD, standard deviation.

[a]Data represent no (%) of participants unless otherwise specified.

[b]BMI calculated as weight in kilograms divided by height in meters squared.

84 of 84 initially FV-naive participants (100%) were seropositive, as were 99 of 100 initially FV-primed participants (99.0%) (Table 2). All FV-naive participants across the TAK-426 dosage groups were seropositive through 8 months, and all 10-µg group participants remained seropositive when assessed at 14 months, with a small decline to 93.8% at 26 months. All FV-primed participants who received 10-µg doses of PIZV were seropositive through 14 months, and 76.2% remained seropositive at 26 months. FV-naive participants who received placebo remained seronegative through month 14, but 5 of 19 participants who were initially FV naive seroconverted at month 26, indicating natural infection with ZIKV or another FV with stimulation of cross-reactive antibodies.

The kinetics of PRNT antibody GMTs are illustrated in Figure 2*A*, which shows the rapid increase in titers observed after a single 10-µg dose of PIZV in naive participants, increasing to the same level observed in initially FV-primed participants, with a further increase after the second dose to a peak of 3690 (95% CI, 2677–5086) 1 month after dose 2. FV-primed participants also responded to PIZV, with the GMT peaking at 2591 (95% CI, 1649–4069) 1 month after dose 2, a level similar to that in the FV-naive group after 2 doses. Titers waned in both groups to month 8, which was 6 months after the second vaccination, when they appeared to reach a plateau level that was maintained up to 2 years after vaccination. Titers in placebo recipients remained relatively constant up to month 14, but there was an increase in GMTs in both groups at month 26, supporting the suggestion of natural ZIKV or other FV infection in some participants. NAb responses measured using the fit-for-purpose RVP neutralization assay mirrored those measured using the PRNT assay, although RVP titers were numerically higher (Figure 2*B*). There were no significant differences in the levels of immune response by age or sex (Supplementary Table 1 and Supplementary Figure 1).

Comparison With Natural Infection

Figure 3 displays the GMTs (95% CIs) of samples from cohort B (109 human convalescent serum and plasma samples) that were tested concomitantly in the RVP assay. The levels of PIZV-induced NAbs up to 1 month after dose 2 are comparable with those observed 7 days to 4 months after onset of symptoms of ZIKV natural infection. When cohort A FRNT titers were arranged according to their experience of prior DENV infection and by time between symptom onset and sampling, the kinetics were comparable with those of the immune responses measured using PRNT in PIZV vaccinees, irrespective of dengue history (Figure 4). Titers declined with increased time after infection, with rapid decreases over the first 3 months, and then plateaued, paralleling our observations in the FV-naive and FV-primed participants after two 10-µg PIZV doses.

Safety

There were no deaths, hospitalizations, or vaccine-related SAEs reported up to the cutoff 24 months after dose 2, and no participants withdrew from the study owing to an AE. A total of 12 SAEs in 11 participants were reported over the entire duration of the study (Table 3) (in 2 placebo recipients and 9 vaccinees). Nine SAEs were reported in the first 14 months (up to 12 months after dose 2), and 3 occurred in the second year of surveillance. None of the reported SAEs were considered to be related to the study procedures. Two pregnancies were reported, both in the PIZV cohort, with no effects noted in the newborns.

DISCUSSION

After our previous report that PIZV doses of 2–10 µg were well tolerated and immunogenic 1 month after the second dose [16], we selected the high dose (10 µg) for further clinical development. In this ongoing assessment, we confirm that no deaths or vaccine-related SAEs were reported up to 24 months after administration of the second dose. Observed SAEs detected in the study population were considered unrelated to vaccine and occurred only in the first year after vaccination.

After achieving 100% seropositivity for ZIKV NAbs 1 month after the second vaccination with 2-, 5-, or 10-µg PIZV, 100% seropositivity was maintained for ≥6 months in initially FV-naive participants. In the 10-µg PIZV group, this 100% level

Table 2. Seropositivity Rates for Zika Virus Neutralizing Antibodies Measured Using a Plaque Reduction Neutralization Test in Flavirus-Naive and Flavirus-Primed Cohorts

Timing During Study	Seropositivity rate by PRNT (95% CI), %							
	Placebo		2-µg PIZV		5-µg PIZV		10-µg PIZV	
	FV Naive (n = 28)	FV Primed (n = 34)	FV Naive (n = 25)	FV Primed (n = 33)	FV Naive (n = 29)	FV Primed (n = 34)	FV Naive (n = 30)	FV Primed (n = 33)
d 0	0	88.2 (72.6–96.7)	0	75.8 (57.7–88.9)	0	85.3 (68.9–95.1)	0	75.8 (57.7–88.9)
mo 1	0	85.3 (68.9–95.1)	72.0 (50.6–87.9)	96.8 (83.3–99.9)	82.1 (63.1–93.9)	100 (89.7–100)	96.4 (81.7–99.9)	100 (89.4–100)
mo 2	0	87.1 (70.2–96.4)	100 (85.2–100)	96.7 (82.8–99.9)	100 (87.7–100)	100 (88.8–100)	100 (87.7–100)	100 (88.4–100)
mo 8	0	76.7 (52.7–90.1)	100 (83.2–100)	84.0 (63.9–95.5)	100 (86.3–100)	100 (86.8–100)	100 (85.2–100)	100 (86.8–100)
mo 14	0	65.6 (46.8–81.4)	ND	ND	ND	ND	100 (83.9–100)	100 (87.2–100)
mo 26	26.3 (9.2–51.2)	85.2 (66.3–95.8)	ND	ND	ND	ND	93.8 (69.8–99.8)	76.2 (52.8–91.8)

Abbreviations: CI, confidence interval; FV, flavivirus; ND, not determined; PIZV, purified formalin-inactivated whole Zika virus vaccine; PRNT, plaque reduction neutralization test.

was maintained up to 1 year after vaccination, and for up to 2 years in 93.8% and 76.2% of participants in the FV-naive and FV-primed groups, respectively. There was no significant difference in the levels of immune response by age or sex. The decline in ZIKV NAbs in those receiving PIZV was greatest in the first 6 months after vaccination, after which the NAbs plateaued and remained at a consistent level. The longitudinal profile of NAbs measured using the FRNT assay in participants, after ZIKV infection (cohort A), followed a pattern similar to that of PIZV-induced antibodies measured using PRNT (Figure 4). It is not unexpected to observe a decline in vaccine-induced NAbs after immunization with an inactivated vaccine, which does not necessarily indicate a lack of antibody-mediated immune protection. Further characterization of the humoral immune responses (eg, PIZV boostability, B-cell memory) is planned for future clinical studies and will provide further insight into the observed decline. Future vaccine and ZIKV natural infection–induced immune responses comparisons will be performed using a validated RVP assay and analyzing blood samples concomitantly in a single laboratory.

An effective vaccine remains a global unmet medical need owing to the severe spectrum of disease caused by ZIKV infection in pregnant women (including high child mortality rates in the first 3 years of life [24, 25]) and Guillain-Barré syndrome in other adult patients [26, 27]; the potential reemergence of an epidemic owing to a large number of susceptible populations residing where the vector proliferates; and the lack of a licensed prophylactic or curative treatment for ZIKV infection. Such a vaccine is also important for travelers and military personnel requiring rapid vaccine-induced protective immunity. The current report provides evidence of the safety of the high dosage (10 µg) and the persistence of the immune response up to 2 years after the second vaccination in healthy 18–49-year-old adults living in the United States and its territory, Puerto Rico. Furthermore, the levels

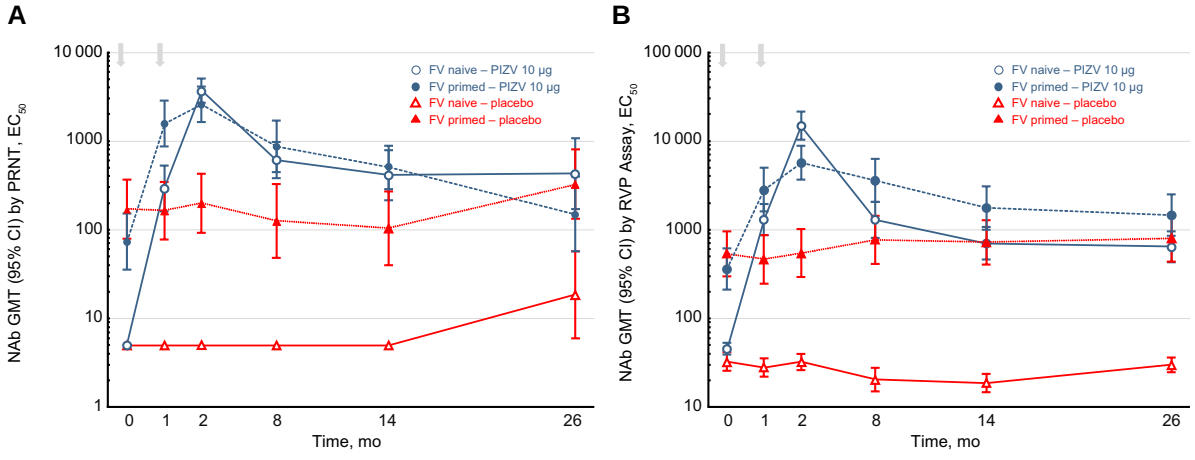

Figure 2. Zika virus-specific neutralizing antybody responses measured by PRNT and RVP over time (PIZV) at months 0 and 1 (*gray arrows*). Geometric mean titers (GMTs) and 95% confidence intervals (CIs) are shown for each group. Abbreviation: EC_{50}, half maximal effective concentration; PRNT, plaque reduction neutralization test; RVP, reporter virus particle.

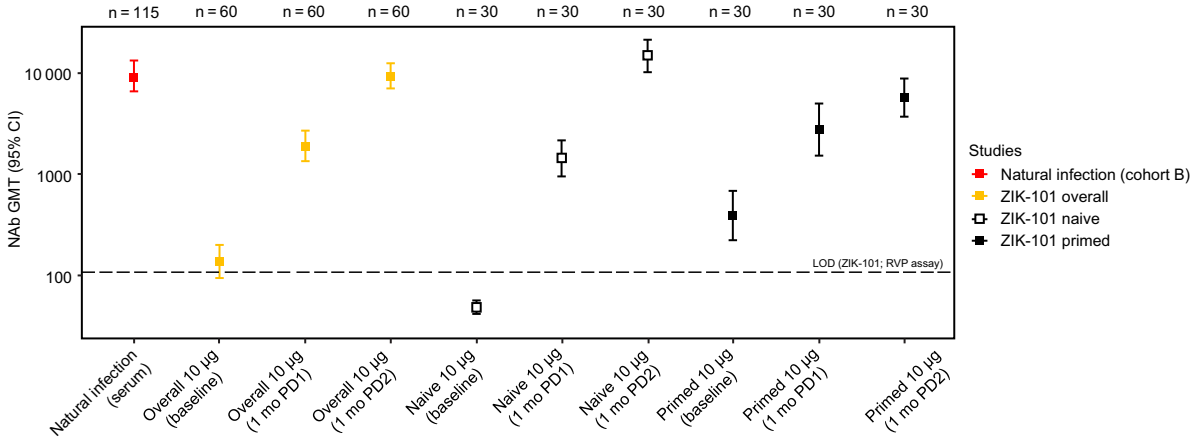

Figure 3. Comparison of Zika vaccine (PIZV) and natural infection (cohort B) Zika-virus specific neutralizing antibodies measured by RVP. Abbreviations: LOD, limit of detection; PD1, post dose 1; PD2, post dose 2; RVP, reporter virus particle.

and kinetics of NAbs achieved after vaccination are comparable with those observed in convalescent patients after confirmed ZIKV infection.

Other groups have applied several different approaches to ZIKV vaccine development [28, 29], including messenger RNA– and DNA-based candidates. A purified formalin-inactivated virus vaccine based on the same PRVABC59 strain as our vaccine candidate has been tested using different schedules; this identified an immune response only after the second dose, with an optimal schedule of 0 and 4 weeks [30]. However, that study found poor persistence of the immune response, with detectable antibodies in only 10% of participants 1 year after vaccination [31].

Because it remains unknown how PIZV could induce cross-reactive DENV antibodies, such as those observed after natural ZIKV infection that could increase the risk of severe dengue disease [32–34], our future clinical studies will continue to determine FV status at baseline and monitor SAEs and DENV-related SAEs throughout the entire follow-up. Further studies will also be needed to evaluate the safety of the vaccine in dengue-endemic areas.

In conclusion, we confirm that PIZV has an acceptable safety profile in healthy adults aged 18–49 years, with no vaccine-related SAEs through 2 years after vaccination. Two vaccinations elicited immune responses that persisted at high titers (GMTs >100) that are comparable with those observed

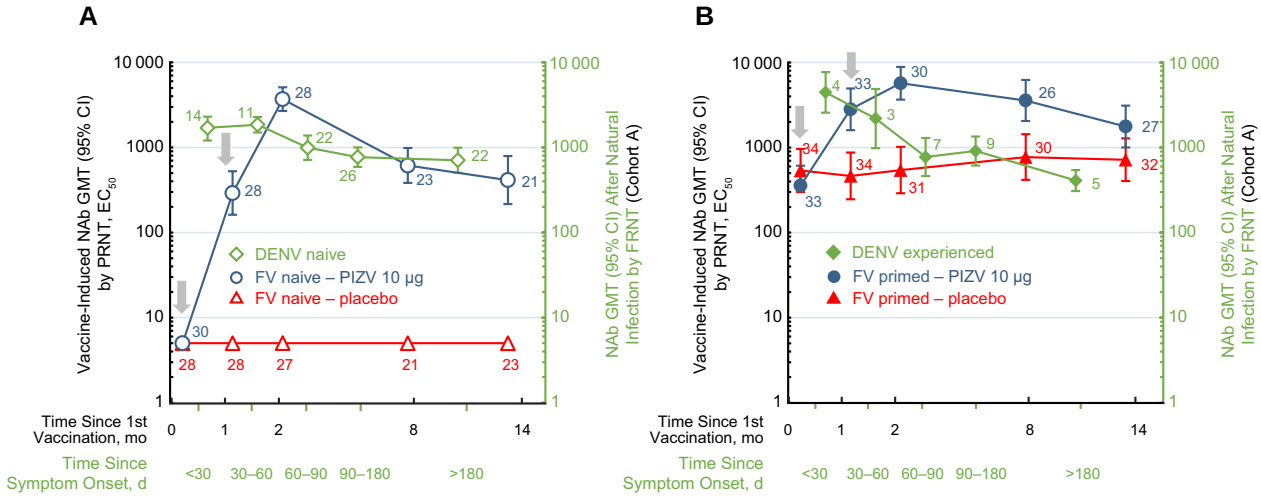

Figure 4. Zika vaccine (PIZV) and natural infection (cohort A) Zika-virus specific neutralizing antibodies measured by PRNT and FRNT over time. Abbreviation: EC_{50}, half maximal effective concentration; PRNT, plaque reduction neutralization test; FRNT, focus reduction neutralization test.

Table 3. Serious Adverse Events Reported and Related Outcomes Through Month 26

Type of SAE or Outcome	SAEs or Outcomes, No. (%)							
	Placebo		2-µg PIZV		5-µg PIZV		10-µg PIZV	
	FV Naive (n = 31)	FV Primed (n = 36)	FV Naive (n = 31)	FV Primed (n = 37)	FV Naive (n = 31)	FV Primed (n = 37)	FV Naive (n = 32)	FV Primed (n = 36)
SAEs	1 (3.2)	1 (2.8)	1 (3.2)	2 (5.4)	0	0	2 (6.3)	5 (13.9)
Vaccine related	0	0	0	0	0	0	0	0
Not related	1 (3.2)	1 (2.8)	1 (3.2)	2 (5.4)	0	0	2 (6.3)	5 (13.9)
Before mo 14	0	1 (2.8)	1 (3.2)	2 (5.4)	0	0	2 (6.3)	2 (5.6)
mo 14–26	1 (3.2)	0	0	0	0	0	0	3[a] (8.3)
Hospitalization	1 (3.2)	1 (2.8)	1 (3.2)	2 (5.4)	0	0	2 (6.3)	4 (11.1)
Death	0	0	0	0	0	0	0	0

Abbreviations: FV, flavivirus; PIZV, purified formalin-inactivated whole Zika virus vaccine; SAE, serious adverse event.

[a]Three participants reported a total of 4 SAEs (1 participant reported 2 of the 4 SAEs reported).

in convalescent ZIKV-infected patients up to 2 years after vaccination, in both FV-naive and FV-primed adults. These safety and immunogenicity profiles of the high dose (10-µg) PIZV confirm its suitability for further clinical development.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Data sharing. The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be available within 3 months after initial request to researchers who provide a methodologically sound proposal. The data will be provided after its deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Data are available on request via application at https://search.vivli.org.

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