

5-2021

Efficacy of vaccine candidates against Zika infection and Congenital Zika Syndrome: A systematic review and meta-analysis

Hannah Lund
University of Nebraska Medical Center

Follow this and additional works at: https://digitalcommons.unmc.edu/coph_slce



Part of the [Public Health Commons](#)

Recommended Citation

Lund, Hannah, "Efficacy of vaccine candidates against Zika infection and Congenital Zika Syndrome: A systematic review and meta-analysis" (2021). *Capstone Experience*. 139.
https://digitalcommons.unmc.edu/coph_slce/139

This Capstone Experience is brought to you for free and open access by the Master of Public Health at DigitalCommons@UNMC. It has been accepted for inclusion in Capstone Experience by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.

Efficacy of vaccine candidates against Zika infection and Congenital Zika Syndrome: A systematic review and meta-analysis

Hannah Lund, Epidemiology

Committee

Abraham D. Mengist, PhD
Shinobu Watanabe-Galloway, PhD
David Brett-Major, MD MPH

Abstract

There have been previous reviews looking into the efficacy of vaccine candidates against Zika infection in non-humans primates, but there hasn't been a review looking into the efficacy against Congenital Zika Syndrome (CZS). The aim of this project was to systematically review literature on efficacy of vaccine candidates against Zika infection and CZS. A protocol was developed following PRISMA guidelines. English articles published since 2015 were included. Clinical trials (CCTs) that compared the efficacy of four Zika virus vaccine candidates' (PIV, DNA, mRNA, and Adenovirus) against Zika infection and CZS in human and non-human primate models were included. Grey literature and studies with mice models were excluded. Literature was searched from PubMed, Scopus, CINAHL and Cochrane Library and screened against predetermined inclusion and exclusion criteria. Bias and quality of the studies was assessed using the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies. Efficacy of the vaccine candidates was evaluated using two outcomes: protection against Zika infection and whether CZS occurred. Studies were combined using a meta-analysis technique to determine the summary estimates of the efficacy of the vaccine candidates against Zika infection. All seven studies showed that the four vaccine types were protective against Zika infection, and one study showed that a DNA vaccine was protective against CZS. The meta-analysis found that the summary risk of Zika infection was 0.08 (0.01, 0.15) in vaccinated nonhuman primates versus unvaccinated. The development of a vaccine against Zika infection has progressed quickly into clinical trials, but authorization of a vaccine could falter because efficacy field trials are not currently possible. There still needs to be more research into the disease mechanism of CZS before more vaccine efficacy studies occur.

TABLE OF CONTENTS

1. Introduction
 - 1.1. What is Zika?
 - 1.2. Clinical Features
 - 1.3. Burden of Zika
 - 1.4. Zika Vaccine Candidates
 - 1.5. Knowledge Gap and Rationale
2. Methods
 - 2.1. Eligibility Criteria
 - 2.2. Outcomes
 - 2.3. Literature Search and Study Selection
 - 2.4. Data Extraction
 - 2.5. Quality and Bias Assessment
 - 2.6. Meta-analysis
3. Results
 - 3.1. Search Results and Selection Process
 - 3.2. Description of Studies
 - 3.3. Study Findings
 - 3.4. Meta-analysis and Publication Bias Results
 - 3.5. Quality and Bias Assessment Results
4. Discussion
 - 4.1. Summary and Public Health Implications
 - 4.2. Strengths and Limitations
 - 4.3. Challenges and Approaches to Future Research
 - 4.4. Conclusion

Bibliography

Appendix A

Raw Data

Biography & CV

1. Introduction

1.1 What is Zika?

In 2016, the World Health Organization declared the Zika virus (ZIKV) to be a Public Health Emergency of International Concern.¹ Although Zika has been known since the mid 20th century, it was not until 2015 that it began to affect the western hemisphere. Zika is a single strand RNA virus in the flavivirus family along with Dengue, West Nile, and Yellow Fever.² The virus spread by the vectors, *Aedes aegypti* and *Aedes albopictus*. The virus can also be sexually transmitted. The virus can remain in the male urogenital tract for 90 days to 9 months post-infection.¹

1.2 Clinical Features

The majority of infections are asymptomatic or have mild symptoms including fever, rash, muscle, and joint pain.³ There has been evidence of Guillain-Barre syndrome being associated with Zika infection in adults.⁴ When a pregnant woman becomes infected with ZIKA, it can cause the fetus to be born with CZS or even result in preterm birth or miscarriage.³

There are several clinical features of CZS. First, CZS is cranial morphology with evidence of fetal brain disruption sequence characterized by severe microcephaly and severe neurological impairment.⁵ Another clinical feature of CZS are brain anomalies. Those seen in infants affected by ZIKV were similar to another congenital disorder known as congenital cytomegalovirus (CMV). However, there were marked differences between the two, specifically in the location of calcifications. In CZS they are seen more in the subcortical region and in the periventricular in CMV. In one study, 42 pregnant women suspected of having Zika had fetal imaging done and found either calcifications or other central nervous system abnormalities.⁵ These abnormalities are likely due to the way ZIKV targets neural progenitors. There are often ocular abnormalities seen in those affected by CZS. One study found that infection in the first trimester significantly

correlated with ocular abnormalities.⁵ Finally, CZS is associated with congenital contractures including clubfoot and arthrogryposis. The mechanism through which congenital contractures occurs is still unknown, but it is thought to be due to ZIKV since it is not seen in other infants with faciobrachial dystonic seizures (FBDS) but has occurred with intrauterine infections.⁵

1.3 Burden of Zika

From 2015 to 2018, there were 583,451 suspected cases and 223,477 confirmed cases of ZIKV throughout North, Latin, and South America and Caribbean.⁶ In addition to the ZIKV infection, there were a total of 3,720 confirmed cases of CZS, with an unknown number of suspected cases.⁶ Several studies have been done looking at the aftermath of CZS. One study by Franca and others collected data on 1,500 live born babies with microcephaly in Brazil.⁷ They were able to categorize them based on the probability of the microcephaly being a result of CZS. They found 76 definite cases, 54 highly probably cases, 181 moderately probable cases, 291 slightly probably cases, and had 899 discarded cases, cases that did not meet the clinical criteria for microcephaly.⁷ They found that the mortality rate of the discarded cases was 14 per 1,000 and was 51 per 1,000 for the probable and definite cases.⁷

Another study done in Brazil looked at outcomes associated with microcephaly. The most common were irritability (85%), pyramidal syndromes (56%), and epileptic seizures (50%).⁸ With pyramidal syndromes, the most notable symptoms is spasticity, which is a muscle control disorder that is characterized by stiff muscles and hyperactive reflexes. They also found that 97% had brain calcifications.⁸ Children with microcephaly require more time and care than children without the condition. A qualitative study examined the effects on parents with children who have microcephaly. Parents explained that they were unsure of how to properly care for their child with microcephaly and that they would benefit from a workshop teaching them skills. They

also mentioned that some nurses were not comfortable vaccinating the child upon bringing in their child for vaccinations.⁹ This study highlighted the need for both a vaccine and expanded health services. Without a vaccine, more parents in these areas where Zika is endemic will live in fear that their child will have CZS and that they may not be able to care for their child to their best abilities.

1.4 Zika Vaccine Candidates

As of May 2020, there are 30 different vaccine candidates in Phase I in the preclinical phase, with half still in the research phase.¹⁰ The vaccine candidates are different types, including purified inactivated virus (PIV), DNA, Adenovirus (Ad), and mRNA.¹ A review study published in 2018 summarized the vaccines that are currently in clinical trials.¹ Protection against ZIKV was achieved via antibodies that bind the envelope of the virus (ENV). This has prompted vaccine developers to focus on the ENV as the antigen of interest. Several of the vaccine types currently in Phase 1 of clinical trials (PIV, DNA, and Ad) had 100% short-term protection but with varying long-term protection in monkeys.¹ The mRNA vaccines had 100% short-term protection, but the study claimed that their long-term protection is still unknown in mice and nonhuman primates.¹ All four of these vaccine types have been able to induce neutralizing antibodies in mice and nonhuman primate studies.^{1,11}

1.5 Knowledge Gap and Rationale

Zika virus vaccine candidates examined so far showed promising levels of efficacy in mice and non-human primate models.¹² PIV, DNA, and Ad vaccines were capable of protecting from Zika infection in rhesus monkeys.¹ As of 2020, thirteen vaccines have moved into Phase 1 of clinical trials, and one vaccine candidate has moved into Phase 2.¹² The purpose of this review was to summarize literature that compared the effectiveness of vaccines against Zika infection

and CZS based on non-human primate models instead of mice models to provide insight into which vaccine may be the best choice. Mice models were excluded because they do have different fetal development and placental structure than humans.¹⁰ Nonhuman primates can also give more accurate insight into the dosage and administration of the vaccine candidates than mice models.¹⁰

2. Methods

2.1 Eligibility Criteria

Randomized controlled trials (RCTs) or Controlled Clinical Trials (CCTs) that compared Zika virus vaccine candidates' (PIV, DNA, mRNA, and Adenovirus) efficacy against CZS in human and non-human primate trials were included. Articles published in English since 2015 were included. Articles were excluded based on the following criteria: grey or non-formally published literature, articles not relevant to the topic, letters, abstracts only, reviews, articles published in other languages, articles published prior to 2015, and mice models.

2.2 Outcomes

The primary outcome was whether there was protection against Zika infection. There was protection if vaccinated subjects had no detectable viremia following the Zika challenge. The secondary outcome was whether CZS occurs. Presence of CZS would be determined by the presence of congenital deformities such as microcephaly.

2.3 Literature search and study selection

The following terms were used in searches of PubMed, CINAHL, Cochrane Library, and Scopus databases: (“Zika Virus” OR “Congenital Zika Syndrome” OR Zika) AND (Vaccine OR vaccination OR immunization). Additionally, article bibliographies were examined for potential studies. After transferring the articles from the databases to EndNote, duplicates were removed

and then exported into Excel. Then, titles and abstracts were screened based on the inclusion and exclusion criteria. Articles that were approved for full-text review were further screened based on exclusion/inclusion criteria and the availability of full-text data. Articles were included if they addressed either the primary outcome (protection against Zika infection) or the secondary outcome (protection against CZS). The article searches and screening processes were conducted by a single author.

2.4 Data Extraction

Data was extracted from studies that met the predetermined eligibility criteria. The following data was extracted: Author, study design, sample size, subjects in the study, vaccine type, vaccination procedure, dosage, whether there was protection against Zika infection and/or CZS, and row data from tables and figures that was used to calculate relative risk.

2.5 Quality and Bias Assessment

The Effective Public Health Practice Project (EPHPP) Quality Assessment tool was used to assess both the quality of the studies, as well as any bias within the studies.¹³ The tool looked at six different domains: selection bias, study design, confounders, blinding, data collection methods, and withdrawals or drop-outs.¹³ The purpose was to assist with the synthesis and interpretation of the review's results. The tool provides a guide for rating the individual domains and the overall rating of the studies. Each component of the assessment tool given an individual rating of 1 for "Strong", 2 for "Moderate", or 3 for "Weak." Then a final score of the quality and bias for each article was determined based on the score for each components of the tool. A study was determined as strong quality if there were no weak ratings for all the six components, If there were one weak ratings, the study was considered as a moderate quality. If there were two or more weak ratings, the study was rated as weak quality.

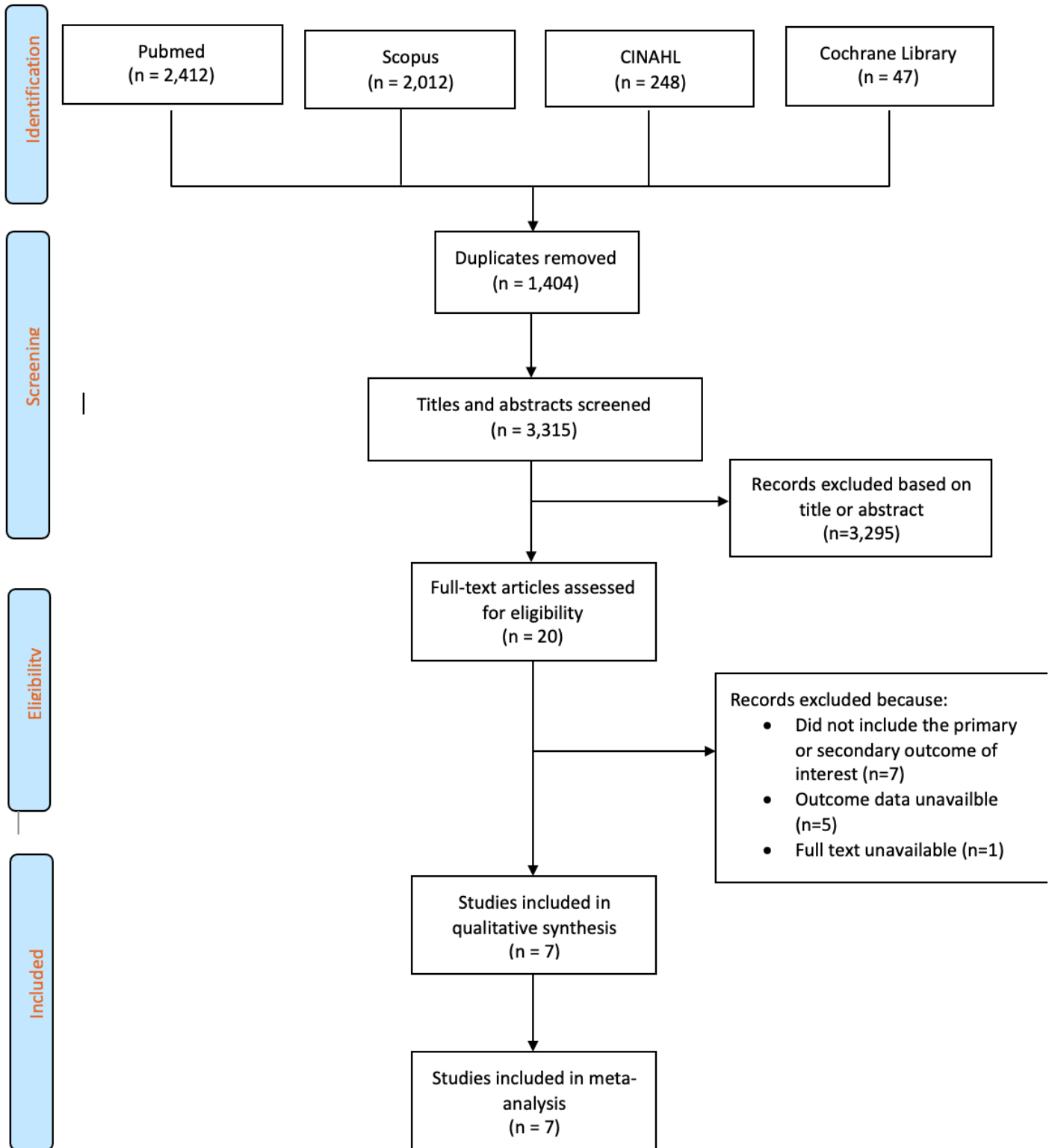
2.6 Meta-Analysis

A random-effects model using the DerSimonian and Laird method was used to combine the estimate the risk ratios of protection against Zika infection post vaccination from the individual studies.¹⁴ We did post-hoc heterogeneity analysis and an evaluation of publication bias. A funnel plot was produced to assess publication bias. The heterogeneity among the studies was determined using the the inconsistency index I^2 , and statistical significance was assessed using the cocrane Chi-square test. A funnel plot was used to evaluate publication bias and statistical significance was evaluated using Egger's regression test.

3. Results

3.1 Search Results and Selection Process

A total of 2,412 citations were found from PubMed, 2,012 from SCOPUS, 248 from CINAHL, and 47 from Cochrane Library. After removing the duplicates, 3,315 unique citations remained. Of the 3,315 articles, 3,295 articles were excluded due to either the title or the abstract, not fitting eligibility criteria. Twenty articles were screened in full text, of which thirteen were excluded due to incomplete data, missing full text, or failure to report on the outcome of interest. Seven articles were selected to be included in the systematic review.



3.2 Description of studies

Four studies looked at PIV vaccines (Abbink, 2016; Dowd, 2016; Lecouturier, 2020; Young, 2020), three studies tested DNA vaccines (Abbink, 2016; Luisi, 2020; Van Rompay, 2019), and only one study each looked at Ad vaccines (Abbink, 2016) and mRNA vaccines (Pardi, 2017). The studies used Zika strain PRVABC59 or strain ZIKV-BR2015 as the challenge strains. All seven studies used nonhuman primates, either rhesus macaques and cynomolgus macaques.

Table 1. Overview of Included Studies

Author/Year	Vaccine Type	Challenge zika Strain	Sample Size	Were vaccinated participants protected from ZIKV challenge?	Relative Risk (95% CI)	Were vaccinated participants protected from CZS?	Relative Risk (CI) ²
Abbink, 2016	DNA, PIV, Adeno	ZIKV-BR2015, PRVABC59	32	Yes	0.0210 (0.0013-0.3268)	NA	NA
Dowd, 2016	PIV	PRVABC59	30	Yes	0.0417 (0.0061-0.2838)	NA	NA
Lecouturier, 2020	PIV	PRVABC59	30	Yes	0.0283 (0.0018-0.4402)	NA	NA
Luisi, 2020	DNA, mRNA	PRVABC59	32	Yes	0.0833 (0.0221-0.3141)	NA	NA
Pardi, 2017	mRNA	PRVABC59	11	Yes	0.0897 (0.0063-1.2853)	NA	NA
Van Rompay, 2019	DNA	PRVABC59, ZIKV-BR2015	30	Yes	0.0274 (0.0018-0.4227)	Yes	0.0374 (0.0025-0.5708)
Young, 2020	PIV	PRVABC59	35	Yes	0.2333 (0.1220-0.4464)	NA	NA

3.3 Study Findings

The primary outcome for this review was protection against Zika challenge post-vaccination. All seven studies evaluated vaccine protection against Zika infection.¹⁵⁻²¹ The study done by Abbink, et al. investigated the protective efficacy of three vaccine types: DNA, PIV, and Ad. All three had the same dosage (5mg) with 8 rhesus macaques per group.¹⁶ The DNA and PIV vaccines were administered to the macaques on weeks 0 and 4. The Ad and placebo vaccines were administered on week 0.¹⁵

The PIV vaccine group and 8 controls were challenged with PRVABC59 or ZIKV-BR2015 (4/group) to assess vaccine protection.¹⁵ All 8 in the PIV group were protected against both challenge strains. All the controls experienced increased viral load, with no difference between the two strains.¹⁵ The DNA and Ad vaccine groups were challenged with ZIKV-BR2015.¹⁶ Neutralizing antibodies were induced in both vaccine groups, although it occurred on week 2 for the Ad group versus week 6 in the DNA group. Both were determined to be protective against Zika challenge.¹⁵

The study carried out by Dowd et. al in 2016 compared the efficacy of two different DNA vaccines: VRC5288 and VRC5283. There were two different dosages, with 6 rhesus macaques per group.¹⁶ The first was 4 mg on weeks 4 and 0. The second was 1 mg on weeks 0 and 4. There was an additional group of 6 that received a placebo.¹⁶ They were challenged with PRVABC59.⁶ All animals that received two doses of 4mg of VRC5283, 1mg of VRC5283, or 4mg of VRC5288 were protected from Zika challenge.¹⁶ One animal that received two 4 mg doses of VRC5288 had detectable viral load and was considered not protected.¹⁶ The viral load was significantly lower than that seen in the control animals. In total, twenty-three of the twenty-four that received either of the two vaccines were protected.¹⁶

The study done by Lecouturier et. al was the only study to use cynomolgus macaques rather than rhesus macaques. It tested the effectiveness of different dosages of their second-generation PIV (SP-PIV) vaccine compared to the first-generation of the PIV vaccine and a placebo.¹⁷ There were 5 groups with 6 participants each. The first group was the 1st gen PIV vaccine at 1mg, SP-PIV at 1mg, SP-PIV at 2mg, SP-PIV at 4mg, and then the control group.¹⁷ Vaccines were administered on weeks 0 and 4 for all groups. Those that received 1mg of SP-PIV also received a booster after 6 months.¹⁷ This group was not challenged. All 18 cynomolgus macaques that were vaccinated with either the 1st generation PIV or SP-PIV and then challenged PRVABC59 were all protected.¹⁷

The study done by Luisi et. al looked at the protective efficacy of a DNA self-amplifying messenger RNA, and a self-amplifying messenger DNA vaccine. There were four groups, with 8 rhesus macaques per group: a) 75 microgram DNA, b) 75 microgram SAM-RNA, c) 4mg SAM-DNA, and d) control group.¹⁸ Group A was vaccinated on weeks 0 and 5, group B on weeks 0 and 6, group C on weeks 0 and 7, and group D on weeks 0 and 4.¹⁸ The animals were challenged with PRVABC59 and then tested neutralizing antibodies. All of the vaccinated animals were protected by their respective vaccines.¹⁸

The study by Pardi, et. al was investigating the protection of an mRNA vaccine against Zika infection using rhesus macaques.¹⁹ The goal was to determine if a low dosage would still be effective against Zika infection.²¹⁹ This study had three dosages. Group 1 vaccinated 1 participant with 600 micrograms of mRNA vaccine; Group 2 vaccinated 1 participant with 200 micrograms of mRNA vaccine; and Group 3 vaccinated 3 participants with 50 micrograms of mRNA vaccine.¹⁹ Group 4 served as the control group, with 6 participants. All of the groups

were given a single dose at week 0 and then challenged with PRVABC59.¹⁹ All 5 of the vaccinated primates were protected against the Zika challenge.¹⁹

The study by Van Rompay, et.al was the only study to look at both protection against Zika infection and CZS.²⁰ The study focused on a DNA vaccine (VRC5283). Eighteen rhesus macaques were vaccinated with two 1 mg doses at weeks 0 and 4.²⁰ Once immunized, the participants were bred. Only thirteen of the treatment group conceived. The groups and controls were exposed to PRVABC59 twice and ZIKV-BR2015 once during their pregnancy.²⁰ The authors tested for neutralizing antibodies in the mother and determined that there was protection against the Zika challenge.²⁰

The study carried out by Young et. al in 2020 compared the efficacy of different dosages of a PIV vaccine.²¹ There were six groups, with 6 rhesus macaques per group. Treatment groups were 2 doses of 1) 0.016 micrograms, 2) 0.08 micrograms, 3) 0.4 micrograms, 4) 2 micrograms, 5) 10 micrograms, and 6) the control group.²¹ Animals were immunized at weeks 0 and 4 and then challenged on day 71 with PRVABC59.²¹ All the animals in dosage groups 3, 4, and 5 were protected from Zika infection. Only three animals from group 2 and two animals in group 1 were protected. All of the controls were infected with Zika.²¹

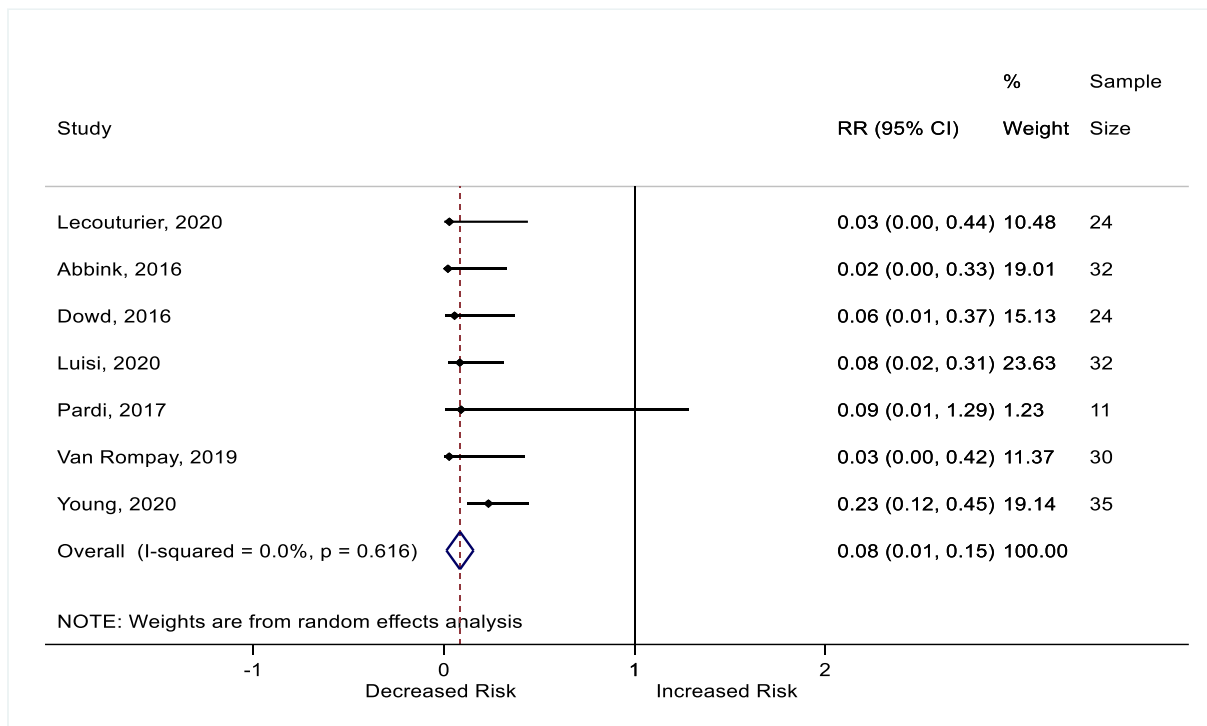
The secondary outcome for this review was the presence of CZS post-vaccination. Only one study tested whether their vaccine of interest protected fetuses from CZS.²⁰ While eighteen macaques were immunized, only thirteen became pregnant.²⁰ Only 10 controls were used, with two losing the fetus due to complications unrelated to Zika infection.²⁰ In order to more accurately model exposure in the wild, the animals were challenged with Zika virus three times, twice with PRVABC59 and once with ZIKV-BR2015.²⁰ The fetus was tested to determine if there were any congenital disabilities such as microcephaly as well as for Zika RNA.²⁰ They

determined that there were no fetal defects present, there was no Zika RNA detected, and that all thirteen fetuses were protected from CZS.²⁰

3.4 Meta-Analysis and Publication Bias Results

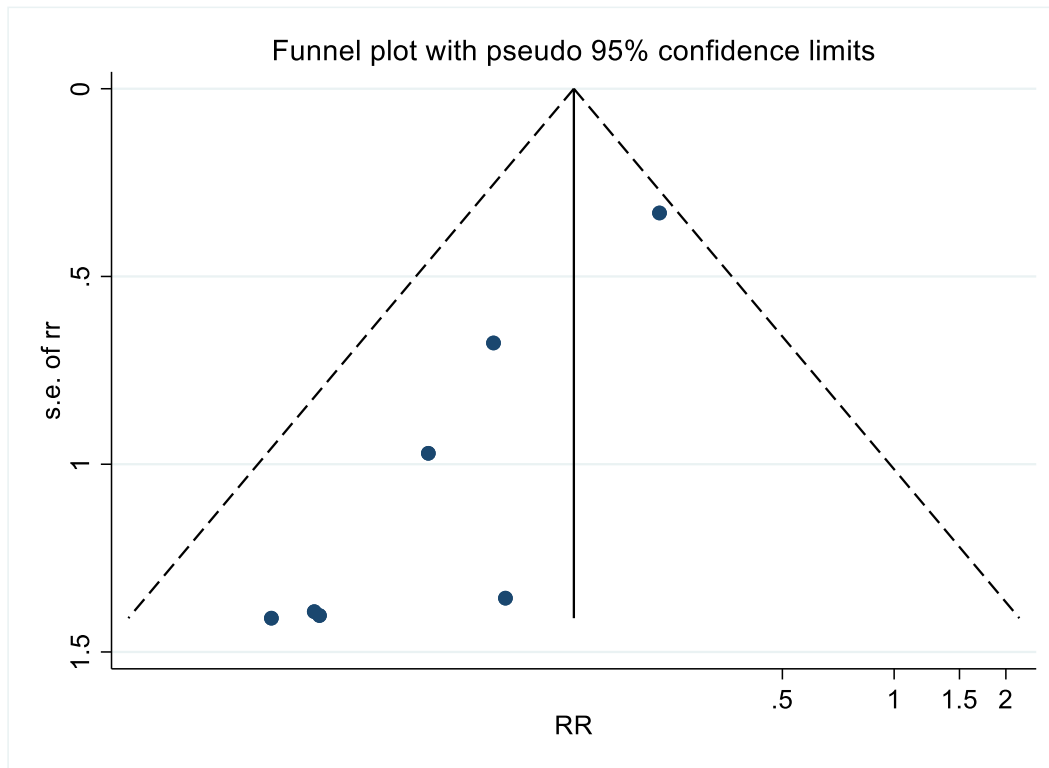
There was zero-heterogeneity among the studies included in this review ($I^2=0$, $p=0.616$). The summary relative risk estimate of Zika infection in those vaccinated was 0.08 (0.01, 0.15) compared to those who were unvaccinated. This value was significant.

Figure 1. Forest plot



The plot shown below shows six of the seven studies lying to the left of the center line, suggesting there is publication bias. The Egger's test for the asymmetry of the funnel plot was also significant (bias= -0.202, $p=0.004$).

Figure 2. Funnel Plot



3.5 Quality and Bias Assessment Results

The quality and bias of the included studies were evaluated using the EPHPP Quality Assessment tool. A summary of the results for each domain is shown in Table 2 and Appendix A Table 1. All the studies were rated as “moderate” or “strong” quality in selecting the study participants, study design, confounders, and data collection methods (Table 2). None of the studies stated that they were randomized except for the one done by Abbink and others in 2016. Abbink did not state the method of randomization. Similarly, only three studies- Lecouturier, 2020; Luisi, 2020; and Pardi, 2017- explicitly stated that the outcome assessors were blinded to the vaccination status of the study participants. For the others, it was unclear if they were blinded or not since it was not mentioned in their methods. Since the study participants were non-human

primates, it was not necessary for them to be blinded. Overall, the quality of the studies was moderate, with low bias.

Table 2. Quality and Bias Assessment of Included Articles

Author, Year	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawal & Dropouts	Final Rating
Abbink, 2016	2	1	1	1	1	2	1
Dowd, 2016	2	1	1	1	1	1	2
Lecouturier, 2020	2	1	1	2	1	1	2
Luisi, 2020	2	1	1	2	1	1	2
Pardi, 2017	2	1	1	2	1	1	2
Van Rompay, 2019	2	1	1	1	1	1	1
Young, 2020	2	1	1	2	1	1	1
Key							
1=Strong							
2=Moderate							
3=Weak							

4. Discussion

4.1 Summary and Public Health Implications

This review included 7 controlled trials in non-human primates studying the efficacy of four different vaccine types against Zika infection. All seven trials had different vaccines dosages and dosage schedules but were all able to protect non-human primates against Zika. The study by VanRompay found that a DNA vaccine provided protection against CZS, with a relative

risk of 0.04 (0.03, 0.57).²⁰ Compared to the previous review on Zika vaccine candidates, this review found additional studies showing vaccine candidate efficacy against Zika infection. This review also added to the relatively sparse literature on vaccine candidate efficacy against CZS. It also provided additional evidence with a meta-analysis. Based on a combined analysis of the seven studies using a meta-analysis technique, the summary relative risk of Zika infection in those vaccinated was 0.08 (0.01, 0.15) compared to those who were unvaccinated. This review can aid in policy surrounding research into a vaccine candidate effective against Zika infection and CZS. The path to authorization of a vaccine is still uncertain, but needs to occur before the next outbreak occurs. This review could serve as evidence needed for different paths to authorization of a vaccine.

4.2 Strengths and Limitations

There were some strengths and limitations to this review. One strength to this review was the broad search terms used. These yielded a high number of articles, and likely captured the majority of the articles related to this topic. Another strength was that the meta-analysis found that the pooled risk of Zika infection in the vaccinated versus unvaccinated was 0.08.

One limitation was that there were a large number of studies and only a single reviewer. Studies that fit the criteria of the review were likely missed during the title and abstract screening process. Another limitation was the presence of publication bias. Those intending to produce a vaccine likely will not publish a study if it will make their product look bad. And a third limitation is that there are still few studies assessing the efficacy of vaccines against CZS in non-human primates. One explanation for the lack of vaccine candidate efficacy studies against CZS using nonhuman primates is that there is no consensus about how Zika causes CZS.²² However,

there are numerous studies focusing on nonhuman primates as models for CZS and attempting to determine specifics behind the disease mechanism.

4.3 Challenges and Approaches to Future Research

Currently, several PIV, DNA, mRNA, and Ad vaccines that have proceeded human trials, either Phase 1 or 2, studying safety, tolerability, and immunogenicity. The next step would be Phase 3 field efficacy trials, which would not be possible with the low number of cases right now.²³ These field efficacy trials would include randomized trials in different areas with disease transmission, which allow an estimate of vaccine efficacy.²³ There are two possible approaches to solving the problem of low incidence of cases.

The first option is the “Accelerated” pathway. Usually this applies to serious or life-threatening illnesses, which means Zika infection on its own would not qualify.²⁴ However, with the serious complications associated with CZS, it would be possible to pursue the accelerated pathway for Zika vaccines.²⁴ To qualify, there would need to be a “reasonably likely” surrogate endpoint to predict clinical benefit.²⁴ Under the traditional pathway, the clinical endpoint would be protection against Zika infection, but under the animal rule, antibody titers could serve as a surrogate endpoint.²⁴

The second is utilizing the “Animal Rule”. This is a rule that is set by the FDA to authorize medicines or vaccines using animal trial data.²³ Similar to the accelerated pathway, there would need to be a strong immune marker to bridge the animal and human data, such as neutralizing antibodies.²⁴ In order to use the animal rule, there would need to be well designed animal studies using an appropriate animal model. As mentioned earlier, nonhuman primate models would be better than mice because nonhuman primates have placental structure and immune response that is similar to humans.¹⁰ The nonhuman primate studies included in this

review could provide the evidence to determine what would be an appropriate antibody titer. However, currently Zika does not qualify for the animal rule while the accelerated pathway is still an option.²⁴

The third, and least likely, option is Controlled Human Infection Models (CHIM).²⁴ In 2016, NIAID and Walter Reed Army Institute of Research determined that Zika CHIM were not ethical.²³ However, this was during the epidemic and since then, a CHIM may be ethically justifiable since the traditional pathway may not be possible. CHIMs would require methods to prevent the spread of Zika to non-participants, which would include excluding females of a reproductive age and the mandatory usage of highly effective contraception.²³ CHIMs would only be applicable to a vaccine against Zika infection, and would not be possible to use to test efficacy of a vaccine that prevents CZS. This would likely be a last resort if the Accelerated pathway or Animal Rule cannot be used or applied.

4.4 Conclusion

Due to the unpredictability of the next outbreak of Zika, the development of a safe and effective vaccine that can protect against Zika infection and CZS remains important, especially in endemic areas where there is still a risk of CZS. This review found that the vaccine candidates were effective against Zika infection in nonhuman primates, with a relative risk of 0.08 (0.01, 0.15). Moving forward, there should be research into the disease mechanism of CZS using non-human primates. Before there is confirmation, or at least consensus, about how CZS occurs, there likely will not be more progress into a vaccine that protects against CZS. On the other hand, vaccine candidates against Zika infection are progressing quickly into clinical trials. The next step would be deciding how to authorize a Zika vaccine without field efficacy trials before the next outbreak.

Bibliography

1. Abbink, Peter, et al. "Zika Virus Vaccines." *Nature Reviews. Microbiology*, U.S. National Library of Medicine, Oct. 2018, www.ncbi.nlm.nih.gov/pmc/articles/PMC6162149/.
2. Barbi L; Coelho AVC; Alencar LCA; Crovella. "Prevalence of Guillain-Barré Syndrome among Zika Virus Infected Cases: a Systematic Review and Meta-Analysis." *The Brazilian Journal of Infectious Diseases: an Official Publication of the Brazilian Society of Infectious Diseases*, U.S. National Library of Medicine, 12 Mar. 2018, pubmed.ncbi.nlm.nih.gov/29545017/.
3. CDC "Facts about Microcephaly." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 18 Feb. 2020, www.cdc.gov/ncbddd/birthdefects/microcephaly.html.
4. Barrett, Alan D T. "Current Status of Zika Vaccine Development: Zika Vaccines Advance into Clinical Evaluation." *NPJ Vaccines*, Nature Publishing Group UK, 11 June 2018, www.ncbi.nlm.nih.gov/pmc/articles/PMC5995964/.
5. Moore, Cynthia A, et al. "Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians." *JAMA Pediatrics*, U.S. National Library of Medicine, 1 Mar. 2017, www.ncbi.nlm.nih.gov/pmc/articles/PMC5561417/.
6. PAHO. "Zika Cumulative Cases- 4 January 2018" January 4, 2018, https://www.paho.org/hq/index.php?option=com_content&view=article&id=12390:zika-cumulative-cases&Itemid=42090&lang=en
7. França, Giovanni V A, et al. "Congenital Zika Virus Syndrome in Brazil: a Case Series of the First 1501 Livebirths with Complete Investigation." *The Lancet*, Elsevier, 29 June 2016, www.sciencedirect.com/science/article/pii/S0140673616309023.
8. Moura da Silva, Antonio Augusto, et al. "Early Growth and Neurologic Outcomes of Infants with Probable Congenital Zika Virus Syndrome." *Emerging Infectious Diseases*, Centers for Disease Control and Prevention, Nov. 2016, www.ncbi.nlm.nih.gov/pmc/articles/PMC5088045/.
9. Sá, F. E., et al. "Parental needs in the care for children with zika virus-induced microcephaly" *Semantic Scholar*, 2018 www.semanticscholar.org/paper/PARENTAL-NEEDS-IN-THE-CARE-FOR-CHILDREN-WITH-ZIKA-S%C3%A1-Andrade/f8d77f02674b48a9e4c5c31bc6f99a9dbaa84315.
10. Nazerai, L, Christensen, JP, Thomson, AR. "A 'Furry-Tale' of Zika Virus Infection: What have we learned from animal models?" *Viruses* 11(1) Published 2019
11. Richner, Justin M., et al. "Modified mRNA Vaccines Protect against Zika Virus Infection." *Cell*, Cell Press, 17 Feb. 2017, www.sciencedirect.com/science/article/pii/S0092867417301952.
12. Pattnaik, Aryamav, Sahoo, Bikash R., Pattnaik, Asit K. "Current Status of Zika Virus Vaccines: Success and Challenges" *Vaccines*, May 31, 2020 <https://www.mdpi.com/2076-393X/8/2/266/htm>
13. Effective Public Health Practice Project. "Quality Assessment Tool for Quantitative Studies" 2010 https://merst.ca/wp-content/uploads/2018/02/quality-assessment-tool_2010.pdf

14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–88.
15. Abbink P, Larocca RA, De La Barrera RA, et al. Protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys. *Science* (80-). Published online 2016. doi:10.1126/science.aah6157
16. Dowd KA, Ko SY, Morabito KM, et al. Rapid development of a DNA vaccine for Zika virus. *Science* (80-). Published online 2016. doi:10.1126/science.aai9137
17. Lecouturier V, Bernard MC, Berry C, et al. Immunogenicity and protection conferred by an optimized purified inactivated Zika vaccine in mice. *Vaccine*. Published online 2019. doi:10.1016/j.vaccine.2019.04.013
18. Luisi K, Morabito KM, Burgomaster KE, et al. Development of a potent Zika virus vaccine using self-amplifying messenger RNA. *Sci Adv* (6) Published online 2020. doi: 10.1126/sciadv.aba5068
19. Pardi N, Hogan MJ, Pelc RS, et al. Zika virus protection by a single low-dose nucleoside-modified mRNA vaccination. *Nature*. Published online 2017. doi:10.1038/nature21428
20. van Rompay KKA, Keesler RI, Ardeshir A, et al. DNA vaccination before conception protects Zika virus–exposed pregnant macaques against prolonged viremia and improves fetal outcomes. *Sci Transl Med*. Published online 2019. doi:10.1126/scitranslmed.aay2736
21. Young G, Bohning KJ, Sahralban-Steele M, et al. Complete protection in macaques conferred by purified inactivated Zika vaccine: defining a correlate of protection. *Scientific Reports* (10). Published online 2020. Doi: 10.1038/s41598-020-60415-6
22. Narasimhan H, Chudnovets A, Burd I, Pekosz A, and Klein SL. “Animal models of congenital zika syndrome provide mechanistic insight into viral pathogenesis during pregnancy.” *PLOS Neglected Tropical Diseases*. Published 2020
23. Vannice, Kirsten S., et al. “Demonstrating Vaccine Effectiveness during a Waning Epidemic: A WHO/NIH Meeting Report on Approaches to Development and Licensure of Zika Vaccine Candidates.” *Vaccine*, Elsevier, 11 Jan. 2019, www.sciencedirect.com/science/article/pii/S0264410X18317134.
24. Grueber, MF, et al. “Clinical development strategies and considerations for Zika Vaccine Licensure” *J Infect Dis* (10) Published online 2017

	Were there important differences between the groups prior to the intervention?	2	1	2	2	2	2	2
	If yes, indicate the percentage of relevant confounders that were controlled for in the design or analysis.	4	1	4	4	4	4	4
Confounders	Rating	1	1	1	1	1	1	1
	Were the outcome assessors aware of the intervention/exposure status of participants	2	2	3	3	3	2	3
	Were the study participants aware of the research question?	2	2	2	2	2	2	2
Blinding	Rating	1	1	2	2	2	1	2
	Were data collection tools shown to be valid?	1	1	1	1	1	1	1
	Were data collection tools shown to be reliable?	1	1	1	1	1	1	1
Data Collection Methods	Rating	1	1	1	1	1	1	1

	Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?	2	4	4	4	4	1	1
Withdrawals/ Drop outs	Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest.)	1	1	1	1	1	1	1
	Rating	2	1	1	1	1	1	1
Final Decision		1	2	2	2	2	1	1

Biography & Resume

Hannah Lund is a Master of Public Health student at the University of Nebraska Medical Center College of Public Health. Her studies have focused on epidemiology. In the summer of 2020, she worked with the East-Central District Health Department in Columbus, NE and developed their community health needs assessment survey. Ms. Lund also works for Nebraska Department of Health and Human Services as a Graduate Assistant for the Chronic Disease Prevention and Control program. In this role, she aids with data collection, entry, and analysis, as well preparing summary reports and data briefs for the program. She also holds several student leadership positions at UNMC, on Student Senate, COPH Student Association, and UNMC One Health. Ms. Lund attended Southwest Minnesota State University, where she earned a bachelor's degree in biology.

HANNAH LUND

Hannah.lund@unmc.edu | 402-841-1632

2464 Harney St

Omaha, NE 68131

1. EDUCATION

- A. Master of Public Health- Epidemiology May 2021
- B. University of Nebraska Medical Center College of Public Health, Omaha, NE
 - Relevant Coursework: Intro to SAS, Epidemiology in Public Health, Epidemiologic Methods, Applied Epidemiology, Theory and Methods of Infectious Disease Epidemiology, Biostatistics I, Biostatistics II, Chronic Disease Epidemiology
- C. Bachelor of Arts- Biology May 2019
- D. Southwest Minnesota State University, Marshall, MN

2. PROFESSIONAL EXPERIENCE

- A. Nebraska Department of Health and Human Services Aug 2020-Present
- B. Chronic Disease Prevention and Control Program
- C. Epidemiology & Evaluation Graduate Assistant
 - Prepare summary reports for diabetes and heart disease grant work.
 - Collect and analyze data in excel to guide future grant work.
 - Participate in progress meetings with Chronic Disease team from CDC.
 - Review progress reports for the diabetes and heart disease programs.
 - Create ArcGIS maps to analyze impact and reach of prevention programs on chronic diseases in the state.
 - Correspond with various partners including NDE, CDC, and Schmeeckle Research.

CHI-Bergan Mercy

Mar 2020- March 2021

Phlebotomist

- Work with patients, doctors, and nurses daily to provide patient care.

UNMC, College of Public Health

Aug 2020- Present

Student Researcher

- Conducting a systematic Literature Review and Meta-Analysis on efficacy of vaccine candidates against Congenital Zika Syndrome

East Central District Health Department

May 2020-July 2020

Public Health Intern

- Developed Community Health Needs Assessment survey and developed a plan and materials for focus groups for the CHNA.
- Organized a Photovoice project with students and local partners to improve community health in one of the four rural counties covered by the health department.
- Handled West Nile surveillance trapping and shipping.
- Scheduled community children for the immunizations program due to staffing being redirected to COVID-19

Southwest Minnesota State University

Jan 2019-May 2019

Undergraduate Student Researcher

- Led a small-scale literature review about Zika virus infection, using an organoid model.

3. LEADERSHIP AND VOLUNTEER EXPERIENCE

Student Senate

May 2020- Present

Senator and Academic Affairs Chair

College of Public Health Student Association

May 2020- Present

Board Member

UNMC One Health

Mar 2020- Present

President and founding member of UNMC chapter

- Created organization to increase interprofessional teamwork with the colleges on UNMC's campus and promote research opportunities for interested students.

Nebraska Medicine Pandemic Planning

Mar - June 2020

Volunteer

- Read and sorted through the team's extensive literature searches

Bridge to Care Refugee Health Fair

Nov 2019

Navigator

- Helped refugee families access the information and services provided by over 20 community organizations.

Computer Skills

SAS, ArcGIS, Excel, Microsoft Office Suite