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Lessons Learned from Zika Virus:
A Systematic Literature Review on Strategic Responses in Puerto Rico and the US Virgin Islands

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Abstract

Lessons Learned from Zika Virus: A Systematic Literature Review on Strategic Responses in Puerto Rico and the US Virgin Islands

By: Binta E. Ceesay

Background: Zika virus (ZIKV) is an arbovirus transmitted by *Aedes aegypti* mosquitoes. The most recent outbreak in the Americas left a tremendous burden with numerous cases of congenital zika syndrome which can cause birth defects like microcephaly and Guillain-Barre Syndrome. A Community Assessment for Public Health Emergency Response (CASPER) was conducted on ZIKV in the US Virgin Islands (USVI) in 2017. That fieldwork was appended by a systematic review of the literature which assessed the lessons learned from strategic responses to ZIKV in American territories, Puerto Rico and USVI.

Methods: CASPER used a two-stage probability sampling method to implement household-based surveys. PubMed and Popline were used to identify peer-reviewed articles that met the inclusion and exclusion criteria. CDC's Stacks and WHO's IRIS databases were used to identify grey-literature. All full-text publications were entered using EndNote X8 and organized into a Summary of Findings table.

Results: The CASPER revealed less than 45% of households knew ZIKV was sexually transmitted compared to 96% of households who knew ZIKV was transmitted by mosquitoes. Results also reveal the most common and trusted sources for ZIKV messaging within the community. The literature search identified 2,513 peer-reviewed articles related to ZIKV strategic response; of those, 42 articles were selected for this review. Twelve grey literature publications were included. The primary topic and areas and policy concerning ZIKV were consolidated around detection, prevention, care & support, and research.

Conclusion: Although ZIKV is no longer a global health emergency, there are adverse health outcomes, the extent of which, are not thoroughly known. This is particularly true of the outcomes for pregnant women and their infants, Further research in both the clinical and policy arenas is required to address this priority population. For example, it will be critical to focus on solutions related to vaccine development within a pregnancy-specific ethical framework and antiviral therapeutics for affected communities. An integrated and multidisciplinary response approach that includes scientists, all levels of government, clinicians, local community members and public health professionals will be the ideal option for addressing ZIKV.

Keywords: Zika Virus, Emergency Preparedness, Public Health Response, Puerto Rico, US Virgin Islands

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LIST OF ABBREVIATIONS

CASPER—Community Assessment for Public Health Emergency Response

CDC—Centers for Disease Control and Prevention

CZS—Congenital Zika Syndrome

GBS—Guillain-Barre Syndrome

IEC—Information, education, and communication

PHEIC—Public Health Emergency of International Concern

PRDH—Puerto Rico Department of Health

SRH—Sexual and Reproductive Health

USVI—United States Virgin Islands

USVIDOH—United States Virgin Islands Department of Health

WHO—World Health Organization

ZIKV—Zika Virus

Z-CAN—Zika Contraception Access Network

INTRODUCTION

When a seemingly inactive virus became an international crisis, Zika virus (ZIKV) was declared a Public Health Emergency of International Concern (PHEIC) in February 2016. With a marked increase in the number of symptomatic cases, the most recent outbreak of ZIKV in 2015, caused alarm in the Americas. Upon the confirmation of the correlation between ZIKV and neurological complications in newborns, the severity of the disease and necessity of proper public health response increased.

Due to the novelty of ZIKV as an epidemic in the Americas, there are many research and development gaps—from pathogenesis and diagnostic tools to therapeutics and challenges in high-risk populations. This thesis presents an assessment of the strategic responses of global health officials to the ZIKV epidemic, specifically in American territories.

The results of this thesis are based on a combination of fieldwork in St. Croix and a systematic literature review of clinical and policy-related approaches. I conducted a household-level survey, Community Assessment for Public Health Emergency Response (CASPER), in collaboration with the Epidemiology Department at the US Virgin Islands (USVI) Department of Health (USVIDOH), and the US Centers for Disease Control and Prevention (CDC). We aimed to assess the territory residents' knowledge, attitudes, and practices pertaining to ZIKV prevention.

The CASPER revealed several knowledge and communication gaps amongst the USVI population. With low knowledge levels concerning ZIKV transmission through sexual contact and even lower levels of condom usage to avoid ZIKV, there is a high need to educate the community on the sexual transmission of ZIKV. The CASPER did not address other significant aspects of ZIKV such as detection and future research agendas. The field work in the USVI

inspired this continual research to understand the responses to ZIKV in American territories—what has been done and the lessons learned to adapt for the ongoing response and future outbreaks.

The following sections present background on the emergence of ZIKV, the problem statement, and research methods. This is followed by the results of the CASPER survey in the USVI and the four strategic response areas in the context of both Puerto Rico and USVI from the current literature. In the discussion, the questions surrounding sexual transmission and the correlations of ZIKV with congenital abnormalities are addressed. Also, challenges regarding ZIKV therapeutics and vaccine development, particularly for pregnant women, are discussed. Finally, I propose a consolidated, integrated approach to combat the ZIKV outbreak with significant public health implications.

History and Emergence of Zika Virus

ZIKV is an arbovirus that is primarily transmitted by the *Aedes* genus of mosquitoes, particularly the *Aedes Aegypti* species, as seen in recent epidemics of the virus in the Americas. ZIKV was first discovered in the Zika Forest in Uganda in 1947, hence the name of the virus (Aliota et al., 2017; Mittal et al., 2017; Munoz-Jordan, 2017). The first human case of ZIKV appeared years later in Uganda in 1962 (Aliota et al., 2017). Continual, sylvatic and enzootic circulation of ZIKV persisted throughout tropical areas of Africa. Despite the spread of ZIKV throughout sub-Saharan Africa and Asia (Esposito, de Moraes, & Lopes da Fonseca, 2017), an epidemic did not occur until 2007 in Micronesia followed by another in French Polynesia by 2013, and the most recent outbreak, reaching the Americas in 2015 (Aliota et al., 2017; Mittal et al., 2017). It is possible that sporadic human infection of ZIKV occurred between discovery and the first epidemic but was likely misdiagnosed as other flaviviruses.

Aside from mosquitoes as vectors, sexual and other non-mosquito-borne transmissions of ZIKV occur and were proven after the recent surges of cases (Aliota et al., 2017). Large quantities of ZIKV RNA can remain in sperm months after symptoms have resolved; it can also be observed in vaginal secretions up to two weeks after onset of symptoms (Munoz-Jordan, 2017). This mode of transmission and level of persistence has not been detected in other flaviviral clinical manifestations in humans (Esposito et al., 2017). Another method of transmission is maternal-fetal transmission. ZIKV RNA can be detected in the serum of pregnant women up to ten weeks after the onset of symptoms (Aliota et al., 2017). ZIKV is also transmitted via contaminated blood products most likely from blood donations (Esposito et al., 2017). The virus has also been detected in saliva, breast milk, and urine. However, the ability of

the virus to infect through those bodily fluids has not yet been proven (Mittal et al., 2017; (Munoz-Jordan, 2017).

Approximately 80% of those infected with ZIKV are asymptomatic (Mittal et al., 2017; Erbelding & Cassetti, 2017; Esposito et al., 2017). When symptoms do arise, they are mild and broad, generic symptoms such as fatigue, malaise, headache, joint aches, low-grade fever (99.4 F) and maculopapular rash (Aliota et al., 2017). The majority of symptoms appear 11.2 days after exposure for most (95%) infected individuals (Mittal et al., 2017). The illness usually lasts no more than five to seven days.

The manifestation of ZIKV is much more consequential for pregnant women. ZIKV infections can cause fetal abnormalities and pregnancy loss; the resulting newborns of ZIKV-infected mothers can suffer from Guillain-Barre Syndrome (GBS), microcephaly, and other nervous systems conditions (Aliota et al., 2017; Mittal et al., 2017) Researchers have grouped the congenital manifestations of ZIKV into "congenital Zika syndrome" (CZS). CZS includes microcephaly, intrauterine growth retardation, cerebral visual impairment, and dysphagia. (Mittal et al., 2017).

The diagnostic tools for ZIKV include clinical diagnosis, cultures, reverse transcription polymerase chain reaction (RT-PCR), plaque-reduction neutralization tests (PRNT) and immunoglobulin M enzyme-linked immunosorbent assay (IgM ELISA) (Mittal et al., 2017; Sharma & Lal, 2017). A clinical diagnosis has low sensitivity considering ZIKV is usually asymptomatic, and the clinical symptoms are similar to that of many other infections. Culturing is complicated and often not useful in research. The remaining methods, although high in sensitivity, can misdiagnose ZIKV as other flaviviruses. The most notable of these misdiagnoses

being dengue (DENV) and chikungunya (CHIKV) due to high cross-reactivity (Mittal et al., 2017; Esposito et al., 2017).

Currently, there is no treatment of ZIKV infection nor is there an approved vaccine to prevent the transmission of ZIKV (Munoz-Jordan, 2017). Because ZIKV infections in adults and children usually do not cause complications, only symptoms are treated. Supportive care is the only management option of clinical manifestations of ZIKV. Therefore, it is even more crucial that a sensitive, reliable diagnostic method is developed to prevent transmission of ZIKV.

At present, ZIKV prevention mechanisms are focused on vector control and personal protection measures such as avoiding standing water reservoirs and Environmental Protection Agency (EPA)-approved repellent. The CDC has issued travel warnings targeting pregnant women or those planning to become pregnant to avoid travel to areas where ZIKV is endemic. The World Health Organization (WHO) has also vigorously campaigned for the development of ZIKV vaccines and therapeutics.

Problem Statement

While the continental United States has had cases of ZIKV outbreak, there is a higher prevalence of cases in its territories in the Caribbean, especially Puerto Rico and USVI. According to the Puerto Rico Department of Health (PRDH), there are 40,630 laboratory-confirmed cases of ZIKV since 2016; 4,134 of which are pregnant women (Departamento de Salud de Puerto Rico, 2018). According to the CDC, as of March 21, 2018, there are 1,032 symptomatic disease cases[1] of ZIKV in USVI (National Center for Emerging and Zoonotic

[1] Includes reported confirmed and probable ZIKV disease cases per the Council of State and Territorial Epidemiologists case definitions

Infectious Diseases [NCEZID], 2018). The CDC presents the outcomes of pregnancies with laboratory evidence of possible ZIKV infection between 2015 and 2018, for all US territories which include Puerto Rico, USVI, and American Samoa. The statistics are as follows: 4,784 pregnant women with any laboratory evidence of possible ZIKV infection (National Center on Birth Defects and Developmental Disabilities [NCBDDD], 2018a), 4,195 completed pregnancies with or without ZIKV-associated birth defects, 157 live-born infants with ZIKV-associated birth defects, and eight pregnancy losses with ZIKV-associated birth defects (NCBDDD, 2018b).

ZIKV continues to be a public health issue despite no longer being listed as a PHEIC. Studies have revealed the devastating consequences of ZIKV particularly with pregnant women and their infected newborn babies. Research has proven a link between ZIKV and infants with CZS and GBS. Determining the most efficient response for high-risk groups will help prevent and reduce transmission. Considering the relative newness of this arbovirus, it is essential to know what information is available and identify gaps in literature to help inform future strategic responses.

Objective and Aims

The overall objective of this review is to assess the effects of strategic responses of ZIKV in two US territories— Puerto Rico and USVI. The specific aims are as follows:

1. To assess the knowledge, attitudes, and practices concerning ZIKV prevention in USVI
2. To identify information and communication gaps in USVI ZIKV response
3. To examine major criteria for strategic response in Puerto Rico and USVI:
    a. Detection
    b. Prevention
    c. Care & Support

d. Research

The results of the fieldwork in USVI accompanied with this literature review can be used in the future to provide valuable information to enhance response strategies for ZIKV especially as it no longer remains a PHEIC but transitions into a seasonal, endemic state.

METHODS

CASPER Methods

CASPER is a two-stage cluster sampling method used at the household level in both disaster and non-disaster situations (CDC, 2012). There was a sampling frame of 43,214 households, based on the 2010 US Census. In the first stage, 30 census block groups (clusters) were selected from a sampling area with a probability proportional to the number of households within the cluster. On St. Croix, 12 census blocks (including two blocks which were selected twice) were selected, 16 census blocks selected on St. Thomas, and none selected on St. John. For the second stage, each census block was subdivided into clusters in which survey teams randomly selected seven households to interview.

Surveys were conducted over four days, two per each island. Eligible participants, those over age 18 and a resident of the household, were interviewed by two-member teams. Participants were read a consent form and agreed to partake in the survey. No personally identifiable data was collected. Data was synthesized, cleaned, and analyzed by CDC staff. Using Epi Info 7.2.1, the weighted population-based frequencies, proportions, and 95% confidence intervals were reported.

Ethical Considerations

The CASPER was determined by CDC as not subject to Institutional Review Board review.

Systematic Literature Review Methods

A systematic literature review was conducted using a predefined search strategy. Inclusion and exclusion criteria were developed prior to the literature search. Studies meeting the standards were subsequently reviewed.

Inclusion and Exclusion Criteria

Separate inclusion criteria were established for peer-reviewed and grey literature. For peer-reviewed literature, all articles must address ZIKV. Articles especially related to Puerto Rico and USVI were included. Additional inclusion criteria include articles addressing general strategic response areas: detection, prevention, care & support, and research. Full-text articles accessed through databases or via Emory University were included.

Grey literature included for this review were accessed only from the CDC's Stacks database and WHO's IRIS database. Only the most recently updated publications were included.

Articles in languages other than English were excluded in this review due to limited resources. Articles published before 2015, the beginning date of the recent ZIKV epidemic, were excluded.

Data Synthesis

Full-text articles and publications meeting the inclusion criteria were obtained and screened. All documents included ("Zika") and were published after 2014. Tables 2 and 3 below contain the search terms used for peer-reviewed articles and grey literature respectively. Articles from databases PubMed and Popline were exported into EndNote X8.

Grey literature material from the CDC and WHO was manually entered into EndNote X8. Publications, namely technical reports and documents, were obtained from CDC's Stacks

database and WHO's IRIS database. Duplicates were removed, and titles and abstracts were reviewed for inclusion. Full-text reviews were conducted to assess the final list of articles to be included. Microsoft Excel was used to organize the documents by year, author, type of publication, location, keywords, and significant findings. The results of the systematic review are presented in the section below.

Table 2. Search Terms for Peer-Reviewed Literature

Response Area	**Search Terms**
General PH Response	Zika AND emergency response
General PH Response	Zika AND strategic response
General PH Response	Zika AND emergency preparedness
General PH Response	Zika AND guidelines
Geographical Scope	Zika AND Virgin Islands
Geographical Scope	Zika AND Puerto Rico
Geographical Scope	Zika AND West Indies
Geographical Scope	Zika AND US territories
Detection	Zika AND testing
Detection	Zika AND screening AND Americas
Detection	Zika AND detection
Detection	Zika AND diagnosis AND Americas
Detection	Zika AND surveillance
Prevention	Zika AND risk communication
Prevention	Zika AND personal protection
Prevention	Zika AND integrated vector management
Prevention	Zika AND family planning
Care & Support	Zika AND pregnancy AND Americas
Care & Support	Zika AND Guillain Barre Syndrome AND Americas
Care & Support	Zika AND complications AND Americas
Care & Support	Zika AND high-risk population
Research	Zika AND vaccination
Research	Zika AND remedies
Research	Zika AND therapeutics

Table 3. Search Terms for Grey Literature

Database	**Search Term**
CDC—Stacks	Zika Virus AND guidance OR guidelines[2]
WHO—IRIS	Zika Virus AND Author=WHO

Ethical Considerations

This literature was determined to be exempt from Institutional Review Board consideration because no human-subjects were involved, and the study is a systematic review of existing literature.

[2] Note: The researcher wanted to exclude other irrelevant document types such as "coloring books," "journal articles" (since those were included in peer-reviewed articles search), "webcasts," etc.

RESULTS

USVI CASPER Results

In addition to the literature found, I also report the findings from the CASPER. In June 2017, we at the USVIDOH along with the CDC conducted a CASPER survey which assessed the population's awareness and behaviors on ZIKV after over a year of comprehensive community outreach and education (Roth et al., 2017). This CASPER also assessed the population's perceptions of the communication strategies used for ZIKV messaging and household preparedness for future disasters such as hurricanes.

Of the 321 households contacted, 201 completed the survey (completion rate: 62.6%). Over 40% of households included at least one woman of childbearing age. Respondents were questioned on the ZIKV messaging they received; television was the most common source (73.7%) and the most trusted source (20.0%). The most recalled prevention messages included: draining standing water (60.0%), wearing mosquito repellent (24.6%), and wearing long sleeves and pants (14.9%). Among the least recalled messages were using condoms/abstaining from sex (4.5%) and delaying pregnancy (2.0%) (Roth et al., 2017).

Concerning knowledge levels, more than 95% of household agreed that ZIKV was transmitted by mosquitoes and 90.1% agreed it could be spread from mother to child. However, significantly less (44.8%) agreed that ZIKV was sexually transmissible (Roth et al., 2017).

Respondents were questioned about personal protective measures taken to avoid ZIKV; approximately 45% reported avoiding areas of mosquito exposure and 27.2% reported always using mosquito repellant. However, only 16.1% of households reported using condoms specifically as a prevention method for ZIKV. 40.3% of household reported never using condoms. Only 0.5% of respondents indicated household members delayed pregnancy in

response to ZIKV. As for vector control mechanisms, 71.3% of households clean their yard/remove garbage weekly. Although 60.0% of respondents recalled messaging about draining standing water, only 42.7% of the households reported doing so weekly (Roth et al., 2017).

Households were asked about desired measures they believed USVIDOH should implement. Many households (77.6%) believe that USVIDOH should be spraying or fogging to prevent mosquito-borne diseases. Despite varying knowledge and awareness levels, nearly 38% of households specified that USVIDOH should provide education (Roth et al., 2017).

The 2016 knowledge, attitudes, and practices (KAP) assessment (Prue et al., 2017) inspired the 2017 CASPER. The 2016 KAP assessment was an interview styled survey, focusing mainly on pregnant women (38.7%) and general community members. It evaluated ZIKV-related awareness, beliefs, and actions using a convenience sampling method. The survey provided information on ZIKV messaging at the time of the response and how to bolster future efforts. One major advantage of the 2017 CASPER was its two-stage probability sampling method. This population-based method was more representative of the USVI population.

Overall, the results from this CASPER were consistent with that of the 2016 KAP survey focusing on knowledge, attitudes, and practices (KAP) towards ZIKV conducted by the USVIDOH (Prue et al., 2016). Knowledge level regarding modes of ZIKV transmission were low when the 2016 KAP survey was completed. Respectively, 11.5% and 9.1% of pregnant women and community members mentioned that ZIKV can be sexually transmitted. Although data from the CASPER suggests an improvement in knowledge levels concerning sexual transmission of ZIKV, a gap still remains. Likewise, corresponding practices were low as well; Among the pregnant women who were sexually active during their pregnancy, only 18.8% reported always using a condom while 57.5% revealed never using a condom (Prue et al., 2017).

In the 2017 CASPER, households more frequently recalled ZIKV messaging related to preventing mosquito bites compared to messaging and information related to sexual transmission of ZIKV including condom usage, delaying pregnancy, abstaining from sexual intercourse. This may be attributed to previous campaigns for DENV and CHIKV which focused on vector control (Roth et al., 2017).

Although the KAP survey and subsequent CASPER provided insightful information on the state of ZIKV in the USVI, it lacked information and research regarding other strategic response areas. It focused specifically on knowledge, attitudes, and practices pertaining to ZIKV prevention, identifying information gaps and communication strategies, and assessing household and environmental qualities associated with vector control. Areas that especially need further understanding included ZIKV detection and surveillance, care and support of ZIKV infected populations, and research for ZIKV therapeutics and vaccine development. Puerto Rico, having a larger burden of ZIKV, also needed to be addressed. Through the literature review, these gaps in information were addressed to gain a comprehensive understanding of the strategic response on the two territories most impacted by the ZIKV epidemic.

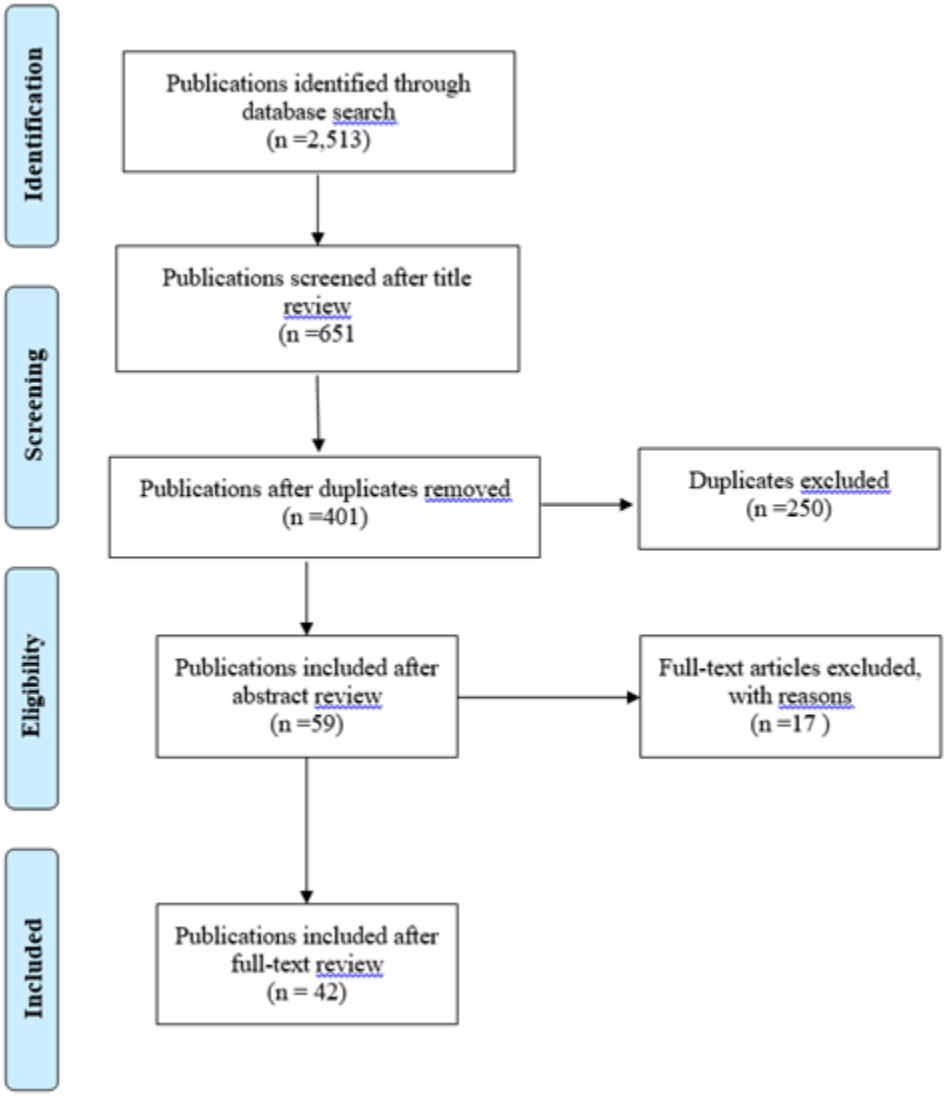
Literature Review

Search Results

The researcher reviewed titles of 2,513 peer-reviewed articles. The abstracts of 401 articles were subsequently reviewed. Of these, 59 publications were considered for full-text review. Forty-two of these peer-reviewed publications were included in this systematic literature review (Figure 1. Peer-Reviewed Literature PRISMA Flowchart). The majority of the studies included were published in 2017 (61.9%, N=26). The studies included were largely focused on Puerto Rico (30.9 %, N=13) and only two on USVI (4.7 %). Other studies were not American territory specific and focused on Latin America (11.9 %, N=5) in general.

As for grey literature, articles were identified through the CDC's and WHO's respective databases. A total of 46 results were identified based on the inclusion and exclusion criteria under CDC Stacks. Nine were included after title review, of which five were included in this analysis after full-text review. From the WHO IRIS database, a total of 85 results were identified fitting the search criteria. Of those, 15 were selected after title review, and subsequently, seven were included in the analysis after full-text review. These results from the CDC and WHO were guidelines and/or technical reports and updates. None were location specific.

Figure 1. Peer-Reviewed Literature PRISMA Flowchart



The results of this systematic literature review were divided into the four major strategic response areas: detection, prevention, care & support, and research. This section presents information on ZIKV detection methods including diagnostic testing methods and surveillance systems. Prevention mechanisms are discussed focusing on personal protection, vector control and risk communication. Strategies focusing on CZS, GBS, and other health outcomes for both mothers and newborns are also identified. Research gaps especially in vaccine development for

pregnant women are presented. These four major areas are all important in addressing future recommendations and focusing on key target groups such as ZIKV-positive pregnant women and their infants. All publication findings are displayed in Appendix B. Finally, the limitations of this review and CASPER survey are presented.

Detection and Surveillance of ZIKV

Diagnostic Testing

The majority of articles discuss the detection of ZIKV. Five articles go more in depth regarding detection mechanisms for ZIKV (Goldfarb, Jaffe, & Lyerly, 2017; Mittal et al., 2017; Munoz-Jordan, 2017; Sharma & Lal, 2017; Zorilla, G. Garcia, F. Garcia, & De La Vega, 2017). Detecting ZIKV has been a challenge due to its high similarity to other flaviviruses. To date, there is no standardized test to detect ZIKV. The primary diagnostic mechanisms aside from clinical diagnosis include RT-PCR-based detection, antibody-based detection which includes PRNT and ELISA (Mittal et al., 2017; Sharma & Lal, 2017). RT-PCR is the most promising method in that it can detect 37 strains of ZIKV RNA with high sensitivity. It is inexpensive, fast without any confounding diagnoses. Furthermore, it can be easily detected through multiple biofluids (Mittal et al., 2017; Munoz-Jordan, 2017). ZIKV RNA can be detected via serum within the five to six days of infection using RT-PCR or antibody-based detection (Sharma & Lal, 2017). PRNT and ELISA are considered to be the gold standard for diagnosing flaviviruses (Mittal et al., 2017); however, those methods can provide confounding diagnoses when detecting ZIKV. PRNT has enhanced sensitivity compared to ELISA and helps eliminate false-positives (Sharma & Lal, 2017). Despite the use of these detection methods, there is a need for further research and increased specificity of ZIKV tests due to cross-reactivity and low viremia (Munoz-Jordan, 2017; Sharma & Lal, 2017).

As additional research has been conducted on ZIKV, the testing recommendations have shifted as well. The updated CDC (2017a) guidelines recommend ZIKV testing for the following situations:

> Symptomatic pregnant women with possible exposure to Zika virus; Asymptomatic pregnant women with ongoing possible exposure to Zika virus; Pregnant women with possible exposure to Zika virus who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus infection; Non-pregnant symptomatic individuals with possible exposure to areas with risk of Zika virus transmission (p. 2).

Zorrilla et al. discuss detection in pregnancy specifically. The primary specimen for pregnant testing is maternal serum via RT-PCR (WHO, 2016a; Zorrilla et al., 2017). There are additional difficulties in accurate fetal diagnosis of ZIKV such as the invasive procedure to collect amniotic fluid samples. Many of the manifestations of CZS occur later in pregnancy making it challenging to detect ZIKV regardless of early testing. Studies have revealed prolonged maternal viremia which can lead to infections in the fetal brain and placenta causing CZS. Ultrasound evaluations are also used in diagnosing ZIKV via detection of CZS which can occur as early as 19 weeks. (Zorrilla et al., 2017).

Blood Donations

Detection of ZIKV in blood donations is a known method of transmission, however, only two articles have thoroughly discussed it. Vasquez et al. (2016) examine the potential for transmission of ZIKV through blood donations. Although there have been no cases of ZIKV via contaminated blood in the US and its territories, the US Food and Drug Administration (FDA) requires rapid assessment of blood donations to avoid blood transfusion-transmission, which has

been reported in French Polynesia and Brazil (Sharma & Lal, 2017; Vasquez et al. 2016). The FDA also issued guidelines via the Organ Procurement and Transplantation Network (OPTN) of the Health Resources and Services Administration (HRSA) to avoid transmission via human cells and organ transplants (CDC, 2017b).

The Chevalier et al. (2017) study emphasized how asymptomatic infections are a significant contributor to blood transfusion-transmission. The authors discussed using blood donations as a surveillance tactic for real-time ZIKV incidence estimates. This information can be captured from "a large, diverse convenience sample of the general population" (Chevalier et al., 2017, p. 793) which may not be feasible to attain during a PHEIC. Using blood donation surveillance along with clinical surveillance can provide more accurate incidence rates. This study suggests that there was a larger proportion of people infected with ZIKV (469,321 persons) than reported through surveillance (≈10,000 infections) (Chevalier et al., 2017).

Surveillance Systems

Thorough surveillance systems were established at the beginning of the epidemic and are still in place to detect ZIKV especially in at-risk areas such as Puerto Rico and USVI. The WHO provides interim guidelines (WHO, 2016d) for various surveillance methods. However, for Puerto Rico, USVI, and the continental US, many systems are a collaborative effort between the CDC and local health authorities. One primary surveillance system is the National Arboviral Surveillance System (ArboNET). ArboNET is the national arboviral passive surveillance system. CDC and state and territorial departments of health manage the system for human and non-human diseases (NCEZID, 2015). CDC incorporated ZIKV case reporting and diagnostic testing into existing DENV and CHIKV surveillance systems (Dirlikov et al., 2016c). Both PRDH and USVIDOH use ArboNET for ZIKV monitoring. The CDC (2017a) has also developed a vector

control surveillance system, Mosquito NET, which is an online portal that collects data on mosquito populations, presence and information for insecticide resistance testing.

The US Zika Pregnancy and Infant Registry (USZPR) is a comprehensive, collaborative system with CDC and state, local, territorial and tribal departments of health to surveil and inform on ZIKV infection during pregnancy and following birth (Broussard et al., 2017; CDC, 2016b; CDC, 2017b). The goal of USZPR is to identify adverse pregnancy outcomes and to update clinical recommendations for care and support (CDC, 2017b). Pregnant women or infants with laboratory evidence of ZIKV can be registered regardless of whether symptoms are present or not. Information is transferred from healthcare providers and health departments to CDC where it is reviewed, analyzed and processed for the registry.

Additional surveillance systems explicitly used in Puerto Rico include GBS Passive Surveillance System (GBS PSS), Pregnancy Risk Assessment Monitoring System (PRAMS), and Zika Active Pregnancy Surveillance System (ZAPSS). The GBS PSS was established after an increase of GBS cases in Puerto Rico. It allows health providers to report suspected cases of GBS throughout the island, after which, specimens are tested for ZIKV, DENV, and CHIKV. Data is logged in an integrated data management system, and results are presented in weekly reports (Dirlikov et al., 2016b; Dirlikov et al., 2016c).

The Pregnancy Risk-Assessment Monitoring System (PRAMS) collects data to monitor maternal and child health indicators (CDC, 2016b). In Puerto Rico, this was used through a population-based rapid assessment, Zika Postpartum Emergency Response (ZPER) which was conducted between August 2016 and December 2016 to assess birth outcomes in relation to ZIKV (CDC, 2016b; D'Angelo et al., 2017). Results revealed that women in Puerto Rico were

highly concerned about ZIKV during pregnancy, however, not enough were consistently taking the proper personal protection measures (D'Angelo et al., 2017).

The Zika Active Pregnancy Surveillance System (ZAPSS) is co-operated by PRDH and CDC. It is a surveillance system used to evaluate the association between ZIKV infection and pregnancy such as adverse outcomes of pregnancy and implications for children up to age three (CDC, 2016c). The information gathered from ZAPSS is used to not only to inform future clinical recommendations but also raise awareness of pregnancy outcomes and encourage personal protection measures (CDC, 2016b; Dirlikov et al., 2016c).

Prevention Mechanisms

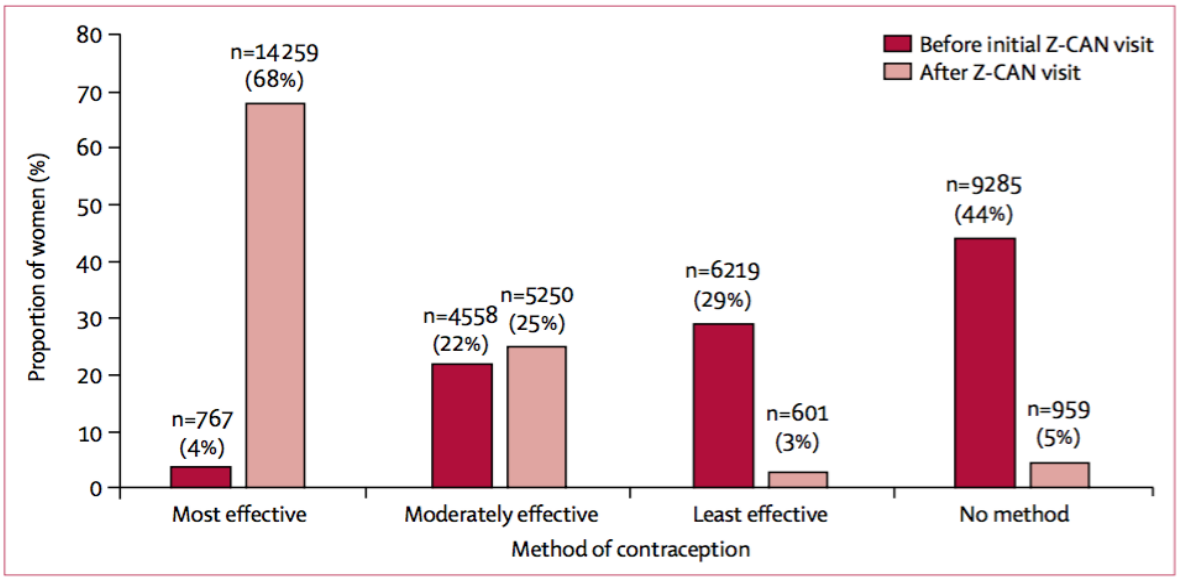
Personal Protection

ZIKV has a similar set of personal protection measures to many other mosquito-borne diseases. The overall objective is to avoid bites from infected mosquitoes. Measures include using insect repellant, especially those which are registered with the US EPA and wearing long-sleeved clothing and pants (Gubler, Vasilakis, & Musso, 2017; Prue et al., 2017; Santibanez et al., 2017). Using bed nets and avoiding peak mosquito times is also recommended (Prue et al., 2017). Additional personal protection measures include the use of condoms and contraceptives because ZIKV is sexually transmitted (CDC, 2017b; Prue et al., 2017; WHO, 2016a). The CDC Foundation and local health departments, including PRDH and USVIDOH, created Zika Prevention Kits for distribution in the community. The kits included locally adapted ZIKV health information packets, insect repellent, bed nets, larvicidal tablets, and condoms (Dirlikov 2016c, Prue et al., 2017).

The PRDH had two additional programs with the CDC related to ZIKV and contraceptives (CDC, 2016b). The first was the Contraceptive Assessment in Puerto Rico during

Zika (CAPRZ). The assessment used Puerto Rico's existing Behavioral Risk Factor Surveillance System to estimate unmet contraceptive needs and understand knowledge, awareness, and practices of ZIKV (CDC, 2016b). The second program was the Zika Contraception Access Network (Z-CAN) which consisted of an interdisciplinary network of health providers that offered free, full-range reversible contraceptive and counseling to women during the 2016-2017 ZIKV outbreak in Puerto Rico (CDC, 2016b). Lathrop et al. (2018) presents further details on a Z-CAN study. Between May 4, 2016, and August 15, 2017, 153 health providers through the Z-CAN program provided 21,124 people with sexual and reproductive health (SRH) services. 20,110 people (95%) received same-day reversible contraceptive methods (Lathrop et al., 2018). Figure 2 below illustrates the increased proportion of women in Puerto Rico using contraception before and after the implementations of Z-CAN program.

Figure 2. Contraceptive methods used by women before and after their initial visit to a Zika Contraception Access Network (Z-CAN) provider in Puerto Rico, as of Aug 15, 2017 (N=21 124).



Note. Reprinted [adapted] from "The Zika Contraception Access Network: a feasibility

programme to increase access to contraception in Puerto Rico during the 2016–17 Zika virus outbreak," by E. Lathrop et al., 2018, *The Lancet, Volume 3*, 1. Copyright © 2018 Lathrop, Romero, Hurst, Bracero, Zapata, Frey, Rivera, Berry-Bibee, Honein, Monroe, and Jamieson.

Two studies discuss the cost-effectiveness of contraception as a prevention method for ZIKV (R. Li et al., 2017; Tepper et al., 2016). Tepper et al. explain the high unmet need for contraception in Puerto Rico based on the fact that about two-thirds of pregnancies are unintended. Several barriers to contraception accessibility include poor quality sex education, limited SRH services, cultural barriers such as religion, and high costs (Roa, 2016; Tepper et al., 2016). High costs tend to preclude patients from seeking care and in the case of ZIKV, increases the possibility of sexual and vertical transmission in (Watson, Nuzzo, Shearer, & Meyer, 2017). Higher accessibility of contraception would lead to higher rates of contraceptive use and less unintended pregnancies, thereby decreasing vertical transmission of ZIKV (Roa, 2016; Tepper et al., 2016; Velez & Diniz, 2016). There are higher healthcare costs due to increased healthcare resource needs associated with ZIKV infection (Dirlikov et al., 2016a). The R. Li et al. (2017) study proves that increasing SRH services, notably contraceptive use, is a cost-saving prevention strategy for ZIKV. By reducing unintended pregnancies and thereby ZIKV-related adverse birth outcomes in Puerto Rico by 25%, $62 million can potentially be saved in ZIKV-related costs (R. Li et al., 2017).

Vector Control

Vector control is an integral part of preventing the spread of ZIKV. The goal of vector control in this context is to eliminate *Aedes* mosquitoes in a "coordinated and effective manner" (CDC, 2017b). Because mosquitoes require very little stagnant water was breeding grounds, they are difficult to control, posing a barrier for many people (Rasanathan, MacCarthy, Diniz,

Torreele, & Gruskin, 2017). It is recommended that people discard any standing water in or around their homes to avoid the proliferation of mosquitoes. Using air-conditioning, and ensuring doors and windows are properly screened is recommended to avoid bites (Thomas et al., 2016). Areas with extensive transmission of ZIKV may require aerial or truck insecticide spraying for more efficient coverage. The CDC also recommends that vector control be complemented with proper surveillance to monitor and evaluate the effectiveness (2017b).

WHO's vector control guidelines encourage implementing integrated vector management (IVM). It aims "to improve the efficacy, cost-effectiveness, ecological soundness and sustainability of mosquito control" (WHO, 2016e, p. 17). IVM prevention strategies include risk communication, community engagement, evidence-based decision making and capacity-building (WHO, 2016e).

In February 2016, an insecticide resistance study of *Aedes aegypti* mosquitoes was conducted in Puerto Rico to inform on future vector control techniques. Results revealed that deltamethrin was the most efficient pyrethroid insecticide (Dirlikov, 2016c). However, later data suggest that mosquitoes in Puerto Rico were resistant to all aerial formulations of pyrethroid insecticides. The US federal government subsequently recommended an organophosphate insecticide, Naled, for vector control, considering its successful use in continental US (McCarthy, 2016).

Sharma and Lal discuss additional entomological approaches to vector control for ZIKV (2017). In 2014, a study conducted in urban areas of Puerto Rico revealed a 50-70% reduction in *Aedes* aegypti after implementing lethal traps. Other vector control strategies include introducing genetically modified male mosquitoes who carry a lethal, dominant gene that kills offspring after mating with wild female mosquitoes (Sharma & Lal, 2017). One final approach is to alter *Aedes*

mosquitoes with the endosymbiotic bacterium, *Wolbachia* which causes a ZIKV inhibitory effect (Sharma & Lal, 2017; Erbelding & Cassetti, 2017).

Risk Communication & Community Engagement

Risk communication and community engagement are critical components of the prevention response to a PHEIC. Prompt communication and effective engagement with fundamental health stakeholders and target communities is necessary throughout the duration of a public health response (Duchin, 2016). In the context of ZIKV, the primary aim of risk communication is to provide messaging around transmission prevention. This communication includes messaging around protection from mosquito bites, vector control, and personal protection practices (WHO, 2016c). Communicating to the general public about these risks and how to mitigate them is the core of ZIKV prevention (McCloskey, 2016; WHO, 2016c).

Santibanez et al. (2017) discuss ten major steps in engaging the community in the ZIKV response. Principle areas of focus include community engagement, identifying risk factors, establishing connections with community gatekeepers, and consideration for the local and cultural context. It is imperative to understand the community background and how previous and current concerns can play into reception of risk communication. Using previously established community gatekeepers such as religious or local leaders is integral to both risk communication and community engagement. These gatekeepers serve as a liaison between the community and the authorities addressing the ZIKV outbreak.

Care and support for CZS and resulting complications

One case-control study by dos Santos Oliveira et al. in particular discusses the maternal mental health of pregnant women and mothers who may be infected with ZIKV. With increasing evidence confirming the causality of ZIKV infection in pregnant mothers and CZS in their

newborns, their maternal mental health is at risk. Expectant parents may experience increased stress due to the possibility of CSZ in their newborns. Quality of life was assessed via a WHO questionnaire collected 24 hours after birth. The authors discovered "that ZIKV-related microcephaly is a factor significantly associated with high levels of anxiety and low scores in psychological domain during the first 24 hours after birth." Additional concerns for parents included fear of stigmatization of microcephaly. dos Santos et al. recommended multidisciplinary counseling and psychoeducational coping strategies (Broussard et al., 2017; dos Santos Oliveira et al., 2016). The recommendations from the CDC (2017b) and WHO (2016b, 2017b) support this strategy.

The WHO recommends specialized and individualized care for pregnant women with evidence of ZIKV and associated-microcephaly. They should be offered non-directive care to make fully-informed decisions. Women who choose to carry to term should be provided appropriate care and support to manage socio-mental health and environmental stressors. Women who decide to terminate their pregnancy also need to be sufficiently provided information about all their options to the full extent of the law (WHO, 2016a).

The WHO (2016b) also released guidance on psychological support for pregnant women dealing with ZIKV complications. Although the guidance focuses on microcephaly, the recommendations can also be applied to other ZIKV-related neurological conditions such as GBS. Providing accurate and supportive information, education and communication (IEC) is one of the most essential recommendations. Health care providers need to disseminate up to date and accurate information especially when supporting families dealing with ZIKV infection. High levels of concern and anxiety can be caused by misinformation spread throughout communities. It is recommended that IEC are clear, concise and culturally appropriate. Additionally,

organizing health visitation schedules to follow up with care and monitoring development of the child is a critical part of the care and support process. Key features of the WHO's recommendations include asking about a patient's needs and concerns, listening carefully and confidentially, encouraging the joining of support groups, and sharing resources for decision-making assistance. These steps help reduce stress and improve positive coping mechanisms (WHO, 2016b).

The WHO provides a toolkit resource with a comprehensive outline of addressing ZIKV outcomes (2017b). The toolkit is divided into three modules for three specific target audiences: health care professionals, public health planners and managers, and community workers. The areas of focus include those mentioned in other WHO guidance (2016a, 2016b) such as psychosocial support for families, supportive IEC, monitoring children with CZS, and management of severe conditions (Broussard et al., 2017; WHO, 2017b). The toolkit goes into detail and provides specific guidelines for each target audience to successfully build their capacity to improve care and support for their respective communities (2017b).

Broussard et al. discuss many of the recommendations from the CDC and WHO in relations to care and support for those affected by ZIKV. One notable resource mentioned is the Zika Care Connect (ZCC). ZCC is a resource established per interim CDC guidelines, for pregnant women seeking clinical care. ZCC is a network of health providers including OB/GYN specializing in and dedicated to caring for ZIKV infection patients. Broussard mentions pediatric care and support and the need for increased "services from occupational, speech, and language" as well as developmental care, educational needs and additional specialists (Broussard et al., 2017; Esposito et al., 2017).

Research priorities for ZIKV

Vaccine Development and Therapeutics

Seven peer-reviewed articles go into detail about ZIKV vaccinations and therapeutics. Vannice et al. (2017) discuss the current ZIKV vaccine development and research priorities. To date, there is no clinically approved vaccination for ZIKV, however, there are 30 ZIKV vaccines in development. At the time of their publication, three candidates, per the FDA regulations, have advanced to human trials. There are ethical and safety concerns for vaccine target groups, for example, unknowingly pregnant woman in human trials. Another safety concern is the possible augmentation of other flavivirus infections, especially DENV, from the antibodies produced against ZIKV (Esposito et al., 2017).

For further ZIKV research and vaccine development, the risk-benefit ratio for both mothers and fetuses must be considered when introducing new vaccines (Vannice et al., 2017). Omer and Beigi (2016) explain this barrier in their research. The authors emphasize the importance of pregnant women in vaccine trials and how they are a frequently overlooked target group despite being the most critically affected by ZIKV. There are several barriers to develop a vaccine for pregnant women, one of which is the lack of a broadly accepted ethical framework. Therefore, there is not a fair review of the risks and benefits for pregnant women or their fetuses in clinical vaccine trials (Omer & Beigi, 2016; Emory Health Sciences [EHS], 2016). Pregnant women are such a key group affected by ZIKV and the detrimental effects seen in their newborns may outweigh the risks of taking the vaccines during pregnancy.

Another barrier is the limited data available on the effect of vaccines during early pregnancy. This is critical considering a many detrimental ZIKV effects occur during this stage

of pregnancy. Additional clinical research before pregnancy or in the first trimester will be very informative (Omer & Beigi, 2016).

Fernandez and Diamond (2017) emphasize the necessity of weighing the risks and benefits and how additional data is needed to investigate the risks of ZIKV in pregnant women. Previous vaccination research has failed to conclude adverse outcomes in fetuses and vaccinated mothers (p. 64). Outright excluding women in ZIKV clinical trials can be harmful. For vaccines recommended during pregnancy, such as pertussis and influenza, pregnant women were originally excluded however, the benefits of immunizing them outweighed the risks (Cohen, 2017). The vaccination for ZIKV has the potential to do the same if the benefits prove to outweigh the risks.

C. Li et al. (2017) research discuss the potential for an FDA-approved drug in preventing ZIKV infection. The researchers studied the impact of chloroquine (CQ) as an antibody-based therapeutic which has been studied in mice models. Although antibody-based therapies have shown success in mice models, there are several limitations including the high costs, limited supply, and untested safety measures in human models. The researchers selected CQ after screening 16 Ebola virus inhibitors, all of which were FDA-approved. Among those, CQ was found to have efficiently inhibit ZIKV in vitro. The research in the mice models further validated that CQ "suppresses ZIKV infection in mouse models in vivo and protects embryonic brains from ZIKV infection and its associated microcephaly" (C. Li et al., 2017, p. 190). CQ is used as anti-malaria treatment and was previously investigated in two DENV infection clinical trials. Not only is CQ widely available but has been proven clinically-safe in pregnant women and their infants, two key factors for global distribution pending approval.

Mittal et al. (2017) and Aliota et al. (2017) emphasize the need for further research and development for anti-ZIKV therapies. As seen with the CQ, the notion of drug repurposing is encouraged as a promising method to inhibit ZIKV transmission (Aliota et al., 2017; Mittal et al., 2017). Drugs that have been FDA-approved and under consideration include sofosbuvir, niclosamide, ivermectin, mefloquine, and daptomycin (Mittal et al. 2017). The authors underscore lessons learned from HIV epidemic in suggesting combination therapy to control ZIKV; focusing on pre-exposure prophylaxis as an agent to prevent transmission as a more effective strategy than treating ZIKV in pregnant women (Aliota et al., 2017; Mittal et al., 2017).

Limitations

The CASPER had its own limitations. First, the surveys were household-based and used self- reporting thus, there was the potential for social desirability and recall bias from participants. This may have inflated knowledge and positive perception levels from the surveys. The findings may be limited because one individual was responding on the behalf of an entire household. Additionally, the systematic selection of households was challenging due to varying cluster size, terrain, and inaccessibility of homes in certain areas.

There were several limitations to the literature review. First, this study had a specific geographical scope. Although it discusses US territories, it was specific to USVI and especially Puerto Rico. This limits the generalizability to other US territories or areas of the US. Another limitation was the scarce peer-reviewed literature on the USVI. Of the 42 peer-reviewed articles, only two were related to USVI and other material addressed the Latin American/ Caribbean area in general. This highlights the importance for additional research and data on ZIKV in USVI.

Furthermore, the search focused on the four strategic response areas as identified by the WHO. These generalized topic areas may exclude other response fields that are critical to

emergency preparedness and strategic responses to public health issues. Only including literature from the WHO and CDC also excluded additional grey literature that may have been useful to this review.

Finally, all literature included was published only in English. It would have been significant to include articles in other languages notably Spanish for Puerto Rico and any literature about Latin America at large. These excluded articles may have provided additional information reinforcing the conclusions and recommendations for further ZIKV research.

DISCUSSION

The literature covered a vast array of response and policy areas concerning ZIKV. The current efforts to contain the ZIKV are dependent on how well each of the strategic areas is implemented. There has been detailed research conducted on detection and prevention of ZIKV. However, there is a need for further research on the pathogenesis of ZIKV. Pathogenic information can help in development for vaccinations, especially for target groups. The literature has suggested there are large amounts of evidence and information for diagnostic tools, personal protection mechanisms including safe sex practices, vector control, and entomological research. This review has revealed the need for additional research and to address the following public health implications as they relate to ZIKV.

As ZIKV transitions from a PHEIC to a continual global health concern, similar to HIV/AIDS, it is important that the response adapts as well. A comprehensive, integrated approach is the ideal method in successfully combating the ZIKV epidemic. Former Director-General of WHO asserted the need to shift from individual case management "towards the longer term building of capacities in countries to cope with these added burdens" (Gulland, 2016, p. 1).

The results from the CASPER revealed the need to further understand areas regarding ZIKV diagnostics, care for those suffering from CZS, and treatment and vaccine development for ZIKV. The literature review explored areas of research that the CASPER did not provide. The CASPER discussed ZIKV prevention, vector control, and communication strategies. The literature review provided supplementary information emphasizing the CASPER results concerning low knowledge and practices related to preventing the sexual transmission of ZIKV. The literature also underscores the need for enhanced risk communication and community engagement.

Based on the information highlighted from the CASPER and the literature, there are five principal and recurring recommendations that public health agencies and other stakeholders should heed for optimal strategic response. These include: increased public funding for emergency response, improved risk communication and community engagement, enhanced access to contraceptives, the addressing of human rights issues in the context of ZIKV, and further areas of research including vaccine development for target populations (e.g., pregnant women).

Public Health Implications

Increase Public Funding

Financing a global health response is not an easy task, especially when an outbreak is as unexpected and high-caliber like ZIKV. The fluctuating methods for funding undercut the full capacity for proper emergency response. Financial investments at federal, state, and local levels are necessary. However, state, territorial and local departments of health end up relying heavily on CDC for their funding (McCloskey & Endericks, 2017). The Public Health Emergency Preparedness (PHEP) cooperative agreement has been the sole source of federal funding in support of public health emergency preparedness throughout the nation (Redd & Friden, 2017). This agreement is critical in the strategic response to epidemics such as ZIKV, although, with an almost 40% decline in funding from its peak in FY2006 (Watson et al., 2017), it is hindering the progress for preparedness activities. To ensure adequate response to at-risk ZIKV areas and other public health emergencies, there must be an increase in the PHEP funds to accelerate research leading to vaccine development (Patel, 2016).

Establishing a separate fund particularly for emergency responses is crucial as well. Once an emergency occurs, departments of health shift from preparedness to response activities. In the case of ZIKV as with many other emergencies, there was a substantial reliance on emergency funding which caused delays in detection of the virus and decreased laboratory capacity. By allocating a section of the health budget for public health emergency response, it will ensure quick and timely distribution of funds to state, territorial and local health departments upon the declaration of an emergency (Watson et al., 2017; Kluge et al., 2018).

Improve Risk Communication

Risk communication is an integral part of the strategic response to public health emergencies. It is vital that those at risk of contracting ZIKV are aware of all their options and make informed decisions to protect themselves from infection by utilizing experts and health officials providing IEC.

Risk communication must also be timely and culturally appropriate. IEC must be tailored to the individual communities. Community engagement in ZIKV response efforts is another important aspect (Duchin, 2016; Forman, Mehta, Louis, Finneseth, & Yarrington, 2017). Communication specialists should engage with the local communities for the most efficient method of delivering risk communication messaging. It is recommended to have continual, reliable and frequently updated information between stakeholders and key populations (WHO, 2016c). Understanding the risk factors varying populations face will also help with risk communication. Researchers should determine what language and communication barriers that may impede prevention efforts.

Ideological risk factors should be considered especially with the sensitivity of discussing sexual transmission of ZIKV and consequential pregnancies. In faith-based communities that

prohibit contraceptives, a different approach must be taken to minimize the sexual transmission of ZIKV. The use of community gatekeepers, people of influence or in trusted positions, will allow the target audience to be more responsive to the information they receive (Santibañez et al., 2017).

It is vital to listen to communities and not dismiss their fears and concerns. Simultaneously, effectively clarifying misconceptions and misinformation is important (WHO, 2016c). Gaining the community's opinion on insecticide spraying methods was influential in how the USVIDOH proceeded with vector control measures. Approximately 75.3% of households believe that the USVIDOH should be spraying or fogging for vector control purposes. Citizens recalled and approved truck spraying in past years but were wary of aerial spraying and associated that with mistrust of the government (Roth et al., 2017).

Results from the CASPER survey reaffirm the necessity for community engagement in risk communication. After over a year and a half of IEC promoted throughout the community, the population's awareness and perceptions of ZIKV provided robust information to tailor future messaging from the USVIDOH. Evidence from the CASPER suggests that the USVIDOH can adapt their messaging for better reception. For example, the most preferred modes of communication were broadcast and print media, while TV was the most trusted. Future communications methods should target these modes for the most effective outreach (Roth et al., 2017).

Monitoring and evaluating these messages is as imperative as distributing them. To understand what is working and changing will allow public health agencies to see how to amend their IEC as the community responds to the epidemic. The 2016 KAP survey conducted by the USVIDOH helped inform their ZIKV messaging (Prue et al., 2016). Recognizing the knowledge

gaps in the community allowed program planners to bolster their efforts and tailor future programs to increase ZIKV transmission knowledge and emphasize protective measures (Prue et al., 2016). By incorporating risk communication into the following survey in June 2017, it created an evaluation of their approach which was modified as the epidemic was winding down.

Improved risk communication is also essential in vaccine development especially for pregnant women due to safety concerns. Proper risk communication must be in place to ensure all risks and benefits are shared. There have been instances of low public trust in immunization programs. Health providers and policymakers need to build trust when communicating the risks and benefits of potential ZIKV vaccines to patients and the general population for the best reception and uptake (Bouder, 2015).

Enhance Access to Contraceptives

With increasing evidence linking ZIKV to CZS in infants as well as other neurological complications such as GBS, it is paramount that preventative measures be improved. Until ZIKV vaccinations are available, increasing access to contraceptives, and other SRH services and education is a key recommendation. Sexual transmission of ZIKV and subsequent pregnancies can be averted with a focus on contraception methods as a primary prevention strategy.

Evidence from the 2017 USVI CASPER underscores the need for increased SRH education and services related to ZIKV. Only 44.8% of households agreed that ZIKV could be sexually transmitted. Most households (90.1%) agreed that ZIKV can spread from mother to unborn child. Despite that, only 16.1% of households responded that they always used condoms to prevent ZIKV (Roth et al., 2017). Results indicate that IEC around sexual transmission should be reevaluated. One consideration from the CASPER is to develop a culturally sensitive awareness campaign specifically on the sexual transmission of ZIKV and further promote

personal protection measures related to SRH (e.g., condom usages, contraceptives and delaying pregnancy).

With Puerto Rico leading with the number of ZIKV cases in the US and its territories, it is critical that such prevention measures be encouraged. Although women have been advised about the link between ZIKV and adverse birth outcomes, Puerto Rico has a very high rate of unintended births (Tepper et al., 2016). In the framework of ZIKV, preventing unintended pregnancies is especially important in reducing the chances of CZS. Tepper et al. (2016) estimated 138,000 women of reproductive age do not desire to nor use effective contraception in Puerto Rico. Barriers to accessing contraception include cost, limited availability, especially of long-acting reversible contraceptives, and lack of SRH education (R. Li et al., 2017; Velez & Diniz, 2016; Tepper et al., 2016; Rodríguez-Díaz, Garriga-Lopez, Malave-Rivera, & Vargas-Molina, 2017). Establishing coordinated response to address those barriers will allow many women who desire to avoid or delay pregnancy the opportunity in a long-lasting, effective manner.

Z-CAN is one example of a program that increases contraceptive access and improves SRH services. The program was designed to decrease the impact of ZIKV on mothers and infants by concentrating on gaps in contraceptive access (CDC, 2016b). The implementation of this large-scale comprehensive program proved to be very successful in Puerto Rico. The program saw substantial increases in contraceptive method usage by women after their initial visits to a Z-CAN provider compared to before the visit. This program proves the ability and capacity to rapidly establish a high-caliber program with contraceptive services in an emergency response (Lathrop et al., 2018).

Preventing unintended pregnancies have beneficial outcomes for both mother and child. Research has revealed the potential cost-effective and cost-saving results of increasing access to contraception specific to Puerto Rico. Studies suggest an increase in access to contraception will lead to a 25% reduction in unintended pregnancies and ZIKV-associated microcephaly, and a $65.2 million reduction in ZIKV-related costs (R. Li et al., 2017). With extreme health and monetary benefits, increasing contraceptive access is a highly recommended prevention strategy (R. Li et al., 2017; Tepper et al., 2016).

Address Human Rights

The WHO stated that "the burden of Zika falls on the poor" (Velez & Diniz, 2016). Women facing the largest SRH burdens often have high socio-economic burdens as well. Birth control and proper SRH is a human right; "the right to health has long been understood to include the right to choose 'the number, spacing and timing of their children" (Rasanathan et al., 2017, p. 528). Women of childbearing age in ZIKV-affected areas should have access to multiple birth control options including safe-abortion practices. Similar to the HIV epidemic, promotion of condoms rather than abstinence is more effective in combating the epidemic.

An effective approach to tackling ZIKV would be to address the human rights faults. It is understood that equitable access to safe, affordable and effective forms of contraception will address SRH rights disparities (Velez & Diniz, 2016). Unfortunately, recommendations for safer sex practices and vector control methods are challenging for affected populations. Recommendations should address structural challenges to vector control and access to SRH services. Working with the community would elucidate their concerns and assist in creating truly effective response reform (Rasanathan et al., 2017).

It has long been apparent the differences in government infrastructure in US territories compared to the continental US (Rodriguez-Vila, Nuti, & Krumholz, 2017). The ZIKV epidemic presents the US government an opportunity to address the disparities in healthcare in its territories. The recent devastation from Hurricanes Maria and Irma have only further exacerbated such disparities in Puerto Rico and USVI (Zorrilla, 2017). With populations in rural areas not able to access electricity and running water, less immediate concerns such as SRH, are deprioritized (Roa, 2016). Now vector control becomes a critical issue; hurricanes and their aftermaths can worsen mosquito-borne virus transmission and in this case, reactivate the ZIKV outbreak (Zorrilla, 2017; Rodríguez-Díaz et al., 2017). Addressing environmental concerns in impoverished populations with a higher mosquito population is critical.

Further Research Agendas

Lastly, further ZIKV research is recommended because, due to its novelty, little research has been conducted until this most recent outbreak. Additional information is needed in all aspects of the disease from pathogenesis to therapeutics. The evidence-based research will give health agencies a better understanding and tools to effectively and efficiently combat the arbovirus.

Vector control is a standard and prominent preventive measure with mosquito-borne diseases. One challenge, however, is finding an insecticide or larvicide that the mosquito species are not resistant to (Erbelding & Cassetti, 2017). Further research into mosquito olfaction is necessary for identifying novel strategies and technologies for vector control. This could subsequently address multiple mosquito-borne diseases.

The research conducted on ZIKV up to this point has revealed concerns that need to be further investigated (Hoffman & Silverberg, 2018). Particularly, for diagnostic testing, it is

important to develop serological tests to differentiate ZIKV from other flaviviruses. Since there is considerable cross-reactivity between ZIKV and DENV, there needs to be a focus on high accuracy diagnostic testing approaches (Erbelding & Cassetti, 2017). Evidence establishing the causality between ZIKV and microcephaly will provide clinical information and guide policy changes (Iskander, Rose, Ghiya, 2017). Further research concerning potential high-risk sexual transmission of ZIKV is also needed. Communities with a high prevalence of unprotected sex, such as men who have sex with men, are at risk for sexual transmission of ZIKV (WHO, 2017a). Results from this literature review support the need for research on US territories, in particular, USVI. American territories and underrepresented populations have been excluded from national databases. Without robust data, healthcare disparities will continue to occur (Rodríguez-Víla et al., 2017). General research on ZIKV is necessary, but additional research on communities and at-risk populations are equally significant.

Vaccination Development for Pregnant Women

Currently, there are no clinically approved vaccines for ZIKV, but work is being done to adapt potential vaccines from existing flavivirus vaccines. Therefore, additional research should be conducted on "the effect of pre-existing immunity against other flaviviruses on the immunity against ZIKV" (Sharma & Lal, 2017). Although there is low genetic variation in the different ZIKV strains, research should explore vaccine that contains cross-protection for the two ZIKV lineages but does not simultaneously induce "antibody enhancement" of other flaviviruses.

Pregnant women are an overlooked target group in vaccine development. Although women of childbearing age and their partners have been warned about the association of ZIKV and CZS, many subsequent pregnancies are unplanned. In order to protect the fetus, the mother must achieve immunity. Vaccinations would help stop sexual and mother-to-child transmission

of ZIKV. Focusing on this population can "translate into a global improvement in maternal-child health" (Hydzik, 2016, n.p.). Addressing these public health implications as they relate to vaccine development for pregnant women is a fundamental ZIKV preventative approach.

The risk to benefit ratio of vaccinating pregnant women and the effects on their fetuses must be analyzed (Omer & Beigi, 2016). The cost of ZIKV vaccine compared to treatment cost must be assessed. Additional research and public health policy need to be integrated for the successful development and execution of a ZIKV. Although it is typically difficult to maintain the scientific and financial interest of the healthcare community as the epidemic declines, it is imperative research continues especially with the development of vaccines and therapeutics for ZIKV. These should be prioritized as an optimal initial strategy in confronting the ZIKV (Haque, Akçeşme, & Pant, 2017).

CONCLUSION

This review highlights the significant progress made since the ZIKV epidemic began a few years ago. It also illustrates that there are additional consolidated efforts to be made. A shift to a more structured and integrated approach in the strategic response to ZIKV in the future will help avoid any impending outbreaks and contain the effects of the current epidemic.

This systematic review demonstrates that ZIKV infection is a relatively novel topic in the global health community. The majority of cases of ZIKV are asymptomatic, however, those that are infected, specifically pregnant women, have more severe outcomes including CZS, GBS, and other congenital complications in their newborns. Future research should focus on understanding the causal relationship between ZIKV and GBS, and vaccine and therapeutic developments. Pregnant women and their unborn fetuses are the most severely affected populations, so strict attention to prevent ZIKV mother-to-child transmission is a key focus area.

Second, the human rights aspects of ZIKV is another strategic area to be addressed. The ongoing response must prioritize marginalized populations who are most vulnerable to ZIKV. An enhanced understanding of the geographic and socio-economic disparities among affected communities will continue to be critical in advancing ZIKV prevention and care and support.

Although ZIKV has transitioned from an emergency to a seasonal, endemic concern, it is critical that research and continued public attention is given to this critical issue. Should a similar outbreak occur, governments, multilateral organizations, clinicians and other public health professionals must concentrate strategic response on targeted critical areas. There is a dire need for increased public funding for emergencies and ongoing global health burdens. This research highlights that focus on the most affected areas of the US, USVI and Puerto Rico, is critical for an effective strategic response.

Overall, the strategic planning and actions for ZIKV in Puerto Rico and USVI have addressed the critical areas of ZIKV however, improvements remain. Such changes will have extensive population-based health benefits. Now is the time to implement the necessary actions before another public health emergency occurs.

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APPENDIX

Summary of Findings Table

First Author, Year	Geographic Area	Strategic Response Area/ Key Words	Key Points
Aliota, 2017	United States	Care & Support: Clinical manifestation; Research: Therapeutics, Vaccinations	Background information on transmission mechanisms and the spectrum of congenital defects. Provides current updates on vaccination development, antiviral therapeutics, and diagnostic testing; to date, no clinically approved vaccine or antiviral therapeutics.
Broussard, 2018	United States	Care & Support: CZS; Prevention: Emergency Response; Research	Surveillance on ZIKV birth defects to help inform research objectives and priorities; Several pregnancy cohort studies with public health agencies being conducted globally. Using the surveillance and research to inform best practices for obstetric, maternal-fetal, pediatric and interdisciplinary care.
CDC, 2016a	United States	Detection: Surveillance; Prevention: Vector Control	Guidelines and recommendations for conducting surveillance for *Aedes aegypti* and *Aedes albopictus* mosquitoes and subsequent reporting. Also information on testing insecticide resistance for the vector of ZIKV, DENV, and CHIKV.
CDC, 2016b	Puerto Rico	Care & Support: Pregnancy, GBS + other neurological complications, ZIKV+ population; Detection: Surveillance	CDC in collaboration with PRDH established several systems in place to combat the current ZIKV outbreak including: Zika Active Pregnancy Surveillance System (ZAPSS), Contraceptive Assessment in Puerto Rico during Zika (CAPRZ), Pregnancy Risk Assessment Monitoring System (PRAMS) Zika Postpartum Emergency Response (ZPER) Survey, Zika Contraception Access Network (Z-CAN) Evaluating the Diagnostic Utility of PCR-testing for Zika Virus on Whole Blood (Epi-Aid).

CDC, 2016c	Puerto Rico	Detection: Surveillance	Summary of ZAPSS in Puerto Rico; surveillance system by PRDH and CDC to evaluate the association between ZIKV infection and pregnancy, adverse outcomes of pregnancy and through early childhood up to age 3.
CDC, 2017a	United States	Detection: Diagnostic Testing, Surveillance;	Overview of ZIKV detection, testing methods, laboratory guidance, and reporting. Testing recommendations are for symptomatic and asymptomatic pregnant women with possible ZIKV exposure, pregnant women with possible ZIKV exposure as identified in ultrasounds, and non-pregnant symptomatic individuals with possible exposure to areas at risk of ZIKV transmission.
CDC, 2017b	United States	Prevention: Preparedness; Emergency Response	Updated guidance and resources addressing preparedness (case surveillance, pregnancy, and birth defect surveillance, vector control, blood and tissue safety, communication) and response (CDC Emergency Response Teams, At-Risk geographic areas, and response to suspect vs. confirmed cases) activities for ZIKV in the US.
Chevalier, 2017	Puerto Rico	Detection: Screening; Blood Donations	Asymptomatic infections are a large contributor to blood transfusion-transmission. There is a need for integrated efforts: screening of blood results, immediate communication of results to patients (especially to avoid sexual transmission) and local PH authorities, appropriate prevention messaging, etc.
D'Angelo, 2017	Puerto Rico	Prevention; Pregnant Women, Vertical Transmission	Targeting messaging to pregnant women and those of reproductive age to encourage consistent use of preventative measures; Pregnancy Risk Assessment Monitoring System (PRAMS) discussed
Dirlikov, 2016a	Puerto Rico	Prevention: Preparedness; Care & Support: Patient Management	Increased ZIKV transmission will lead to additional health care needs for patient management of GBS (3-5 times more than in years without ZIKV transmission)
Dirlikov, 2016b	Puerto Rico	Detection: Surveillance, Reporting	Reports of GBS occurring and confirmed throughout PR; Emphasizes the need for reporting method for GBS to the appropriate surveillance systems such as GBS PSS.

Dirlikov, 2016c	Puerto Rico	Detection: Surveillance; Prevention: Vector Control;	PRDH & CDC incorporated ZIKV case reporting/ diagnostic testing into existing dengue & chikungunya surveillance systems; Study conducted to develop vector control strategies especially focused on preventing infection of pregnant women
dos Santos Oliveira, 2016	Latin America	Care & Support: Microcephaly, Maternal Mental Health	Need for psychosocial support for newborns and especially mothers which can make a significant contribution to maternal mental health.
Duchin, 2016	United States	Prevention: Emergency Response, Preparedness	Key elements for public health emergency response: robust surveillance and disease investigation capacity, strong collaborative systems, mutual communication exchange, excellent incident management systems, proactive engagement from all stakeholders, and effective community engagement.
Erbelding, 2017		Prevention: Vector Control; Research: Vaccinations	Difficult to keep up the momentum now that ZIKV is no longer a PHEIC; need further research and information in understanding the mosquitos to ensure an effective vector control insecticide is established that does not end up being resistant in such mosquitos.
Esposito, 2017		Detection; Research: Vaccinations	Additional research needed on their impact of ZIKV infections on pregnancy; further testing for vaccines for children and pregnant women separately
Fernandez, 2017		Research: Vaccinations	Presents the current efforts of ZIKV vaccine development, issues with cross-reactivity concerning DENV, and greatest challenges towards rapid implementation.
Forman, 2017		Prevention: Emergency Response; Challenges	Necessities for ZIKV response include universal screening methods, use of electronic methods, and community engagement
Goldfarb, 2017		Detection: Diagnostic Testing; Care & Support: Guidelines	Shift to shared decision making for ZIKV diagnosis is becoming an issue; a critical need for supplementing/augmenting the CDC guidelines for testing/diagnosis

Gulland, 2016	Latin America	Detection: Surveillance, Reporting	Increasing rates of ZIKV transmission and GBS in affected areas; discussion of vaccine development; A shift from individual case management to larger scale approaches is needed to properly address ZIKV outbreak
Haque, 2018		Research: Vaccinations	A systematic review of challenges in establishing a ZIKV vaccine and ways to overcome the barriers. Explains the traditional platforms and new tools used to create ZIKV vaccinations
Hoffman, 2018		Prevention: Emergency Response; Delays	Surveillance capacity challenges are not the reason for delays, rather slow political mobilization; there was a two-month delay between when PAHO warned about the severe outcomes of ZIKV and when the WHO declared a PHEIC. Several hypotheses on what elicits faster responses for certain PHEIC
Iskander, 2017	United States	Prevention: Emergency Response, Preparedness	The use of a scientific response structure will help urgently address public health emergencies and guide future policy. Several uses of science in emergency response of ZIKV such as establishing the causality between ZIKV and microcephaly.
Kluge, 2017	United States	Prevention: Emergency Response, Preparedness; Global Health Systems	Emergency responses to health threats involve coordination, financing, incident management systems, public awareness and community engagement, underpinned by strong government commitment and resources.
Lathrop, 2018	Puerto Rico	Prevention: Personal Protection; Contraception	The Zika Contraception Access Network (Z-CAN) is a large-scale implementation of a program providing extensive access to contraceptives during a PHEIC.
Li, C., 2017	United States	Prevention; Research: Therapeutics, Vaccines	Positive effect of chloroquine as a ZIKV inhibitor in mice, continued research and testing can lead to it being used in humans as a prevention/therapeutic tactic; furthermore, chloroquine is easily accessible globally and safe for pregnant women who are a critical at-risk group

Li, R., 2017	Puerto Rico	Prevention: Personal Protection; Contraception Access; Cost-effectiveness	Reducing unwanted pregnancies and delaying pregnancies via increased contraception have significantly reduced the health care costs associated with ZIKV and Zika-associated microcephaly
McCarthy, 2016	Puerto Rico	Prevention: Vector Control; Aerial Spraying	Using similar guidelines for mainland US: EPA is encouraging aerial spraying targeting *Aedes aegypti* mosquitoes which is especially a concern to avoid infection of pregnant women and avoid birth defects; US government will fund it; however, the decision is up to PR government
McCloskey, 2017		Prevention: Emergency Preparedness, Risk Communication	The purpose of the PHEIC declaration for ZIKV was not to stop the spread of the disease that same way it way for Ebola; need to address funding; cannot rely on an ongoing threat to sustain funding and response capacities.
Mittal, 2017		Research: Pathogenesis, Therapeutics; Detection: Diagnostic tools	Extensive background information including the clinical presentation of ZIKV infection and epidemiology of ZIKV. Also, includes pathogenesis and animal models to further study ZIKV
Munoz-Jordan, 2017	United States	Detection: Diagnostic Testing	Outlines CDC guidelines for testing pregnant women; thorough information about various detection methods of ZIKV
Omer, 2016		Research: Vaccinations	Despite the safety and ethical concerns for pregnant women, there is a need to develop vaccines targeting this population. Pregnant women and their unborn fetuses are the most critical group of people affected by ZIKV; the risk vs. benefits should be thoroughly assessed.
Prue, 2017	US Virgin Islands	Prevention: Risk Communication, Community Engagement; KAP survey	Insights into knowledge levels and perceptions amongst the community about ZIKV; Gaps in awareness and knowledge need to be addressed in future ZIKV IEC

Rasanathan, 2017		Prevention: Human Rights; Emergency Response	Engaging human rights in the response of ZIKV is critical to provide effective and sustainable change and response plans. Key areas in which human rights relate to the ZIKV response include vector control, SRH, knowledge, and technology (namely for diagnostic testing and vaccine development), and health system preparedness.
Redd, 2017	United States	Prevention: Emergency Response, Preparedness	Includes lessons learned from previous outbreaks; the need for a multidisciplinary approach, improvements in communication strategies, and increased funding supporting emergency responses in particular
Roa, 2017	Latin America	Prevention: Personal Protection, Contraception; Human Rights	ZIKV outbreak exposes systematic failures especially in SRH; provides an opportunity for adjustments and improvements; recommendations focus on postponing pregnancies however 56% of pregnancies are unintended therefore there is the need for better quality sex education, access to contraception, and addressing of cultural barriers.
Rodríguez-Díaz, 2017	Puerto Rico	Prevention: Health Justice	Recommendations for preventing ZIKV must be taken in context; mistrust of government, etc. from local communities makes it even more difficult for implementing proper prevention techniques; More resources towards prevention via sexual intercourse and proper SRH services
Santibañez, 2017	United States	Prevention: Risk Communication, Community Engagement	Ten Step approach to engaging community and faith-based organization with strategic ZIKV response. Key areas of focus include community engagement, identifying risk factors, establish connections with community gatekeepers, take into consideration the local and cultural context for appropriate messaging, etc.
Sharma, 2017		Detection; Prevention: Vector Control	Includes thorough background information especially on pathogenesis and epidemiology as well as vaccine and antiviral therapeutic development progress; no clinically

			approved vaccines or anti-therapeutics, however, focus on establishing drug especially for pregnant infected women.
Tambo, 2017	Latin America	Prevention: Human Rights; Emergency Response	Responders must take into consideration the ethical and legal parameters when addressing prevention strategies for ZIKV programming. Interventions should attempt to uphold human rights doctrines; focus on SRH rights and increase to those services in especially vulnerable areas.
Tepper, 2017	Puerto Rico	Prevention: Personal Protection, Contraception Access, Cost-effectiveness	Study proves cost-effective methods to address ZIKV; critical to have a collaborative response to increase contraception in PR to avoid pregnancy and related ZIKV complications
Thomas, 2016	Puerto Rico	Detection: Surveillance, Reporting	PRDH works with CDC for surveillance and monitoring purposes. Improvements for laboratory and epidemiologic capacity are essential especially since a multidisciplinary approach is required in addressing ZIKV. Education and community clean-up campaigns as well as focus on pregnant women are all also necessary
Vannice, 2016		Prevention: Emergency Response; Research: Vaccinations	Vaccine development status; approximately 30 ZIKV vaccines for various target groups being worked on.
Vasquez, 2016	Puerto Rico	Detection: Screening; Blood Donations	PRDH and CDC working on rapid assessment for blood donations; a need for importation of blood from unaffected areas.
Velez, 2016	Latin America	Prevention: Human Rights; Contraception	According to WHO: "the burden of Zika falls on the poor." Many recommended protective measures are difficult for those in developing countries to adhere to; such measures include: afford A/C, proper window screens, and insect repellents.

Watson, 2017	United States	Prevention: Emergency Response, Preparedness	Need for increased federal funding for public health preparedness programs especially in localities that are at highest risk; Must address insurance and healthcare cost that pose a barrier to those seeking prevention and care methods
WHO, 2016a	Global	Care & Support: Pregnancy, GBS; Prevention	Thorough guidance of all pregnant women residing in areas with ZIKV transmission regarding prevention methods (vector control and personal protection), symptomatic treatment, various diagnostic testing and future research priorities.
WHO, 2016b	Global	Care & Support: Pregnancy, GBS + other neurological complications, ZIKV+ population	Information for families dealing with ZIKV complications particularly microcephaly and other neurological complications. Areas of focus include accurate and supportive IEC, dealing with common reactions/stigmatizations, basic psychosocial support, strengthening social support, stress reduction and parenting advice.
WHO, 2016c	Global	Prevention: Risk communication, Preparedness	Guidance on risk communication and community engagement concerning ZIKV prevention; Key messages include: core messaging for individual protection and community empowerment, community-based control and preventive behaviors for vector control, protective behaviors for high-risk and general population groups, identification of symptoms and care-seeking for affected persons, and enabling environment for vector control and ZIKV prevention
WHO, 2016d	Global	Detection: Surveillance, Guidance	Comprehensive guidelines for the various surveillance activities in the context of ZIKV based on geographic location and risk levels associated with ZIKV infection and resulting complications.

WHO, 2016e	Global	Prevention: Preparedness, Emergency Response	Extensive guidelines on ZIKV strategic response plan. Includes a situation update and risk assessment, response update on the key WHO areas (detection, prevention, care and support, and research) and an updated joint operations plan.
WHO, 2017a	Global	Research; Prevention: Personal Protection	Updated status on sexual transmission of ZIKV. Includes detailed sexual transmission framework, ongoing-evidence based studies, research gaps, and priorities.
WHO, 2017b	Global	Care & Support: ZIKV+ population	The toolkit provides manuals for health care professionals, public health planners and managers, and community workers. The manuals within outline methods for mainstreaming services for those affected by ZIKV and coordination and delivery for enhanced care and support.
Zorrilla, 2017		Detection: Diagnosis; Clinical Manifestations; CZS	Explanations of the clinical manifestation of ZIKV in pregnant women and the birth outcomes of their children. Discusses laboratory and ultrasound evaluation diagnosis processes as well.