EMERGING INFECTIONS

Durability and correlates of vaccine protection against Zika virus in rhesus monkeys

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An effective Zika virus (ZIKV) vaccine will require long-term durable protection. Several ZIKV vaccine candidates have demonstrated protective efficacy in nonhuman primates, but these studies have typically involved ZIKV challenge shortly after vaccination at peak immunity. We show that a single immunization with an adenovirus vector–based vaccine, as well as two immunizations with a purified inactivated virus vaccine, afforded robust protection against ZIKV challenge in rhesus monkeys at 1 year after vaccination. In contrast, two immunizations with an optimized DNA vaccine, which provided complete protection at peak immunity, resulted in reduced protective efficacy at 1 year that was associated with declining neutralizing antibody titers to subprotective levels. These data define a microneutralization log titer of 2.0 to 2.1 as the threshold required for durable protection against ZIKV challenge in this model. Moreover, our findings demonstrate that protection against ZIKV challenge in rhesus monkeys is possible for at least 1 year with a single-shot vaccine.

INTRODUCTION

The development of a safe and effective Zika virus (ZIKV) vaccine has emerged as a global health priority (1–5). ZIKV infection has been shown to be associated with fetal microcephaly and other congenital malformations (6–9), as well as Guillain-Barré syndrome in healthy adults (10). Protective efficacy of DNA vaccines, RNA vaccines, adenovirus (Ad) vector–based vaccines, purified inactivated virus (PIV) vaccines, and live attenuated virus vaccines has been demonstrated against ZIKV challenge in rodents and nonhuman primates (11–19), and several vaccine candidates are currently in clinical trials (3–5).

Nonhuman primate challenge studies reported to date have only assessed protection at peak immunity shortly after vaccination (11, 13, 15). Here, we report the 1-year protective efficacy of three leading vaccine platforms (PIV, DNA, and Ad) in rhesus monkeys and the immune correlates of protection.

RESULTS

We previously designed a DNA vaccine expressing an engineered form of ZIKV BeH1815744 prM-Env containing a deletion of the cleavage peptide (amino acids 216 to 794; also termed M-Env), and we showed that this vaccine protected against ZIKV challenge in both mice and rhesus monkeys (11, 12). We compared antigen expression and immunogenicity of DNA vaccines expressing this engineered M-Env, the corresponding full-length prM-Env, and full-length prM-Env containing the stem region of Japanese encephalitis virus (JEV), which has been shown to increase secretion of soluble subviral particles (Fig. 1A) (15). The DNA-M-Env vaccine exhibited the highest Env expression by Western blot (Fig. 1B). Groups of Balb/c mice (n = 5 per group) were then immunized by the intramuscular route with a single 50 µg immunization of DNA vaccines expressing M-Env, prM-Env (full length), or prM-Env (JEV stem). The DNA-M-Env vaccine induced the highest antibody responses by enzyme-linked immunosorbent assay (ELISA) at week 4 (P = 0.003 and P = 0.002 comparing titers induced by DNA-M-Env titers with titers induced by DNA-prM-Env (full length) and DNA-prM-Env (JEV Stem), respectively; Fig. 1B). After challenge with 10² viral particles (VP) [10² plaque-forming units (PFU)] of ZIKV-BR by the intravenous route (12), only the DNA-M-Env vaccine afforded complete protection (Fig. 1C). Env-specific log ELISA titers >2.0 were associated with protection (P < 0.0001; fig. S1). We speculate that the improved performance of the deleted M-Env immunogen may reflect the inefficiency of natural cleavage in the full-length prM-Env immunogen and the lack of the cleavage peptide in the deleted M-Env immunogen.

We next compared the immunogenicity and protective efficacy of multiple ZIKV vaccine candidates in Balb/c mice. Groups of mice (n = 5 per group) were immunized once by the intramuscular route with 10⁸ VP Ad26-M-Env, 10⁸ VP RhAd52-M-Env, 1-µg PIV with alum, 50-µg DNA-M-Env, 50-µg DNA-prM-Env, or sham vaccine. Env-specific ELISA titers were higher in the Ad26-M-Env, RhAd52-M-Env, and PIV groups as compared with the DNA-M-Env and DNA-prM-Env groups over 20 weeks of follow-up (Fig. 2A). At week 20, all mice were challenged with ZIKV-BR, as described above. Complete protection was observed in the groups of mice that received the Ad26-M-Env, RhAd52-M-Env, and PIV vaccines (Fig. 2B). In contrast, protection was observed in only 80% (four of five) of mice that received the DNA-M-Env vaccine and in only 20% (one of five) of mice that received the DNA-prM-Env vaccine (Fig. 2C), which elicited the lowest Env-specific antibody responses (Fig. 2A), consistent with the previous experiment.

To evaluate the durability of ZIKV vaccine efficacy in nonhuman primates, we immunized 16 rhesus monkeys by the subcutaneous route with 5-µg ZIKV PIV vaccine with alum (n = 8) or sham vaccine (alum

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We followed ZIKV-specific neutralizing antibodies by microneutralization (MN50) assays (11, 12) for over 52 weeks (Fig. 3A). Median log MN50 titers in the PIV-vaccinated monkeys were 1.88 at week 4 after the initial immunization and increased to 3.71 at week 8 after the boost immunization. Neutralizing antibody titers then declined by 1.33 logs over the next 10 weeks to median log MN50 titers of 2.38 at week 18, and titers then remained largely stable until week 52. Low Env-specific cellular immune responses were also observed by interferon-γ enzyme-linked immunospot assays (fig. S2).

At week 52, all monkeys were challenged with $10^6$ VP (10^3 PFU) of ZIKV-BR by the subcutaneous route, as previously described (11, 20). Viral loads were quantitated by real-time polymerase chain reaction (RT-PCR). Sham controls exhibited about 7 days of viremia with median peak log viral loads of 6.47 on days 4 to 5 after challenge (Fig. 3B). Virus was detected for a longer period of time in certain tissue compartments of the sham controls, including cerebrospinal fluid (CSF) and lymph nodes (LN) (Fig. 3, C and D), consistent with previous findings from our laboratory and others (20–23). In contrast, PIV-vaccinated monkeys showed no detectable viremia (<2 log copies/ml) in 75% (six of eight) of animals ($P = 0.007$ compared with sham controls) and low and transient viral blips in 25% (two of eight) of animals. These two PIV-vaccinated monkeys also showed low levels of virus in LN.

We next evaluated the durability of protection afforded by the DNA-M-Env and the RhAd52-M-Env vaccines in nonhuman primates. We immunized 15 rhesus monkeys by the intramuscular route with two immunizations of 5-mg DNA-M-Env at weeks 0 and 4 ($n = 7$), a single-shot immunization of $10^{11}$ VP RhAd52-M-Env at week 0 ($n = 4$), or sham vaccine ($n = 4$). MN50 titers were low after the first DNA-M-Env vaccination but reached peak median log titers of 2.23 by week 8 after the boost immunization (Fig. 4A). MN50 titers in these animals persisted and proved remarkably
stable over a year of follow-up, with median log MN50 titers of 2.42 (range, 2.30 to 2.54) at week 52 (Fig. 4A). Env-specific cellular immune responses were also induced in these animals (fig. S3).

After challenge with 10^6 VP (10^3 PFU) of ZIKV-BR at week 52, only 29% (two of seven) of DNA-M-Env–vaccinated animals were protected, and 71% (five of seven) of animals in this group exhibited viremia (Fig. 4B). Notably, the two DNA-M-Env–vaccinated monkeys that were protected were the animals with the highest log MN50 titers. Because the DNA-M-Env vaccine afforded complete protection when challenged at peak immunity (11), we speculate that the abrogation of protection reflects the decline of neutralizing antibody titers over the year before challenge to subprotective levels. In contrast, a single immunization with RhAd52-M-Env provided protection in 100% (four of four) of monkeys at 1 year (P = 0.02 compared with sham controls, Fig. 4, B to D), likely reflecting the persistent MN50 titers in these animals.

We next assessed the capacity of week 52 prechallenge serum from the PIV-, DNA-M-Env–, and RhAd52-M-Env–vaccinated monkeys to neutralize a panel of ZIKV strains, and we observed cross-neutralization of viral strains from Brazil (BR), Uganda (UG), Thailand (TH), Philippines (PH), and Puerto Rico (PR) (fig. S4). We also evaluated the capacity of serum antibodies to enhance ZIKV infection in vitro in K562 cells. As expected, all animals with detectable neutralizing antibodies resulted in enhanced infection in K562 cells at relatively high dilutions of sera (figs. S5 and S6), suggesting that this in vitro assay does not readily distinguish between protective and enhancing antibodies. No animals demonstrated enhanced ZIKV viremia in this study, including monkeys with subprotective neutralizing antibodies and enhanced infection in K562 cells. We also observed that MN50 titers increased in all the vaccinated animals after challenge (figs. S7 and S8), which may reflect either a lack of complete sterilizing immunity or alternatively an immunologic boost by the 10^6 VP dose of the challenge virus. Supporting the latter possibility is the lack of observed increased cellular
immune responses in the RhAd52-M-Env–vaccinated animals after challenge (week 52) was inversely correlated with the peak log ZIKV viral load after challenge ($r = -0.81, P < 0.0001$; Fig. 5). Moreover, MN50 titers were higher in protected animals than in infected animals ($P < 0.0001$). Specifically, 92% (12 of 13) of animals with MN50 titers >2.0 and 100% (12 of 12) of animals with MN50 titers >2.1 at week 52 were protected. In contrast, 100% (six of six) of animals with MN50 titers <2.0 were infected. Similar results were obtained by an immune correlates analysis that included all animals including the sham controls (fig. S10). Moreover, adoptive transfer studies using purified immunoglobulin G (IgG) from week 52 plasma samples confirmed that the vaccine-induced rhesus monkey antibodies afforded passive protection in Balb/c mice (fig. S11).

**DISCUSSION**

Here, we demonstrate that a single-shot immunization with RhAd52-M-Env provided complete protection against ZIKV-BR challenge in 100% (four of four) of rhesus monkeys after 1 year. Two immunizations with the ZIKV PIV vaccine also provided robust protection in 75% (six of eight) of animals after 1 year. In contrast, DNA vaccines expressing the same optimized M-Env insert elicited neutralizing antibody titers that declined to subprotective levels during this time period. Protective efficacy strongly correlated with MN50 titers at the time of challenge, which defined the threshold of protection in this model to be log MN50 titers of 2.0 to 2.1 (MN50 titers of 100 to 125).

**Fig. 4. Long-term immunogenicity and protective efficacy of the ZIKV DNA-M-Env and RhAd52-M-Env vaccines in rhesus monkeys.** (A) Log ZIKV-specific microneutralization (MN50) titers after immunization of rhesus monkeys by intramuscular with two immunizations of 5-mg DNA-M-Env ($n = 7$) at weeks 0 and 4 (red arrows) or a single-shot immunization of $10^{11}$ VP RhAd52-M-Env ($n = 4$) at week 0 (red arrow). The dotted lines reflect log MN50 titers of 2.0. Red bars reflect medians. Vaccinated and sham control rhesus monkeys were challenged by the subcutaneous route with $10^6$ VP (10³ PFU) ZIKV-BR. Viral loads are shown in (B) plasma, (C) CSF, and (D) LN. Viral loads were determined on days 0, 1, 2, 3, 4, 5, and 7 for the plasma samples and on days 0, 3, 14, and 35 for the other samples. $P$ values determined by Fisher’s exact tests. NS, not significant.

Previous ZIKV vaccine studies in nonhuman primates from our laboratory and others have challenged animals shortly after vaccination at peak immunity (11, 13, 15). Although these data provide an important assessment of the theoretical short-term protective efficacy of vaccine candidates, it is critical for a ZIKV vaccine to provide long-term durable protection. Vaccine-elicited antibody responses...
typically decline with different kinetics depending on the vaccine modality and are likely affected by multiple immunologic and other factors. The PIV vaccine induced high MN50 titers after vaccination that declined over 3 months but still remained above the protective threshold in most of the animals. In contrast, the DNA-M-Env vaccine induced moderate MN50 titers that were sufficient for protection at peak immunity (11), but these responses declined to subprotective levels within 2 to 3 months. The RhAd52-M-Env vaccine induced moderate MN50 titers after a single-shot immunization, but these responses remained stable with minimal decline over 52 weeks. The immunologic basis of the persistent neutralizing antibody responses elicited by RhAd52-M-Env remains to be determined.

The strong correlation between ZIKV-specific antibody responses and protective efficacy in both mice and rhesus monkeys, as well as the robustness of this immune correlate across different antigens and different vaccine platforms, suggests the potential generalizability of these observations. Together with previous adoptive transfer studies using polyclonal antibodies from vaccinated animals (11, 12) and monoclonal antibodies (24), we suggest that ZIKV-specific neutralizing antibodies represent the primary mechanistic correlate of protection for ZIKV vaccines. These insights should prove useful in the clinical development of ZIKV vaccines, although the quantitative titer threshold required for ZIKV protection may differ between rhesus monkeys and humans. For other flavivirus vaccines in humans, neutralizing antibody titers of >10 have been reported as correlates of protection (25–27). Whether or not higher titers will be required for protection against ZIKV in humans remains to be determined. Future studies should also define the Env regions and epitopes that are the target of protective neutralizing antibodies.

The potential for cross-reactive dengue virus (DENV)–specific antibodies to interfere with the immunogenicity and/or protective efficacy of ZIKV vaccines is an important research question. Previous studies have suggested that DENV–specific antibodies can increase ZIKV replication in vitro and in mice (28–30), but studies in primates have not replicated these findings to date (31, 32). Dedicated studies of ZIKV vaccines in DENV-exposed animals and humans are therefore warranted. It also remains uncertain whether vaccine protection against virus replication in peripheral blood and tissues will translate into prevention of congenital Zika syndrome.

Together, our data demonstrate durable 1-year protection against ZIKV challenge by a recombinant Ad vector–based vaccine and a PIV vaccine in rhesus monkeys. ZIKV Ad, PIV, DNA, and RNA vaccines are currently being evaluated in clinical trials (33). Our study also defines the threshold MN50 titers that correlate with long-term protection in this model, although the relationship between the rhesus monkey model and humans remains to be determined. Nevertheless, these findings provide insights that support clinical development of ZIKV vaccines for humans.

**MATERIALS AND METHODS**

**Study design**

The objective of these studies was to evaluate the immunogenicity and protective efficacy of ZIKV vaccines in mice and rhesus monkeys. Studies were powered (n = 4 to 8 per group) to detect large differences in protective efficacy. Animals were randomly allocated to groups. Immunologic and virologic assays were performed blinded. All animal studies were approved by the appropriate Institutional Animal Care and Use Committee.

**Animals, vaccines, and challenges**

Female Balb/c mice were purchased from commercial vendors and housed at Beth Israel Deaconess Medical Center (BIDMC). Thirty-one outbred, Indian-origin male and female rhesus monkeys (Macaca mulatta) were housed at Bioqual Inc., Rockville, MD. Vaccine constructs have been described previously (11, 12). In the first monkey vaccine study, animals were immunized by the subcutaneous route with 5-μg ZIKV PIV vaccine derived from the PRVABC59 isolate with alum (Alhydrogel, Brenntag Biosector) or alum alone at weeks 0 and 4 (n = 8 per group). In the second monkey vaccine study, animals were immunized by the intramuscular route with 5-mg DNA vaccines expressing M-Env (pRM-Env amino acids 216 to 794 derived from the BeH815744 isolate with the cleavage peptide deleted) at weeks 0 and 4 (n = 7), a single immunization of 10¹¹ VP RhAd52 expressing M-Env at week 0 (n = 4), or sham controls (n = 4). Rhesus monkeys were challenged at week 52 by the subcutaneous route with 10⁶ VP (10⁵ PFU) ZIKV-BR (Brazil ZKV2015). Studies in Balb/c mice used 1-μg ZIKV PIV, 50-μg DNA vaccines, or 10⁹ VP Ad vaccines and were challenged with 10⁵ VP (10⁵ PFU) ZIKV-BR.

**Real-time polymerase chain reaction**

RT-PCR assays were used to monitor viral loads, essentially as previously described (11, 12). RNA was extracted from plasma or other samples with a QIAcube HT (Qiagen). The wild-type ZIKV BeH815744 Cap gene was used as a standard. RNA was purified (Zymo Research), and RNA quality and concentration was assessed by the BIDMC Molecular Core Facility. Log dilutions of the RNA standard were reverse-transcribed and included with each RT-PCR assay. Viral loads were calculated as VP per milliliter or per 1 × 10⁶ cells and were confirmed by PFU assays. Assay sensitivity was 100 copies/ml or 1 × 10⁶ cells.

**Adoptive transfer studies**

Polyclonal IgG was purified with protein G purification kits (Thermo Fisher Scientific) from week 52 plasma samples from rhesus monkeys vaccinated with the PIV, RhAd52-M-Env, DNA-M-Env, and sham vaccines. Total IgG was buffer-exchanged into 1× phosphate-buffered saline (PBS) and pooled for each group. Purified IgG was infused intravenously into groups of naïve recipient Balb/c mice (n = 5 per group) before ZIKV-BR challenge 2 hours after infusion. Mice received 400 μl (high dose) or 25 μl (low dose) of a solution (10 mg/ml) of purified IgG.
Enzyme-linked immunosorbent assay
Mouse and monkey ZIKV Env ELISA kits (Alpha Diagnostic International) were used to determine end point binding antibody titers using a modified protocol. Ninety-six-well plates coated with ZIKV Env protein were first equilibrated at room temperature with 300 μl of kit working wash buffer for 5 min. Six microliters of serum was added to the top row, and threefold serial dilutions were tested in the remaining rows. Samples were incubated at room temperature for 1 hour, and plates were washed four times. One hundred microliters of anti-mouse or anti-human IgG horseradish peroxidase (HRP)—conjugate working solution was then added to each well and incubated for 30 min at room temperature. Plates were washed five times, developed for 15 min at room temperature with 100 μl of 3,3',5'-tetramethylbenzidine (TMB) substrate, and stopped by the addition of 100 μl of stop solution. Plates were analyzed at 450 nm/550 nm on a VersaMax microplate reader using Softmax Pro 6.0. software ( Molecular Devices). ELISA end point titers were defined as the highest reciprocal serum dilution that yielded an absorbance >2-fold more than background values. Log10 end point titers are reported.

Neutralization assay
A high-throughput ZIKV microneutralization (MN) assay was used for measuring ZIKV-specific neutralizing antibodies, essentially as previously described (11, 12). Briefly, serum samples were serially diluted threefold in 96-well microplates, and 100 μl of ZIKV-PR (PRVABC59) containing 100 PFU was added to 100 μl of each serum dilution and incubated at 35°C for 2 hours. Supernatants were then transferred to microtiter plates containing confluent Vero cell monolayers (World Health Organization, NICSC-011038011038). After incubation for 4 days, cells were fixed with absolute ethanol/methanol for 1 hour at −20°C and washed three times with PBS. The pan-flavivirus monoclonal antibody 6B6-C1 conjugated to HRP (6B6-C1 was a gift from J. T. Roehrig, U.S. Centers for Disease Control and Prevention) was then added to each well, incubated at 35°C for 2 hours, and washed with PBS. Plates were washed, developed with TMB for 50 min at room temperature, and stopped with 1:25 phosphoric acid, and absorbance was read at 450 nm. For a valid assay, the average absorbance at 450 nm of three noninfected control wells had to be ±0.5, and virus-only control wells had to be ≥0.9. Normalized absorbance values were calculated, and the MN50 titer was determined by a log midpoint linear regression model. The MN50 titer was calculated as the reciprocal of the serum dilution that neutralized ≥50% of ZIKV, and seropositivity was defined as a titer ≥10, with the maximum measurable titer of 7290. Log10 MN50 titers are reported. For the cross-strain virus neutralization assays, the following ZIKV strains were used: Brazil (BR; Fortaleza/2015, renamed Paraiba/2015), Uganda (UG; Uganda/1947; MR766), Thailand (TH; SV0127/14), Philippines (PH; CPCC074000Y01U00B001), and Puerto Rico (PR; PRVABC59).

Antibody-dependent enhancement assay
Twofold serial dilutions of heat-inactivated sera were mixed with an equal volume of ZIKV (sufficient to achieve about 15% infection of 5 × 10^4 K562-DC-SIGN cells) and incubated for 1 hour at 37°C. This mixture was added to a 96-well plate containing medium [RPMI 1640 supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin, 1% L-glutamine (200 mM), and 1% nonessential amino acids (10 mM)] with 5 × 10^4 K562 cells per well in duplicate and incubated 18 to 20 hours overnight in a 37°C, 5% CO_2, humidified incubator. After overnight incubation, the cells are fixed, permeabilized, and immunostained with flavivirus group–reactive mouse monoclonal antibody 4G2, and secondary polyclonal goat anti-mouse IgG phycoerythrin-conjugated antibody (catalog no. 550589, BD Biosciences). The percent infected cells are quantified on a BD Accuri C6 Plus Flow Cytometer (BD Biosciences).

Statistical analyses
Analysis of virologic and immunologic data was performed using GraphPad Prism version 6.03 (GraphPad Software). Comparisons of groups were performed using t tests and Wilcoxon rank sum tests. Correlations were assessed by Spearman rank correlation tests.

SUPPLEMENTAL MATERIALS
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Fig. S1. Immune correlates analysis in mice.
Fig. S2. Cellular immune responses in the ZIKV PRV vaccine study.
Fig. S3. Cellular immune responses in the ZIKV DNA-M-Env and RhAd52-M-Env vaccine study.
Fig. S4. Cross-neutralization analysis of a panel of ZIKV strains.
Fig. S5. Antibody-dependent enhancement assays in the ZIKV PRV vaccine study.
Fig. S6. Antibody-dependent enhancement assays in the ZIKV DNA-M-Env and RhAd52-M-Env vaccine study after challenge.
Fig. S7. MN50 titers in the ZIKV PRV vaccine study after challenge.
Fig. S8. MN50 titers in the ZIKV DNA-M-Env and RhAd52-M-Env vaccine study after challenge.
Fig. S9. Cellular immune responses in the ZIKV DNA-M-Env and RhAd52-M-Env vaccine study after challenge.
Fig. S10. Immune correlates analysis in vaccinated and sham control rhesus monkeys.
Fig. S11. Adoptive transfer studies of rhesus monkey IgG in mice.

Primary data

REFERENCES AND NOTES


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Patience pays off

As an individual may not encounter the pathogen for years after they have been vaccinated, efficacious vaccines typically require induction of long-lasting immunity. Abbink and colleagues vaccinated nonhuman primates with one of several candidate Zika virus vaccines and then waited an entire year before conducting a viral challenge. These vaccines had all shown promising results in previous experiments with a more immediate challenge, but here, one vaccine faltered, likely due to waning antibodies. The researchers performed more experiments to suggest that circulating antibodies are mediating protection for these vaccines. These results are useful for Zika virus vaccine development and instructive for vaccine development in general.