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Research Article

NAVIGATING REGULATORY STRATEGIES TO DEFEAT ZIKA VIRUS IN USA

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ABSTRACT

Z*ika virus has been emerged as the infectious agent daunting the world wide health .The shift of risk profile from mild to serious consequences lead it to declare as 'Public Health Emergency of International Concern' on February 1, 2016 by WHO. Going through the facts associated with Zika epidemic, cases of neuro-complications, Gillian–Barré syndrome (GBS) and microcephaly reported in infants, In order to control the situation authorities have been focused on vector control plan, publication of technical guidances or recommendations in context to pregnant women to health care practitioner and the risk assessment programs within the region are effectively working towards defeating Zika virus in USA. Meanwhile, FDA facilitates the accelerated approval process for ZIKV vaccines and diagnostics in terms of EUA and Expanded access submission to manage the Zika cases. On other site ensures the safe supply of blood, components and HCT/Ps through the guidances from FDA. Such outbreaks which have been reported in past are ambitious to deal with Zika virus disease more efficiently.*

KEYWORDS: *Zika virus, vector control plan, FDA, EUA, CDC.*

INTRODUCTION

Background:

Zika virus outbreak is an infectious emergent daunting the worldwide public health. Historically, 84 countries, territories and subnationals reported with vector borne ZIKV transmission worldwide. Outbreaks of Zika virus disease have been recorded in Africa, the Americas, Asia and the Pacific. Firstly identified in Uganda forest in 1947 in monkeys and in 1952 human case was reported in Uganda and the United Republic of Tanzania. The Island of Yap (Federated States of Micronesia) in 2007 suffered from first outbreak then it was followed by a large outbreak of Zika virus infection in French Polynesia in 2013-2014 and other countries and territories in the Pacific. Large outbreak of ZIKV reported in Brazil 2015-2016, there it was found to be associated with Microcephaly and other congenital syndrome. Consequences lead to declare it as "Public Health Emergency of International Concern" on 1 February 2016 by WHO. It suggests the urgent need for research and development (R&D) of preventative and therapeutic solutions for Zika virus disease. Maximum number of countries and territories has been reported high number of transmission through vector born transmission than other route of transmission [1].

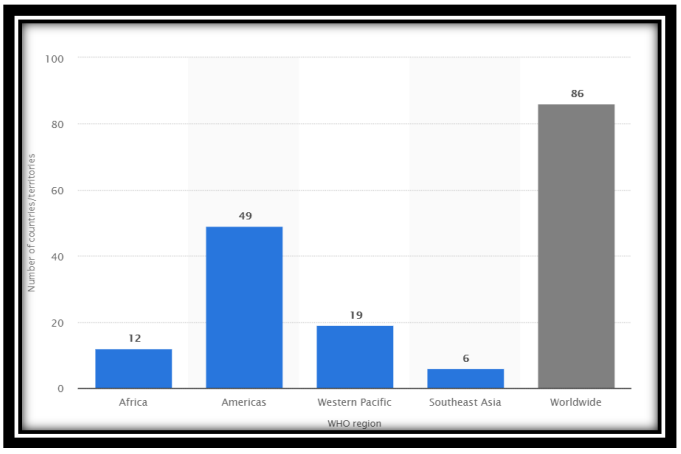

Fig. 1: Number of Countries and territories reporting mosquito born Zika Virus transmission as of February 2018 [2]

Cases Description in USA:

There is a study reporting case of non-vector transmission in U.S.A in 2008.In that study **c**linical and serologic evidences indicated that 2 American scientists infected with ZIKV while working in Senegal in 2008 and one of them transmitted it to his wife most likely through sexual route [3].

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During November 2015–September 2017, a total of 588 travel-associated Zika cases were reported in California, including 139 infections in pregnant women, 10 congenital infections, and 8 sexually transmitted infections. Sixty two case-patients were <18 years of age [4].

In 2017, USA has been categorised in Category 1 that presents area with new introduction or re-introduction with ongoing transmission by WHO in epidemiological situation report [5].

According to the 2016 CSTE surveillance case definition for Zika, 410 cases met the confirmed criteria and 178 were probable. In Americas the time period during year 2015-2016 was more reportable for the emerging cases of Zika virus infection, but later on the number of cases during 2017 declined due to assessment and preparedness efforts by the government [6, 7]. Miami Dade, Hidalgo County and Cameron County Palm Beach County areas has been CDC identified as areas to be at increased risk for ZIKV transmission during defined periods in 2016-18 [8].

Zika Virus Epidemiology:

Agent: ZIKV is an emerging 11-kb single stranded RNA arbovirus belonging to Flaviviridae of genus Flavivirus.

Reservoir: Evidences have been found for the presence of ZIKV antibodies in primate's monkeys and orang-utans in Africa and Asia. In recent pandemic the human host is reported to be responsible for local transmission.

linical Manifestation:

Maximum cases are asymptomatic (approx. 80%) and sever illness is not reported. Mild case has the sign and symptoms like fever, joint pain, headaches, retro-orbital pain, maculo-papular rash usually with itching, and conjunctivitis. Oedema of extremities, vertigo, myalgia and digestive disorder may also occur. In some pregnancy cases, microcephaly and other serious brain anomalies in neonates has been reported infection. In addition to microcephaly and brain damage other disorders like craniofacial disproportion, spasticity, seizures, irritability, ocular abnormalities and cortical disorders and ventriculomegaly in neonates and other neuropathy including acute motor axonal neuropathy, a type of Gillian–Barré syndrome may produce.

Transmission:

The following can be the route of transmission for Zika virus.

Table No. 1: ZIKV transmission mode [9, 10]

S. No.	Transmission mode	Description
1	Vector borne	Bite from the mosquitoes of *Aedes aegypti, Aedes albopictus, Aedes africanus and Aedes vexans species.*
2	Sexual	Virus reproduces itself in man semen.
3	Perinatal	Congenital transmission, ZIKV detected in brain tissue, placenta.
4	Blood born	Transmitted through infected blood and components.

Diagnosis:

Table No. 2: Diagnostic tests (traditional) [9, 10]

S. No.	Test type	Description
1	RNA nucleic acid test (NAT)	RT-PCR is suggested to perform on blood and/or urine collected from patients presenting with an onset of symptoms ≤ 7 days.
2	Serological test	IgM antibody testing is recommended to perform on blood from patients presenting with onset of symptoms ≥ 7 days. If CSF is available, it is to be used for testing on CSF.
3	Plaque reduction neutralization test [PRNT]	ZIKV [PRNT] titer ≥10, regardless of dengue virus PRNT value; or negative Zika virus IgM, and positive or equivocal dengue virus IgM.

METHODS AND MATERIAL

Regulatory Framework to Defeat Zika Virus in USA:

In US, Centre for Disease Control and Prevention (CDC) performs role of analysing, validating, monitoring, and reporting of Zika cases. It conducts the studies of related complication to ZIKV like microcephaly and Gillian–Barré syndrome.

- **CDC's Integrated Mosquito Management:**

IMM control mosquito's population based on an understanding of mosquito biology, the mosquito life cycle, and the way mosquitoes spread viruses to develop plans for controlling mosquitoes. IMM has been scientifically proven to reduce mosquito populations. This includes following steps.

i. Conduct mosquito surveillance:

CDC, "Integrated Mosquito Management for *Aedes aegypti* and *Aedes albopictus*" monitor places where adult mosquitoes lay eggs. The larvae that hatch from eggs are found in these same places

- Tracking mosquito populations and the viruses they may be carrying.
- Determining if EPA-registered insecticides will be effective.

ii. Remove places where mosquitoes lay eggs:

Professionals and the public can remove standing water to reduce mosquito larvae before they become adult flying mosquitoes.

iii. Control larvae and pupae:

Larvicides can be used in dumping water to kill larve before it becomes biting adult.

iv. Control adult mosquitoes:

The public and professionals can use US Environmental Protection Agency (EPA)-registered adulticides according to label instructions.

v. Monitor control programs:

To make sure that mosquito control activities are working, professionals monitor the effectiveness of their efforts to control both larvae and adult mosquitoes [11].

- **CDC Recommendations and Guidances:**

CDC publishes guidance and recommendations for pregnant woman, traveller and health care practitioner to control the cases of Zika virus.

i. Recommendations for Pregnant Woman:

- Asymptomatic pregnant women with on-going possible Zika virus exposure should be offered Zika virus NAT testing three times during pregnancy.
- For pregnant women who have received a diagnosis of laboratory–confirmed Zika virus infection (by either NAT or serology [positive/equivocal Zika virus or dengue virus IgM and Zika virus plaque reduction neutralization test (PRNT) ≥10 and dengue virus PRNT <10 results]) any time before or during the current pregnancy.
- For pregnant women without a prior laboratory-confirmed diagnosis of Zika virus, NAT testing should be offered at the initiation of prenatal care, and if Zika virus RNA is not detected on clinical specimens, two additional tests should be offered during the course of the pregnancy coinciding with prenatal visits.
- In this testing, patients and providers work together to make decisions about testing and care plan that is supportive of patient preferences and values, clinical judgment, a balanced assessment of risks and expected outcomes, and the jurisdiction's recommendations.

ii. Guidance for the Evaluation of Placental and Fetal Tissue Specimens for Zika Virus Infection:

Detection of Zika virus RNA has been reported in placental tissues and in Fetal and infant brain tissue 15–210 days (mean = 81 days) and 119–238 days (mean = 163 days), respectively, from maternal symptom onset. Among 546 live births with travel-associated possible maternal Zika virus exposure in the 50 U.S. states and the District of Columbia in 2016 for which placental specimens were submitted to CDC, 60 (11%) were positive for Zika virus RNA . When restricted to live births without a laboratory-confirmed Zika virus infection based on maternal or infant Zika virus testing of serum or urine, 47 of 482 (10%) were positive for Zika virus RNA. Although, the proportion of live births with positive placental reverse-transcription polymerase chain reaction (RT-PCR) results was relatively low, these results provided definitive evidence of maternal Zika virus infection during that pregnancy. As with serologic and NAT testing of serum and urine, the proportion of pregnancies with a positive Zika virus RT-PCR on tissue specimens is expected to decrease in the setting of declining prevalence of Zika virus disease in the Americas.

Finally, testing of placental and Fetal tissues may be considered in selected scenarios for pregnancies resulting in a miscarriage or Fetal loss/stillbirth (and testing of autopsy tissues in the event of an infant death) to provide insight into the potential etiology of the Fetal loss or infant death, which could inform a woman's future pregnancy planning.

iii. Guidance for Preconception Counselling and Prevention of Sexual Transmission:

CDC recommends waiting at least for 3 months to the men that has the symptoms onset (if symptomatic) or their last possible Zika virus exposure (if asymptomatic) and who are planning to engage in unprotected sex. This recommendation develops shared patient-provider decision making, in which couples and health care providers work together to make decisions about timeframes to wait before trying to conceive after possible Zika virus exposure [12-14].

Table No. 3: Preconception Counselling and Prevention of Sexual Transmission

Exposure Scenario	Recommendations
Couple planning to conceive, only male partner travels to the area with risk for Zika virus transmission	The couple should use condoms or abstain from sex for at least 3 months after the male partner's symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic)
Couple planning to conceive, only female partner travels to the area with risk for Zika virus transmission	The couple should use condoms or abstain from sex for at least 2 months after the female partner's symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic).
The couple should use condoms or abstain from sex for at least 2 months after the female partner's symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic).	The couple should use condoms or abstain from sex for at least 3 months from the male partner's symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic)
One or both partners have on-going exposure (i.e., live in or frequently travel to an area with risk for Zika virus transmission) and couple planning to conceive	Plans for pregnancy, their risk for Zika virus infection, the possible health effects of Zika virus infection on a baby, and ways to protect themselves from Zika should be discussed, If either partner develops symptoms of Zika virus infection or tests positive for Zika virus infection, the couple should follow the suggested timeframes listed above before trying to conceive.
Men with possible Zika virus exposure whose partner is pregnant	The couple should use condoms or abstain from sex for the duration of the pregnancy.

- **FDA Assessment for the Reduction of Risk for ZIKV Infection:**

Considering the ZIKV outbreak in French Polynesia, 2013-2014, 2.8% of blood donors tested RNA positive by nucleic acid testing (NAT). Brazil also witnessed the transfusion derived transmission of ZIKV in December 2015 it becomes mandatory to provide assessment to transfusion process to reduce the risk of ZIKV. FDA avails the recommendations to ensure the safe supply blood of blood products to control the blood born transmission of ZIKV. It suggests the blood establishments to assess to blood donation screening, public health surveillance.

Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components:

This guidance is for immediate implementation in accordance with 21 CFR 10.115(g) (2) without initially seeking prior comment. In August 2016, FDA recognized ZIKV as a relevant transfusion-transmitted infection (RTTI) under Title 21 of the Code of Federal Regulations (CFR) Part 630. Recommendations are applicable to the collection of Whole Blood and blood components but not to the collection of Source Plasma.

- **Risk Assessment of MP NAT Strategy for ZIKV:**
  FDA's computational model, support the use of MP NAT as a strategy to adequately and appropriately detect early infections in an outbreak, while reducing the burden of ID NAT testing.

- **Recommendations:**
  The following recommendations from FDA are intended to reduce the risk of ZIKV transmission through the transfusion of blood and blood components.

- **Testing or pathogen reduction:**
  For the compliance with the requirements in 21 CFR 610.40(a) (3), it is required to;

1. Use either licensed MP NAT or ID NAT to test all donations collected in the U.S. and its territories. Prefer ID NAT in certain threshold conditions;
- When there is detection or notification of a ZIKV reactive donation in a defined geographic collection area.
- When there is notification by CDC or other public health authority, such as a state or local health department, of areas at increased risk for ZIKV transmission in a collection area, even in the absence of ZIKV-reactive donations

OR

2. Use pathogen reduction technology with an FDA-approved pathogen reduction device according to the manufacturer's instructions to collect and prepare blood components. As described under 21 CFR 630.10(a), blood or blood components must not be collected from the donor volunteers a recent history of ZIKV infection and defer such a donor for 120 days after a positive viral test or the resolution of symptoms, whichever timeframe is longer (21 CFR 630.35(a)).

A Recommendations regarding switch between MP NAT and ID NAT when threshold conditions to trigger or detrigger are present:

1. Switch to ID NAT from MP NAT when certain threshold conditions are present in a defined geographic collection area.

Followings are the triggers for the ID NAT:

i. ZIKV reactive donation is found in a defined geographic collection area in form of notification or detection and blood donor screening.
ii. Notification from CDC or other public health authority of an increased risk for ZIKV transmission in a county or county equivalent, even in the absence of ZIKV-reactive donations.

It is recommended to develop a standard operating procedure (SOP) for the blood establishments in same geographic area to communicate such ZIKV-reactive results with other blood establishments in that same geographic area in following consequences.

If collection of ZIKV-reactive donation in a county was from previously listed area of increased risk for ZIKV transmission by CDC. Local mosquito-borne transmission is presumed.

If the collection of ZIKV-reactive donation in a geographic was not from the listed as area at increased risk for ZIKV transmission, assess the donor for possible ZIKV exposure outside the collection area within the 30 days prior to the ZIKV-reactive donation.

2. Even if there have been no ZIKV-reactive donations in the area, convert to ID NAT within 24 hours of obtaining the test result, or being notified of a test result by a different blood establishments. Because there may chances that donor's infection most likely resulted from travel areas or the collection area has not been yet identified as the increased risk for ZIKV transmission
3. Continue ID NAT until Detrigger are not seen to resume MP NAT.

Resume MP NAT after discontinuing ID NAT in case the triggering is based on a ZIKV-reactive donation only, and there is adequate information which reasonably conclude that the donor's infection may not due to local mosquito-borne transmission within the geographic collection area.

Resume MP NAT, when local mosquito-borne ZIKV transmission is presumed in the geographic collection area or ZIKV exposure is not identified and the triggering is based on ZIKV reactive donation only, in such case continue ID NAT at least for 14 days.

MP NAT can be used if CDC or other public health authority does not consider the area at increased risk for ZIKV transmission at least 14 consecutive days.

C Donor and Product Management:

1. While screening with MP NAT, release all units whose test samples comprise a non-reactive minipool and provide all other donation suitability requirements are met (21 CFR 630.30).
2. For testing of each specimen in the minipool to identify the unit(s) that led to the reactivity of the minipool, it is required to resolve a NAT –reactive minipool using ID NAT according to manufacturer's instructions in the package insert (21 CFR 606.65(e)).

3. Manage the donor and the individual donation based on the ID NAT results.

ID NAT non-reactive donations with all other donation suitability requirements (21 CFR 630.30) are being released.

ID NAT reactive for ZIKV, it must not distribute or use the donation unless an exception exists (21 CFR 610.40(h)).

D Labeling of Whole Blood and Blood Components Intended for Transfusion:

In accordance with 21 CFR 606.122(h), the circular of information must include the names and results of all tests performed when necessary for safe and effective use. Circular of information to include the non-reactive test result using a FDA-licensed test for ZIKV (21 CFR 606.122(h)) must be updated [15].

Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products:

In case of ZIKV-associated deaths ZIKV RNA has been found in brain, liver, kidney, lung, and other organs of persons Studies in rhesus macaques also indicate presence of ZIKV in these and other organs and tissues. Same scenario has also been reported French Polynesia, where 2.8% of specimens collected from asymptomatic blood donors were found to contain detectable ZIKV RNA In 2016, screening of asymptomatic blood donors in Puerto Rico identified that approximately 1% of donor specimens were ZIKV RNA positive.

FDA has identified ZIKV as a relevant communicable disease agent or disease (RCDAD) under 21 CFR 1271.3(r) (2). Following non bounding recommendations has been issued by FDA while dealing with HCT/Ps.

A. Recommendations for Living Donors of HCT/Ps:

Following risk factors makes a living donor ineligible for HCT/Ps donation:

i. If the medical diagnosis of ZIKV is reported in the past 6 months.
ii. Residence in, or travel history of an area with an increased risk for ZIKV transmission within the past 6 months.
iii. Sex within the past 6 months with a person who has either of the risk factors listed in items 1 or 2, above.

Additional risk factors should be considered and if reported, they make the birth mother ineligible for the donation of umbilical cord, blood, placenta, or other gestational tissues.

iv. If the mother presents medical diagnosis of ZIKV infection at any point during that pregnancy.
v. Residence in, or travel to, an area with an increased risk for ZIKV transmission at any point during that pregnancy.
vi. Sex at any point during that pregnancy with a person who has either of the risk factors listed in items 1 or 2, above.

B. Recommendations for Non-Heart-Beating (Cadaveric) Donors of HCT/Ps:

Non-heart-beating (cadaveric) donors should be considered ineligible if persons reported with a medical diagnosis of ZIKV infection in the past 6 month [16].

- **FDA Role for Assessing Emergency Use and Accelerated Approval Process for ZIKV Vaccines and Diagnostics.**

Emergency use authorization in case of ZIKV:

Zika virus infection has high cases of asymptomatic nature thus; the virus can pose potentially serious risks to the public health. Access to a diagnostic test that can identify patients with Zika virus infections is critical to supporting response efforts and expanding domestic readiness. Potential links between Zika virus infection and neurological complications (i.e., Guillain-Barré Syndrome), as well as microcephaly and other poor pregnancy outcomes associated with Zika virus infection during pregnancy, have also increased the importance of having a diagnostic test available for Zika virus. FDA working in the direction to ensure timely access to a diagnostic tool.

On February 26, 2016, pursuant to section 564(b) (1) (C) of the Act (21 U.S.C. § 360bbb-3(b) (1) (C)), the Secretary of Health and Human Services (HHS), Sylvia Burwell, determined that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves Zika virus. EUA declaration by the HHS Secretary supports preparedness planning.

Request for an EUA:

Section 564 describes the requirements that are applicable to issue a EUA to a medical product and diagnostics. Following should be considered while requesting for a EUA.

1. Preparedness and response:

The use of medical counter measures are permitted during emergency even if the EUA has been issued before an emergency without the need for further authorization by FDA, assuming that no new information about the product or emergency requires amendment and/or reissuance of the EUA.

2. Information regarding data submission:

An EUA request contains a well-organized summary of the available scientific evidence about product's safety and effectiveness, risks and benefits, and any available, approved alternatives to the product.

3. Format of Submission:

The sponsor of an investigational or marketing application can submit the request for an EUA to the FDA in a marketing application, investigational application, or Master File [17].

Expanded Access Submission for Investigational Drug Development:

Expanded access is essential when the primary objectives are diagnosis, monitoring, or treatment of a patient's disease or condition rather than obtaining information about the drug as of in clinical trials. It avails drugs to such patients who have serious disease or conditions and no comparable or satisfactory alternative therapy for diagnosis monitoring, or treatment is in existence for patient's disease or condition. In accordance with 21 CFR part 312 subpart I, there is provision for expanded access to treatment use of investigational drugs. As per FDA regulation, basically three classes are there…

[312.310] Expanded Access for Individual Patients, including for Emergency Use
[312.315] Expanded Access for Intermediate Size Patient Populations
[312.320] Expanded Access Treatment IND or Protocol

Expanded Access Submission:

There are two regulatory pathways available to make Expanded Access Submission.

1 Expanded Access Protocol Submission, as a part of amendment to an existing IND.
2 New IND Submission, completely distinct with other existing INDs made only for the purpose of treatment use.
3 Submission can be made using form FDA 1571 and the alternative one form FDA by a licence physician /commercial sponsor /drug manufacture with the requirements mentioned in 312.305(b) and additional information if any. Depending upon the satisfaction of requirements, permission can be obtained. In this case sponsor of expanded access IND provides the letter of authorization to FDA from the existing IND sponsor, so the FDA can reference it. The requirements should ensure the information category vised. Then it comes to have IRB review and the approval. In case of emergency use treatment should not be postpone till the IRB review, but IRB should be informed within 5 working days [18].

RESULT AND DISCUSSION

The vector born transmission of Zika virus affects more number of countries in the world, but the integrated mosquito management strategy efficiently working to control vector population for Zika virus. The other tragedy related to ZIKV is found the neuro-complications caused in new born, here it becomes necessary to manage these Zika infected pregnant women cases. In this direction CDC provides the recommendations to health care practitioner regarding result interpretation of diagnostic tests related to ZIKV.

To control pregnancy cases CDC facilitates guidance for travel planning and the preconception counselling to prevent sexual transmission. On the other hand FDA recognise ZIKV as the relate transfusion transmission infection (RTTI) and issued the guidance in favour to blood born transmission "Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Component" that suggest the blood establishments and screening" that suggests the blood establishments and screening of all collected blood using MP NAT and ID NAT. The other guidance of ZIKV is related to HCT/Ps, because the post mortem residue from the ZIKV caused dead body recovered with ZIKV RNA virus. FDA guidance "Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products" recommend the eligibility criteria for organ, tissue and cell donations. Simultaneously, FDA promotes the research and development for ZIKV diagnostics, vaccines and the therapeutic agent for this FDA allows accelerated approval process in terms of EUA and Expanded Access Submission of IND.

CONCLUSION

ZIKV the flavivirus from the same family of DENV, WNY and Japanese encephalitis has the maximum number of cases asymptomatic. It's never expected that it may cause such outbreaks in the various region of the world. In context to USA, various regions has been categorised as the area with increased risk of ZIKV during 2016 to 2018, These consequences lead to draw attention of regulatory agencies in the direction of building ZIKV control framework. In the response to this vector control plan, recommendations and guidances regarding pregnancy cases has been developed by CDC. Moving the step forward FDA issued the guidances to ensure safe supply of blood, blood components and HCT/Ps. To avail the vaccines and diagnostics approval process accelerated in terms of EUA and Expanded Access Submission. These efforts are providing the visionary outputs. The number of cases in USA has been reduced as per the count of CDC sources.

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