

Zika virus vaccines

Peter Abbink , Kathryn E. Stephenson and Dan H. Barouch

Abstract | The recent epidemic of Zika virus (ZIKV) in the Americas has revealed the devastating consequences of ZIKV infection, particularly in pregnant women. Congenital Zika syndrome, characterized by malformations and microcephaly in neonates as well as developmental challenges in children, highlights the need for the development of a safe and effective vaccine. Multiple vaccine candidates have been developed and have shown promising results in both animal models and phase I clinical trials. However, important challenges remain for the clinical development of these vaccines. In this Progress article, we discuss recent preclinical studies and lessons learned from first-in-human clinical trials with ZIKV vaccines.

Zika virus (ZIKV), a flavivirus of the family *Flaviviridae*, was first isolated in 1947 in the Zika forest in Uganda¹. ZIKV is an enveloped, positive-sense single-stranded RNA virus. Its 11 kb genome encodes a single polyprotein that is cleaved into individual proteins. Structural proteins capsid (C), precursor membrane (prM) — which is cleaved into the mature membrane protein (M) — and envelope (ENV) are assembled in virus particles (FIG. 1). The non-structural proteins NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 are involved in replication and control host cell processes to favour virus production. Until recently, infection with ZIKV was generally regarded as a self-limited, mild illness with rash, headache, myalgia and conjunctivitis, and few ZIKV infections were reported globally². In 2007, ZIKV was recognized as the cause of an outbreak in Yap Island, Federated States of Micronesia³, followed in 2013 by an outbreak in French Polynesia⁴ before spreading to the Americas in 2015 (REF.⁵) via Easter Island, Chile⁶. As a result of the sudden rise in congenital abnormalities and occurrences of Guillain–Barré syndrome, the scientific community established a causal association between ZIKV infection and these neurological adverse outcomes^{7–9}. This led the WHO to declare ZIKV and its suspected link to birth defects^{10,11} a Public Health Emergency of International Concern in February 2016 (REF.¹²).

Research on this virus then markedly increased^{13–16}. Studies resolved structures of

the virion and the proteins that contribute to pathogenicity^{17–20} and defined candidate entry receptors and cell tropism^{21,22}. Neuroprogenitor cells have been described as a preferred target for ZIKV, leading to apoptosis of these cells and congenital Zika syndrome (CZS), including microcephaly and other brain malformations^{23,24}. The tyrosine-protein kinase receptor UFO (AXL)^{25–27}, which is highly expressed on human radial glial cells, astrocytes and microglia in the developing human cortex, has been hypothesized to account for the observed neurotropism and the related congenital malformations. However, the role of AXL as an entry receptor for ZIKV remains unknown²⁸.

The close relationship between ZIKV and other well-studied flaviviruses, such as West Nile virus (WNV), Japanese encephalitis virus (JEV), dengue virus (DENV) and tick-borne encephalitis virus (TBEV), has facilitated ZIKV research and the development of vaccines^{29–31}. Experience gained over 2 decades of research on these flaviviruses guided vaccine design and suggested that protection against ZIKV can be achieved by antibodies that bind ENV²⁵. Currently, several vaccine candidates are under development (TABLE 1). These include DNA vaccines, purified inactivated viruses (PIVs), live attenuated viruses (LAVs), mRNA vaccines and viral vectored vaccines (modified vaccinia virus Ankara (MVA), measles virus (MV) and adenovirus (Ad) vectors). These efforts from multiple laboratories have led to

the unprecedented pace of ZIKV vaccine development.

In this Progress article, we discuss recent advances in animal models and the results from the first-in-human phase I clinical trials of ZIKV vaccine candidates. In addition, we address potential challenges for the late-stage development of ZIKV vaccine candidates.

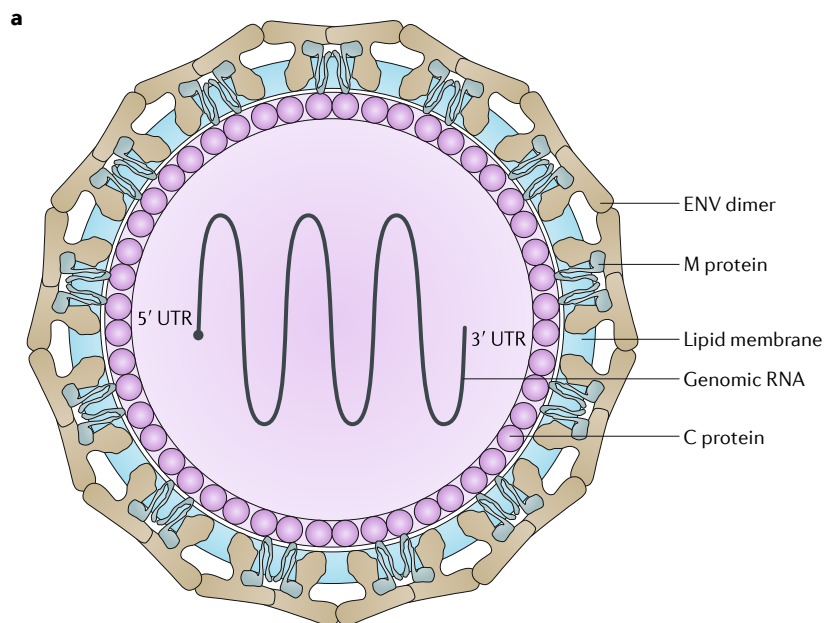
CZS and developmental problems

With the rapid spread of ZIKV through the Americas, many detrimental effects on fetuses and neonates were observed following infection in pregnant women^{32,33}. In Brazil, potential confounders, such as the insecticide pyriproxyfen and the tetanus, diphtheria and pertussis (Tdap) vaccine, did not correlate with the increased incidence of birth defects, whereas ZIKV infection confirmed by reverse transcription-PCR (RT-PCR) or antibody detection did correlate, suggesting that ZIKV was the causative agent of CZS^{8,34}. Furthermore, animal studies have shown that ZIKV infection affects fetal development^{22,35}. Moreover, severe developmental problems have been observed in follow-up studies of children born with microcephaly to women confirmed to have been infected with ZIKV during pregnancy³⁶. Developmental problems are also likely to occur in children infected during pregnancy who are born without microcephaly, although detailed studies have not yet been completed^{37–39}.

The confirmation of ZIKV as the causative agent for CZS, combined with the severe developmental problems of neonates born with CZS, emphasizes the urgent need for a preventive vaccine. Lessons learned from congenital rubella syndrome further support that an effective vaccine might drastically reduce the incidence of infection and prevent birth defects⁴⁰. However, until a vaccine is available, education and other preventive measures need to be implemented to prevent CZS⁴¹, including the development of antiviral medications^{42,43}.

Vaccines in clinical trials

Several vaccine candidates have undergone successful preclinical development. Neutralizing antibodies were induced for all vaccines tested in mice (TABLE 1). All vaccines were able to provide short-term protection



b

C	prM	ENV	NS1	NS2A	NS2B	NS3	NS4A	NS4B	NS5
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Fig. 1 | The Zika virus particle and genome. A single positive-strand RNA copy is packaged in an enveloped virus particle that is assembled by the structural proteins (part **a**). The non-structural proteins are involved in viral replication and immune evasion. Structural proteins capsid (C), precursor membrane (prM) and envelope (ENV) and non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) are flanked by 5' and 3' UTRs (black boxes) (part **b**). The primary target of neutralizing antibodies is the envelope, which together with the membrane protein is properly folded to display binding epitopes. M protein, mature membrane protein.

in mice against challenge with ZIKV. To date, DNA vaccines, mRNA vaccines, PIV vaccines and Ad-based vaccines have also conferred protection in monkeys. There has also been rapid advancement of these candidates into phase I clinical trials⁴⁴. To date, there are 13 open clinical trials testing a range of ZIKV vaccine concepts, including DNA vaccines, mRNA vaccines, PIV vaccines and viral-vector-based vaccines (TABLE 2).

DNA vaccines. DNA vaccines are plasmids encoding a transgene of interest under the control of a promoter. DNA vaccines can be developed and produced rapidly, and they can induce both humoral and cellular immune responses⁴⁵. The first clinical assessment of the safety and immunogenicity of a ZIKV DNA vaccine, expressing the ZIKV precursor membrane and envelope (prM-ENV) genes, was led by GeneOne Life Science and Inovio Pharmaceuticals (clinical trial [NCT02809443](#))⁴⁶. A total of 40 participants were divided equally between two groups and received either a 1 mg or 2 mg dose of the GLS-5700 DNA vaccine by intradermal injection with electroporation at baseline, with boosts at week 4 and week 12

(TABLE 2). The vaccine was well tolerated with no severe adverse reactions related to the vaccine. ZIKV-specific antibody levels at week 14 were assessed by enzyme-linked immunosorbent assay (ELISA) and showed 100% seroconversion for binding antibodies in both dose groups, with a geometric mean titre (GMT) of 1,642 (347–7,760) for the 1 mg dose group and a GMT of 2,871 (705–11,688) for the 2 mg dose group. These results indicated that the vaccine-induced antibody responses were dose-dependent. Neutralizing antibody titres above the detection limit were detected in 60% and 63% of the 1 mg and 2 mg dose groups, respectively. Passive transfer of week 14 serum into interferon (alpha and beta) receptor (*Ifnar*) knockout mice followed by a lethal challenge of ZIKV⁴⁷ resulted in 92% survival of mice, and this survival was independent of neutralizing antibody titre. This phase I clinical trial showed that the DNA vaccine was safe and well tolerated and that vaccine-induced antibodies were able to protect mice from a lethal challenge of ZIKV.

Clinical trials with DNA vaccines have also been conducted by the Vaccine Research Center (VRC) of the US National Institute of Allergy and Infectious Diseases

(NIAID). The first DNA vaccine was designed to express ZIKV prM-ENV with a JEV envelope stem region; the JEV envelope stem was added to increase subvirus particle formation (vaccine VRC5288 and study VRC319; clinical trial [NCT02840487](#)). The second DNA vaccine expressed wild-type ZIKV prM-ENV (vaccine VRC5283 and study VRC320; clinical trial [NCT02996461](#))⁴⁸. In study VRC319, participants received 4 mg doses at 0 and 8 weeks, 0 and 12 weeks, 0, 4 and 8 weeks, or 0, 4, and 20 weeks by intramuscular injection (TABLE 2). In VRC320, participants received 4 mg doses at 0, 4 and 8 weeks through intramuscular injection or split-dose needle and syringe or needle-free injection with the Stratis device⁴⁹. Only mild to moderate vaccine-associated adverse events were reported. Neutralizing antibody responses were highest at 4 weeks after final vaccination. In study VRC319, neutralizing antibody GMT titres were 120 (73–197), with detectable neutralizing antibodies in 89% of the participants. In study VRC320, neutralizing antibody responses were detected in 100% of participants of the split-dose, needle-free delivery group, with neutralizing antibody GMTs of 304 (215–430). Both trials showed that the DNA vaccines were well tolerated and immunogenic. The immunogenicity of the wild-type ZIKV prM-ENV DNA vaccine was higher than the immunogenicity observed with the DNA vaccine that included the JEV envelope stem. The VRC5283 vaccine recently advanced into a phase II efficacy trial in regions endemic for ZIKV transmission in South and Central America, the Caribbean and the United States ([NCT03110770](#)).

Purified inactivated virus vaccines.

Three ZIKV purified inactivated virus vaccine (ZPIV) phase I clinical trials ([NCT02963909](#), [NCT02952833](#) and [NCT02937233](#)) were reported as a combined interim analysis of the preliminary results for the identical group for each individual study⁵⁰. These studies (TABLE 2) were conducted at Walter Reed Army Institute of Research (WRAIR), Silver Spring, Maryland, United States; Saint Louis University, Saint Louis, Missouri, United States; and Beth Israel Deaconess Medical Center (BIDMC), Boston, Massachusetts, United States. ZPIV contains a chromatographic column-purified, formalin-inactivated ZIKV strain (PRVABC59) that was grown in Vero cells. The interim analysis included the group from each study that received the two-dose regimen of 5 µg aluminium hydroxide

Table 1 | Zika virus vaccines in preclinical and clinical development

Vaccine	Antigen	Induction of NAbs	Short-term protection in mice	Immunocompetence	Short-term protection in monkeys	Long-term protection in monkeys	Advanced to clinical trial	Refs
ZPIV	NA	Yes	Yes	Competent	100%	79%	Phase I	66–68
DNA	prM-ENV	Yes	Yes	Competent	100%	29%	Phase I/II	66–69
Ad	prM-ENV	Yes	Yes	Competent	100%	100%	Phase I	67,68,70
				Competent/deficient				
mRNA	prM-ENV	Yes	Yes	Competent/deficient	100%	NR	Phase I/II	53,54
				Competent				
MVA	NS1	Yes	Yes	Competent	NR	NR	Phase I	72
MV	prM-ENV	Yes	NR	NR	NR	NR	Phase I	59
ZIKV-LAV	NA	Yes	Yes	Competent	NR	NR	NA	73–75
				Deficient				
				Competent/deficient				

Ad, adenovirus-based vaccine; MV, measles virus-based vaccine; MVA, modified vaccinia virus Ankara; NA, not applicable; NAbs, neutralizing antibodies; NR, not reported or published; NS1, non-structural protein 1; prM-ENV, precursor membrane and envelope; ZIKV-LAV, live attenuated Zika virus vaccine; ZPIV, ZIKV purified inactivated virus vaccine.

adjuvanted ZPIV vaccine, administered intramuscularly on day 1 and day 29. Adverse events related to the vaccine were mild to moderate, with no serious adverse events reported. Neutralizing antibody titres were determined by microneutralization (MN50) assays at WRAIR for all three trials. A total of 95% of participants had peak neutralizing antibody titres with a GMT of 286 (170–481) after the second dose. Adoptive transfer studies with purified immunoglobulin G resulted in complete protection against ZIKV challenge in 41 out of 50 BALB/c mice and reduced viraemia in the mice that were infected. Results from these trials showed that the inactivated ZIKV vaccine was well tolerated and immunogenic and that vaccine-induced antibodies were protective in adoptive transfer studies in mice. The impact of different doses and immunization schedules will be determined in follow-up analyses of the completed studies.

Another phase I clinical trial with a ZIKV inactivated vaccine (TAK-426) led by Takeda Pharmaceutical Company Ltd is ongoing (NCT03343626). A dose escalation study in 240 healthy individuals will assess the safety and immunogenicity of this vaccine candidate.

mRNA vaccines. A newer class of vaccines, mRNA vaccines⁵¹, has also been developed against ZIKV. mRNA vaccines encode a gene of interest under the control of a promoter. As mRNA is directly translated into a protein after entering the cell cytoplasm, mRNA vaccines bypass the need to traverse the nuclear envelope to be expressed. This pathway could potentially lower the doses

needed for mRNA vaccines while retaining the immunogenicity observed with DNA vaccines. ZIKV prM-ENV mRNA was encapsulated in a lipid nanoparticle for delivery and stability⁵², and immunization of both mice and monkeys with this vaccine induced high levels of neutralizing antibodies that protected against ZIKV infection^{53,54}. In mouse pregnancy models, these mRNA vaccines prevented fetal demise, whereas fetal resorption was observed in nonimmunized infected pregnant mice. However, levels of ZIKV RNA could still be detected in the maternal spleen and brain as well as in the placenta and fetal head in immunized mice⁵⁵. As these results were obtained in an immunocompromised mouse model, which supports increased viral replication, it remains to be determined whether viral replication would be observed in immunocompetent animal models. The first-in-human, phase I/II clinical trial led by Moderna Therapeutics is currently ongoing to assess the safety and immunogenicity of escalating doses of prM-ENV mRNA (NCT03014089) (TABLE 1). mRNA vaccines could be cost-effective, as a large number of doses can be produced efficiently. However, it remains to be determined whether the promising preclinical data translate into humans. Additionally, stability of mRNA vaccines needs to be taken into consideration.

Viral-vector-based vaccines. Viral-vector-based vaccines are another promising approach to immunize against various pathogens. These vaccines induce high humoral and cellular immune responses that have been shown to lead to protection

against infection in preclinical models^{56,57}. An MV ZIKV vaccine developed by Themis Bioscience GmbH is currently in a phase I clinical trial. The MV Schwarz vaccine strain⁵⁸ was engineered to express ZIKV prM-ENV (MV-ZIKA) and was tested for immunogenicity in mice and monkeys⁵⁹. The ongoing clinical trial is assessing the safety and immunogenicity of a high or low dose when given as single or two-dose regimens (NCT02996890). An Ad serotype 26 (Ad26) ZIKV-based vaccine (Ad26.ZIKV.001) expressing the identical antigen as the rhesus Ad serotype 52 (RhAd52) preclinical vaccine candidate, sponsored by Janssen Vaccines and Prevention B.V., is currently also in a phase I clinical trial (NCT03356561). This study aims to test the safety and immunogenicity of two different doses of the vaccine in a double-blind, placebo-controlled clinical trial at two sites in Kansas and Massachusetts, United States. Experience that has already been gained with the Ad26 vaccine vector in clinical trials for other pathogens^{60–63} may facilitate the advancement of this vaccine candidate.

Viral-vector-based vaccines have shown promising results in preclinical models for ZIKV, and certain vectors benefit from prior experience in clinical trials for other pathogens^{51,64}. Development of additional vectors with minimal to no pre-existing immunity is also in progress⁶⁵.

Protection in preclinical models

At the height of the ZIKV epidemic in Brazil, multiple laboratories started to develop vaccine candidates and animal models to assess vaccine efficacy. For example, ZIKV infection in wild-type

Table 2 | Phase I clinical trial seroconversion rates, neutralizing antibody titres with respective assays and adoptive transfer results in mice

Vaccine	Dose	Schedule	NAb seroconversion	MN50 titre	RVP titre	Adoptive transfer in mice
ZPIV (BIDMC)	5 µg	Day 0 and 29, IM	10/10 (100%)	1,061.7 (425.8–2,489.2)	NA	Yes; 41/50 mice had undetectable viraemia
ZPIV (WRAIR)	5 µg	Day 0 and 29, IM	17/20 (85%)	100.8 (39.7–255.7)	NA	No
ZPIV (SLU)	5 µg	Day 0 and 29, IM	25/25 (100%)	345.6 (166.4–718.0)	NA	No
DNA (VRC5288)	4 mg	Weeks 0 and 8 by a single NS dose	12/20 (60%)	NA	67 (40–114)	No
DNA (VRC5288)	4 mg	Weeks 0 and 12 by a single NS dose	15/20 (75%)	NA	55 (39–78)	No
DNA (VRC5288)	4 mg	Weeks 0, 4 and 8 by a single NS dose	16/20 (80%)	NA	81 (51–127)	No
DNA (VRC5288)	4 mg	Weeks 0, 4 and 20 by a single NS dose	17/19 (89%)	NA	120 (73–197)	No
DNA (VRC5283)	4 mg	Weeks 0, 4 and 8 by a single NS dose	10/13 (77%)	NA	48 (28–83)	No
DNA (VRC5283)	4 mg	Weeks 0, 4 and 8 by a split NS dose	14/15 (93%)	NA	150 (99–226)	No
DNA (VRC5283)	4 mg	Weeks 0, 4 and 8 by a split needle-free dose	14/14 (100%)	NA	304 (215–430)	No
DNA (Inovio Pharmaceuticals)	1 mg	Weeks 0, 4 and 12 by injection and followed by electroporation	12/20 (60%)	1:18–1:317	NA	Yes; 92% survival against lethal challenge in <i>Ifnar</i> knockout mice
DNA (Inovio Pharmaceuticals)	2 mg	Weeks 0, 4 and 12 by injection and followed by electroporation	12/19 (63%)	1:18–1:317	NA	Yes; 92% survival against lethal challenge in <i>Ifnar</i> knockout mice

BIDMC, Beth Israel Deaconess Medical Center; IM, intramuscular; MN50, microneutralization; NA, not applicable; NAb, neutralizing antibody; NS, needle and syringe; RVP, reporter virus particle; SLU, Saint Louis University; VRC, Vaccine Research Center; WRAIR, Walter Reed Army Institute of Research; ZIKV, Zika virus; ZPIV, ZIKV purified inactivated virus vaccine.

BALB/c mice and rhesus monkeys largely recapitulated the magnitude and duration of ZIKV viraemia in humans, exhibiting 7 to 10 days of viraemia with minimal clinical symptoms. By contrast, ZIKV infection in immunodeficient mice, such as type I or I/II interferon (A129 or AG129)-knockout mice or signal transducer and activator of transcription 2 (*Stat2*)-knockout mice, were shown to exhibit prolonged viraemia and have been used to study neurological disease in adult and fetal mice.

The protective efficacy of a ZPIV and a DNA vaccine was first demonstrated in mice⁶⁶. Moreover, ZPIV, a DNA vaccine and a RhAd52-vector-based vaccine expressing a modified M-ENV ZIKV antigen were shown to block ZIKV infection in rhesus monkeys⁶⁷. Furthermore, the RhAd52-based vaccine was found to provide durable complete protection in rhesus monkeys against ZIKV a year after immunization with remarkably stable neutralizing antibody titres⁶⁸.

Studies from a number of groups have reported the protective efficacy of

inactivated virus vaccines, DNA vaccines, viral-vector-based vaccines and mRNA vaccines^{53–55,67,69–75} (TABLE 1). DNA vaccines expressing variations of the prM-ENV antigen were quickly developed and tested successfully for efficacy in both mice and monkeys⁶⁹. mRNA vaccines expressing wild-type or modified prM-ENV antigens, leading to the generation of subviral particles, were able to protect mice with a single dose as low as 10 µg (REF.⁵³) or 50 µg for monkeys⁵⁴. Several live attenuated vaccines have also been developed based on the yellow fever virus YF17D model or the JEV vaccine SA14-14-2 backbone or attenuated through systematic deletions in the 3' UTR region in the ZIKV genome^{73–75}. All live attenuated ZIKV vaccines have proved immunogenic and protective in mice and monkeys. Finally, MVA and MV vectors have been engineered to express the NS1 or prM-ENV proteins of ZIKV, respectively. Protection in preclinical models with these candidates has also been reported⁷².

The consistent finding from these studies is that protection against ZIKV

infection is predominantly antibody-mediated. Several assays are available to measure vaccine-induced antibodies. The observation that protection is antibody-mediated is concordant with the antibody-based protection observed for WNV, JEV and DENV^{76–78}. Data suggest that titres of neutralizing antibodies of ~100, as measured by MN50 assays, are protective against ZIKV⁶⁸. The plaque-reduction neutralization test (PRNT) and a ZIKV reporter viral particle (RVP) assay are other methods that are commonly used to measure neutralizing antibodies^{54,69}. Titres between the assays vary, with the RVP assay reportedly being more sensitive and yielding approximately tenfold higher titres⁶⁹. CD4⁺ and CD8⁺ T cell responses may not be required if levels of neutralizing antibodies exceed this protective threshold⁶⁶. However, CD8⁺ T cells induced by ZIKV or DENV infection have been shown to be able to reduce ZIKV viral burden in mice^{79,80}, and further research is needed to determine the impact on short-term and long-term protection.

Protection in pregnancy

ZIKV infection in pregnant women is distinct from infection in non-pregnant women and men^{81–83}. For example, more-extended periods of viraemia have been observed in pregnant women and fetuses⁸⁴, and ZIKV RNA was detected throughout the mother and the fetus in animal models^{85–87}. Immune responses of pregnant monkeys and mice infected with ZIKV appear similar to those of non-pregnant infected animals^{86,88}. The ability of ZIKV to cross the fetal–placental barrier and cause damage to the fetus emphasizes the need for a vaccine and highlights the primary goal of vaccination, that is, to prevent CZS. Therefore, it will be important to measure the efficacy of vaccines to prevent fetal malformations. There are a number of aspects to this research that will need to be considered. For example, is sterilizing immunity required for efficacy or is reducing viral replication sufficient? Additionally, do immune correlates established in non-pregnant animals translate to pregnant animals?

The development of immunodeficient mouse pregnancy models for ZIKV infection has led to important advances owing to the increased viral replication and impact on the central nervous system^{88,89}, and the first prevention of fetal malformations and demise was observed using mRNA and live attenuated ZIKV vaccines^{55,75,90}. However, even though a statistically significant impact on fetal demise was observed, the protection was not sterilizing. ZIKV RNA was still detected in the maternal brain and spleen as well as in the placenta and fetal heads in the majority of animals. Interestingly, pups born to mothers vaccinated with a LAV were protected against lethal intracranial challenge with ZIKV⁷⁵. Further research is needed to assess the impact of low-level viraemia in fetal and maternal compartments. In addition, with the increasing knowledge on the long-term impact on children born without microcephaly but with confirmed ZIKV infection during pregnancy in humans, it is too early to tell if sterilizing immunity is required to prevent all long-term sequelae⁹¹. As a result of the differences between rodents and primates⁹², a monkey pregnancy model would be preferred⁹³, and initial progress has been reported^{86,94}. In both rhesus and pigtail monkeys, efficient transmission of ZIKV from mother to child during pregnancy has been observed. ZIKV viraemia could be detected in various anatomical compartments in the mothers and fetuses, including the brain and placenta^{86,94}. In addition, anomalies to the

brains of the fetuses were detected, ranging from white matter hypoplasia to pathology to the optic nerve and eyes. Similarly, as seen in humans, detrimental effects were more evident when infection occurred in early pregnancy^{95,96}.

It is important to consider that the primary goal of a ZIKV vaccine is to prevent CZS. To realize this goal, vaccines considered for clinical development should ideally be assessed for protective efficacy in preclinical pregnancy models.

Challenges for clinical trials

With the current reduction in ZIKV transmission^{97,98}, a phase III clinical efficacy trial could prove challenging to execute. Further development of animal pregnancy models that can effectively assess protective efficacy against CZS may therefore be important. In addition, ongoing discussions on alternative paths to licensure are being explored. Human challenge clinical trials have been conducted for other diseases, such as typhoid fever⁹⁹ and influenza¹⁰⁰; however, human challenge studies for ZIKV have raised ethical discussions¹⁰¹. Invocation of the FDA Animal Efficacy Rule (also known as the Animal Rule) could also be considered if strong correlations of protection in preclinical models are deemed likely to translate to humans, as outlined below¹⁰². Recently, a vaccine against anthrax was the first vaccine that was approved based on the Animal Rule^{102,103}. According to the FDA, the Animal Rule can be pursued only if human efficacy studies cannot be performed, for example, because the conduct of such trials is unethical or because field trials after an accidental or deliberate exposure are not feasible¹⁰⁴. For the Animal Rule to apply, the results of well-controlled animal studies need to demonstrate that clinical benefits in humans would likely be observed with the same study products. For vaccines, a clear immune correlate would facilitate the use of the Animal Rule. For ZIKV, the correlate of protection in nonhuman primates appears to be neutralizing antibody titres⁶⁸.

Conclusions and perspectives

In summary, several ZIKV vaccine candidates have been shown to be safe, well tolerated and immunogenic in humans. In the majority of trial participants, neutralizing antibody titres were induced that were comparable to titres shown to be protective in preclinical models. In addition, development of animal models to test vaccine efficacy in the prevention of CZS is underway.

The remarkable speed with which ZIKV vaccines have been developed has led to a rapid increase in our understanding of this virus. Nevertheless, important challenges remain for conducting clinical efficacy trials and vaccine licensure. Because of CZS and the potential lifelong impact on children born to mothers infected with ZIKV, a vaccine is urgently needed. The rubella vaccine highlights that prevention of congenital defects can be achieved, and similar success may be possible for ZIKV.

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Author contributions

P.A., K.E.S. and D.H.B. researched data for the article, made substantial contributions to discussions of the content, wrote the article and reviewed and edited the manuscript before submission.

Competing interests statement

P.A. and D.H.B. are co-inventors on ZIKV vaccine patents that have been licensed to Janssen Vaccines & Prevention B.V.

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