Review

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Yellow Fever in Pregnancy: A Comprehensive Review in the Context of the 2024-2026 Outbreak in the Americas Region

Alfonso J. Rodriguez-Morales [*] , Katherine Acevedo-Jimenez , María Eugenia Guevara , Alicia Chang-Cojulun , José Brea-Del Castillo , Melissa Palmieri , Maria L. Avila-Agüero , Francisco Javier Membrillo de Novales , Carlos Torres-Martínez , Sandra X. Olaya , Sergio David Angulo , Jaime A. Cardona-Ospina , Roberto Debbag , Carlos Espinal , Maritza Cabrera , Jaime David Acosta-España , Darío S. López-Delgado , Marco A. Solarte-Portilla , Oscar Fraile , Tatiana Drummond , Rodrigo Nogueira Angerami , Flor M. Muñoz , Irene Benítez , Kleber Luz , María Alejandra López-Zambrano , Cristina Hernán-García , Daniel Leonardo Sánchez-Carmona , Lisette Cortes , Hernán Vargas , Lysien Zambrano , Danna Lucía Calderón-Medina , Diana Alejandra Hernández-Ramírez , Abraham Katime , Álvaro A. Faccini-Martínez , Leidy J. Medina-Lozano , Beatriz Elena Porras-Pedroza , Cristian Biscayart , Ana Carvajal , Lily M. Soto-Ávila , Marbelys Hernández , Rolando Ulloa-Gutierrez , Laura Naranjo-Lara , José Alejandro Mojica , Matthew H. Collins , Herberth Maldonado , Marco A P Safadi , Enrique Chacon-Cruz , José A. Suárez

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Review

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Alfonso J. Rodríguez-Morales [1,2,*], Katherine Acevedo-Jimenez [3], María Eugenia Guevara [4], Alicia Chang-Cojulun [5], José Brea-Del Castillo [6], Melissa Palmieri [7], Maria L. Avila-Agüero [8,9], Francisco Javier Membrillo de Novales [10], Carlos Torres-Martínez [11], Sandra X. Olaya [2,12], Sergio David Angulo [12,13], Jaime A. Cardona-Ospina [2,14,15], Roberto Debbag [16], Carlos Espinal [17], Maritza Cabrera [18], Jaime David Acosta-España [19,20,21,22,23], Darío S. López-Delgado [24], Marco A. Solarte-Portilla [24], Oscar Fraile [25], Tatiana Drummond [26], Rodrigo Nogueira Angerami [27], Flor M. Muñoz [28,29], Irene Benítez [30,31], Kleber Luz [32], María Alejandra López-Zambrano [33], Cristina Hernán-García [34,35], Daniel Leonardo Sánchez-Carmona [35], Lisette Cortes [36], Hernán Vargas [37,38,39], Lysien Zambrano [40], Danna Lucía Calderón-Medina [41], Diana Alejandra Hernández-Ramírez [41,42], Abraham Katime [43,44,45], Álvaro A. Faccini-Martínez [46,47], Leidy J. Medina-Lozano [48,49,50], Beatriz Elena Porras-Pedroza [51], Cristian Biscayart [52], Ana Carvajal [53], Lily M. Soto-Ávila [54], Marbelys Hernández [55], Rolando Ulloa-Gutierrez [56,57,58], Laura Naranjo-Lara [59,60], José Alejandro Mojica [61], Matthew H. Collins [62], Herberth Maldonado [63], Marco A P Safadi [64], Enrique Chacon-Cruz [65] and José A. Suárez [59,60]

1. Faculty of Health Sciences, Universidad Cientifica del Sur, Lima, Peru
2. Grupo de Investigación Biomedicina, Faculty of Medicine, Fundación Universitaria Autónoma de las Américas-Institución Universitaria Visión de las Américas, Pereira, Colombia
3. Program of Family Medicine Specialization, Faculty of Medicine, Fundación Universitaria Autónoma de las Américas-Institución Universitaria Visión de las Américas, Pereira, Colombia
4. Faculty of Medicine, Universidad Centro-Occidental Lisandro Alvarado, Barquisimeto, Venezuela
5. Unidad Nacional de Oncologia Pediatrica (UNOP), Guatemala City, Guatemala
6. Pediatrics and Pediatric Infectious Diseases, Facultad de Ciencias de la Salud del Instituto Tecnológico de Santo Domingo, Dominican Republic
7. Municipal Health Department (SMS/SP), São Paulo Municipal Government, São Paulo, SP, Brazil
8. Pediatric Infectious Diseases Division, Hospital Nacional de Niños 'Dr. Carlos Sáenz Herrera', Centro de Ciencias Médicas, Caja Costarricense de Seguro Social (CCSS), San José, Costa Rica
9. Center for Infectious Disease Modeling and Analysis (CIDMA), Yale University, New Haven, CT, United States of America.
10. CBRN and Infectious Diseases Department, Hospital Central de la Defensa Gómez Ulla, Madrid, Spain
11. Department of Pediatrics, Universidad El Bosque, Cafettor Médica SAS, Bogotá, Colombia
12. Gynecology, Clinica Comfamiliar, Pereira, Risaralda Colombia
13. Research and Teaching Unit, Salud Comfamiliar, Pereira, Risaralda, Colombia
14. Division of Infectious Diseases and Vaccinology, School of Public Health, University of California, Berkeley, Berkeley, CA, United States of America
15. Grupo de Investigación en Infecciones Emergentes y Medicina Tropical, Instituto para la Investigación en Ciencias Biomédicas, Sci-help, Pereira, Colombia
16. Latin-American Vaccinology Society, Buenos Aires, Argentina

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[17] Robert Stempel College of Public Health and Social Work, Florida International University, Miami, FL, United States of America
[18] Centro de Investigación de Estudios Avanzados del Maule (CIEAM), Universidad Católica del Maule, Talca 3480094, Chile
[19] Health Sciences Faculty, Universidad Internacional SEK (UISEK), Quito, 170120, Ecuador.
[20] School of Medicine, Pontificia Universidad Católica del Ecuador, Quito, 170525, Ecuador.
[21] Institute of Microbiology, Friedrich Schiller University Jena, 07743, Jena, Germany.
[22] Research Group of Emerging and Neglected Diseases, Ecoepidemiology and Biodiversity, Health Sciences Faculty, Universidad Internacional SEK (UISEK), Quito, 170120, Ecuador
[23] Centro de Investigación para la Salud en América Latina (CISeAL), Pontificia Universidad Católica del Ecuador, Quito, Ecuador
[24] Hospital Universitario Departamental de Nariño, Pasto, Nariño, Colombia
[25] Hospital Nuestra Señora de Sonsoles (HNSS) / Complejo Asistencial de Ávila, Avila, España
[26] Service of Pediatric Infectious Diseases, Hospital Universitario de Caracas, Caracas, Venezuela
[27] Núcleo de Vigilância Epidemiológica, Seção de Epidemiologia Hospitalar, Hospital de Clínicas, Universidade Estadual de Campinas, Campinas, SP, Brazil
[28] Division of Infectious Diseases, Department of Pediatrics, Baylor College of Medicine, Houston, TX, United States of America
[29] Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX, United States of America
[30] Instituto de Previsión Social, Ministerio de Salud Pública y Bienestar Social, Asunción, Paraguay
[31] Facultad de Ciencias de la Salud, Universidad Católica Nuestra Señora de Asunción, Asunción, Paraguay
[32] Instituto de Medicina Tropical da Universidade Federal do Rio Grande do Norte, Natal, Brazil
[33] Subdirección General de Prevención y Promoción de la Salud, Consejería de Sanidad, Autonomous Community of Madrid, C/López de Hoyos, 35, 28002 Madrid, Spain
[34] Department of Preventive Medicine and Public Health, University of Valladolid, 47005 Valladolid, Spain
[35] Preventive Medicine and Public Health Service, Hospital Clínico Universitario de Valladolid, 47003 Valladolid, Spain
[36] Unidad de Terapia Intensiva Adultos, Centro Clínico Maternidad Leopoldo Aguerrevere, Caracas, Venezuela
[37] Dirección de Salud Pública, Secretaria de Salud del Tolima, Colombia
[38] Grupo de investigación clínica y medicina traslacional, Hospital Federico Lleras Acosta, Ibagué, Colombia
[39] Grupo de Inmunologia molecular, Universidad del Quindío, Armenia, Colombia
[40] Department of Morphological Sciences, School of Medical, Sciences, Universidad Nacional Autónoma de Honduras, Tegucigalpa, Honduras
[41] Service of Internal Medicine-Research Line IMPACTA-Salud, Hospital Federico Lleras Acosta, Ibagué, Tolima, Colombia
[42] Faculty of Medicine, Fundación Universitaria Navarra (UNINAVARRA), Neiva, Huila, Colombia
[43] Programa de Medicina, Universidad del Magdalena, Santa Marta, Magdalena, Colombia
[44] Servicio de Infectología, Hospital Universitario Julio Méndez Barreneche, Santa Marta, Magdalena, Colombia
[45] Comité de Medicina Tropical, Zoonosis y Medicina del Viajero, Asociación Colombiana de Infectología, Bogotá, D.C., Colombia
[46] Servicio de Infectología, Hospital Militar Central, Bogotá, D.C., Colombia
[47] Facultad de Medicina, Universidad Militar Nueva Granada, Bogotá, D.C., Colombia
[48] Programa de Especialización en Infectología, Universidad Nacional de Colombia, Bogotá, D.C., Colombia
[49] Servicio de Medicina Interna, Hospital Militar Central, Bogotá, D.C., Colombia
[50] Servicio de Medicina Interna, Clínica La Colina – Clínica del Country, Bogotá, D.C., Colombia

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[51] Facultad de Medicina, Fundación Universitaria Sanitas, Bogotá, DC, Colombia
[52] Fundación GESICA (Grupo de Estudios Sobre Investigación Clínica en Argentina), Ciudad Autónoma de Buenos Aires, Argentina
[53] Posgrado de Infectología, Hospital Universitario de Caracas, Universidad Central de Venezuela, Caracas, Venezuela
[54] Sección de Inmunología, Instituto de Medicina Tropical, Facultad de Medicina, Universidad Central de Venezuela, Caracas, Venezuela
[55] Clínica de la Mujer, Del Sur Policlínica, El Tigre, Anzoátegui, Venezuela
[56] Servicio de Aislamiento, Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera", Centro de Ciencias Médicas, Caja Costarricense de Seguro Social (CCSS), San José, Costa Rica
[57] Instituto de Investigación en Ciencias Médicas UCIMED (IICIMED), San José, Costa Rica
[58] Cátedra de Pediatría, Facultad de Medicina, Universidad de Ciencias Médicas (UCIMED), San José, Costa Rica
[59] Sistema Nacional de Investigación-SENACYT, Panamá; Bella Vista, Manuel E. Batista y Ave. Jose De Fabrega, Panama City, Panama Province, Panama
[60] Infectotrópico, SA, Panamá
[61] Ministry of Health, Bogota, DC, Colombia
[62] Department of Medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia, United States of America
[63] Centro de Estudios en Salud, Universidad del Valle de Guatemala, Guatemala
[64] Department of Paediatrics, Santa Casa de São Paulo School of Medical Sciences, São Paulo, Brazil
[65] Think Vaccines LLC., Houston, TX 77005, United States of America
* Correspondence: arodriguezmo@cientifica.edu.pe

Abstract

Yellow fever remains a major public health threat in endemic and re-emerging regions of Africa and South America, with recent outbreaks highlighting persistent gaps in prevention and surveillance. Pregnant women represent a particularly vulnerable population, yet the epidemiology, clinical impact, and preventive strategies for yellow fever in pregnancy are insufficiently characterized. Physiological and immunological changes during gestation may increase susceptibility to severe disease and contribute to adverse maternal and fetal outcomes, including miscarriage, stillbirth, preterm birth, and, in rare cases, perinatal transmission. Diagnostic challenges, overlapping clinical presentations with other arboviral and hepatic diseases, and limited access to specialized care further complicate clinical management in many endemic settings. This perspective provides a comprehensive overview of yellow fever in pregnancy during the 2024–2026 outbreak in the Americas, including a risk-stratification framework for prevention. We summarize current evidence on epidemiology, pathophysiology, diagnosis, and supportive care, and examine prevention strategies with particular emphasis on vaccination. Accumulated observational evidence and substantial real-world experience have not demonstrated an increased risk of serious adverse events and generally support the effectiveness of yellow fever vaccination during pregnancy when administered with appropriate clinical judgment. In high-risk settings, the benefits of maternal immunization clearly outweigh theoretical concerns, supporting a flexible, risk-based approach, despite relatively limited evidence. We also discuss national and international policies, post-pregnancy booster recommendations, and the importance of integrating vaccination assessment into antenatal care. Finally, we highlight critical knowledge gaps and research priorities, including the need for prospective registries and strengthened pharmacovigilance. Coordinated clinical and public health strategies are essential to protect maternal and neonatal health and to reduce the burden of yellow fever in endemic and re-emerging settings.

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Introduction

Yellow fever (YF) is one of the most severe mosquito-borne viral diseases worldwide, causing recurrent outbreaks with substantial morbidity and mortality in endemic regions of Africa and South America [1]. Despite the availability of an effective live-attenuated vaccine, recent years have witnessed a marked resurgence of YF in several countries [2], particularly in South America [3], where expanding sylvatic transmission [4], ecological disruption [5,6], population mobility [7], and suboptimal vaccination coverage have contributed to renewed epidemic activity [8]. These dynamics have increased the risk of both rural and peri-urban transmission, raising concerns about potential reemergence of urban cycle YF and international spread [9]. In South America, 376 cases and 158 deaths (42%) have been confirmed during the 2024-2026 outbreak up to February 2, 2026, with cases from Colombia (152), Brazil (127), Peru (65), Bolivia (14), Ecuador (11), Guyana (4), and Venezuela (3, imported cases in Colombia) (https://shiny.paho-phe.org/yellowfever/) (Accessed 9 February 2026) (https://bit.ly/4kkn36E) (Accessed 9 February 2026) [7,10]. Currently, PAHO/WHO platforms do not display the number of cases among pregnant women (this would be important in other conditions, such as measles, dengue).

Pregnant women represent a particularly vulnerable population in the context of YF infection (Table 1) [7,11–16]. However, it remains uncertain whether pregnancy modifies the clinical spectrum or severity of YF in affected women compared with non-pregnant individuals. Regarding fetal risk, available evidence remains extremely limited. Current reviews indicate that only two cases of confirmed vertical transmission have been reported, both characterized by initially asymptomatic neonates who subsequently developed severe disease with fever, multiorgan failure, and coagulopathy, ultimately resulting in death [15].

Table 1. Reported Maternal and Fetal Outcomes Associated with Yellow Fever Infection during Pregnancy [12,16,34,38,39].

Study / Report	Countries	Years	Study Design	Gestational Age at Infection	Maternal Outcomes	Fetal / Neonatal Outcomes	Key Remarks
Historical clinical/ outbreak descriptions, including pregnancy	South America and Africa	20th century (reviewed)	Narrative historical/clinical review	Not consistently reported	Severe hepatitis, hemorrhage, shock, and death in severe cases	Pregnancy loss reported in historical literature	Contextualizes early observations and biologic plausibility

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Perinatal transmission of wild-type yellow fever	Brazil	2009 (published 2011)	Case report/ correspondence	Peripartum	Severe maternal illness	Neonatal infection with fulminant YF and death	Key documented perinatal transmission event
Perinatal yellow fever with maternal and neonatal fatality	Brazil	2019	Case report	Peripartum	Fulminant hepatitis and maternal death	Neonatal liver failure and death; PCR positive	Laboratory-confirmed severe perinatal transmission
Summary of perinatal transmission events	Global	Current guidance	Authoritative guidance	Peripartum	Maternal symptomatic YF near delivery	Two documented infant infections with fatal outcomes	Supports the rarity but severity of perinatal transmission
Synthesis of yellow fever epidemiology and transmission	Global	2020	Review/synthesis	N/A	Summarizes severe disease spectrum	Notes vertical/ perinatal transmission in context	Supporting synthesis (not primary cohort)

Physiological and immunological changes during pregnancy may influence disease severity, clinical presentation, and immune responses, potentially increasing the risk of adverse maternal and fetal outcomes [11,14]. Available evidence, although limited, suggests that YF during pregnancy may be associated with severe maternal illness, miscarriage, stillbirth, preterm delivery, and, in rare cases, vertical transmission

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[7,11–16]. However, the true burden of YF in pregnancy remains poorly characterized, largely due to underreporting, limited surveillance, and the scarcity of prospective studies [17].

On the other hand, clinical management and prevention of YF in pregnant women pose significant challenges. Diagnostic difficulties, overlapping clinical features with other arboviral infections, and restricted therapeutic options complicate timely recognition and appropriate care [18]. Moreover, the use of live-attenuated YF vaccines during pregnancy remains a controversial critical issue and requires careful risk–benefit assessment, particularly in outbreak settings or for unavoidable travel to endemic areas [19,20]. There is data on this matter, as documented in a 2000 study that reported inadvertent vaccination of 480 pregnant women in the early stages of pregnancy as part of a vaccination campaign against YF, with no safety concerns; even applied during the first trimester no malformations, complications to the central nervous system, nor adverse perinatal results were observed [21].

In the context of climate change, increased human mobility, and persistent gaps in immunization programs, the intersection between YF and maternal health has become an increasingly important public health concern [22]. This article provides a comprehensive perspective on YF in pregnancy, addressing its epidemiology, clinical impact, diagnostic and management considerations, and preventive strategies, with particular emphasis on vaccination policies and practical guidance. By synthesizing current evidence and identifying key knowledge gaps, we aim to inform clinicians, researchers, and policymakers and support the development of more effective maternal health and disease prevention strategies in YF-endemic and re-emerging settings.

Epidemiology of YF in Pregnancy

YF remains endemic in large areas of sub-Saharan Africa and tropical South America, where millions of women of reproductive age live in settings with ongoing or periodic viral transmission [23]. Although vaccination has substantially reduced disease burden in many countries, recurrent outbreaks continue to occur, driven by sylvatic transmission cycles, ecological changes, population mobility, and gaps in immunization coverage [24]. In this context, pregnant women residing in or traveling to endemic regions remain at risk of exposure, particularly in rural, peri-urban, and forest-fringe environments where vector density is high [25].

Reliable estimates of the incidence of YF in pregnancy are scarce (Table 1) [7,11–16]. Most national surveillance systems do not routinely disaggregate cases by pregnancy status, and mild or asymptomatic infections are likely underreported. Consequently, available epidemiological data are largely derived from outbreak investigations, hospital-based case series, and sporadic case reports. These sources suggest that infection during pregnancy is uncommon in absolute numbers but likely underestimated, especially in regions with limited access to diagnostic testing and prenatal care [26,27]. Nevertheless, in Colombia during the current 2024-2026 outbreak, as of February 3, 2026, 19.5% of cases have been confirmed among women (https://bit.ly/4a0Jjxi) (Accessed 9 February 2026). A similar situation has been observed in Peru, with 16.2% of the 2024-2026 confirmed cases among women (https://www.dge.gob.pe/sala-fiebre-amarilla/tablero.html) (Accessed 9 February 2026). In Brazil, 10.2% of the 2024-2026 confirmed cases occurred in women (https://www.gov.br/saude/pt-br/composicao/svsa/cnie/painel-febre-amarela) (Accessed 9 February 2026). However, among the total confirmed cases reported in Colombia between 2007 and 2023, only 1 case (4%) was in a female (https://www.sispro.gov.co/Pages/Home.aspx) (Accessed 9 February 2026).

Historical and contemporary outbreaks in South America and Africa have intermittently documented cases among pregnant women, often in the context of large epidemics affecting predominantly unvaccinated populations [28]. In these settings, pregnant women are typically exposed through

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occupational activities, agricultural work, household proximity to forested areas, or travel to endemic zones [29,30]. Urbanization and the expansion of peri-urban settlements have further increased contact between human populations and sylvatic transmission cycles, raising concerns about broader exposure among women of childbearing age [31].

Sociodemographic and structural factors strongly influence the epidemiology of YF in pregnancy. Poverty, limited access to health services, low educational attainment, and geographic isolation contribute to reduced vaccination coverage and delayed healthcare seeking [7]. Migrant populations, seasonal workers, indigenous communities, and residents of border regions are disproportionately affected, reflecting both increased exposure and barriers to preventive services [32]. Additionally, humanitarian crises and forced displacement may exacerbate vulnerability by disrupting immunization programs and surveillance systems [33].

Travel-related exposure represents an additional epidemiological dimension [1,7,18,19]. Pregnant travelers from non-endemic countries may be exposed during visits to endemic areas for tourism, work, humanitarian missions, or family-related travel [1,7,18,19]. Although the absolute number of cases in this group remains low, the risk is amplified in outbreak settings or during prolonged stays in high-transmission zones. Increasing international mobility has therefore expanded the geographic scope of concern beyond traditionally endemic countries [1,7,18,19].

Temporal trends in YF epidemiology also have implications for pregnancy-related risk [34,35]. Recent decades have seen a resurgence of outbreaks associated with deforestation, climate variability, and changes in vector ecology [5,6]. These factors have facilitated the spread of competent mosquito vectors and prolonged transmission seasons, potentially increasing cumulative exposure among pregnant women [36]. Moreover, fluctuating vaccine supply, logistical challenges, and vaccine hesitancy have contributed to persistent immunity gaps in some regions [37].

Overall, the epidemiology of YF in pregnancy is characterized by limited data, substantial underrecognition, and marked geographic and social heterogeneity [11,13,15,17–20]. While reported cases remain relatively infrequent [16], the true burden is likely higher than currently appreciated. Strengthening surveillance systems, integrating pregnancy status into routine reporting, and improving access to preventive services are essential to define better and address the risk of YF among pregnant populations in endemic and re-emerging settings [11,13,15,17–20].

Pathophysiology and Pregnancy-Specific Issues

Pregnancy is characterized by complex physiological and immunological adaptations that may influence susceptibility to viral infections and disease severity (Figure 1) [11,13,14]. These changes include modulation of innate and adaptive immune responses, altered cytokine profiles, and a shift toward immune tolerance to maintain fetal viability. While these mechanisms are essential for successful gestation, they may also impair effective antiviral responses, potentially facilitating higher viral replication and more severe clinical manifestations of YF [11,13,14].

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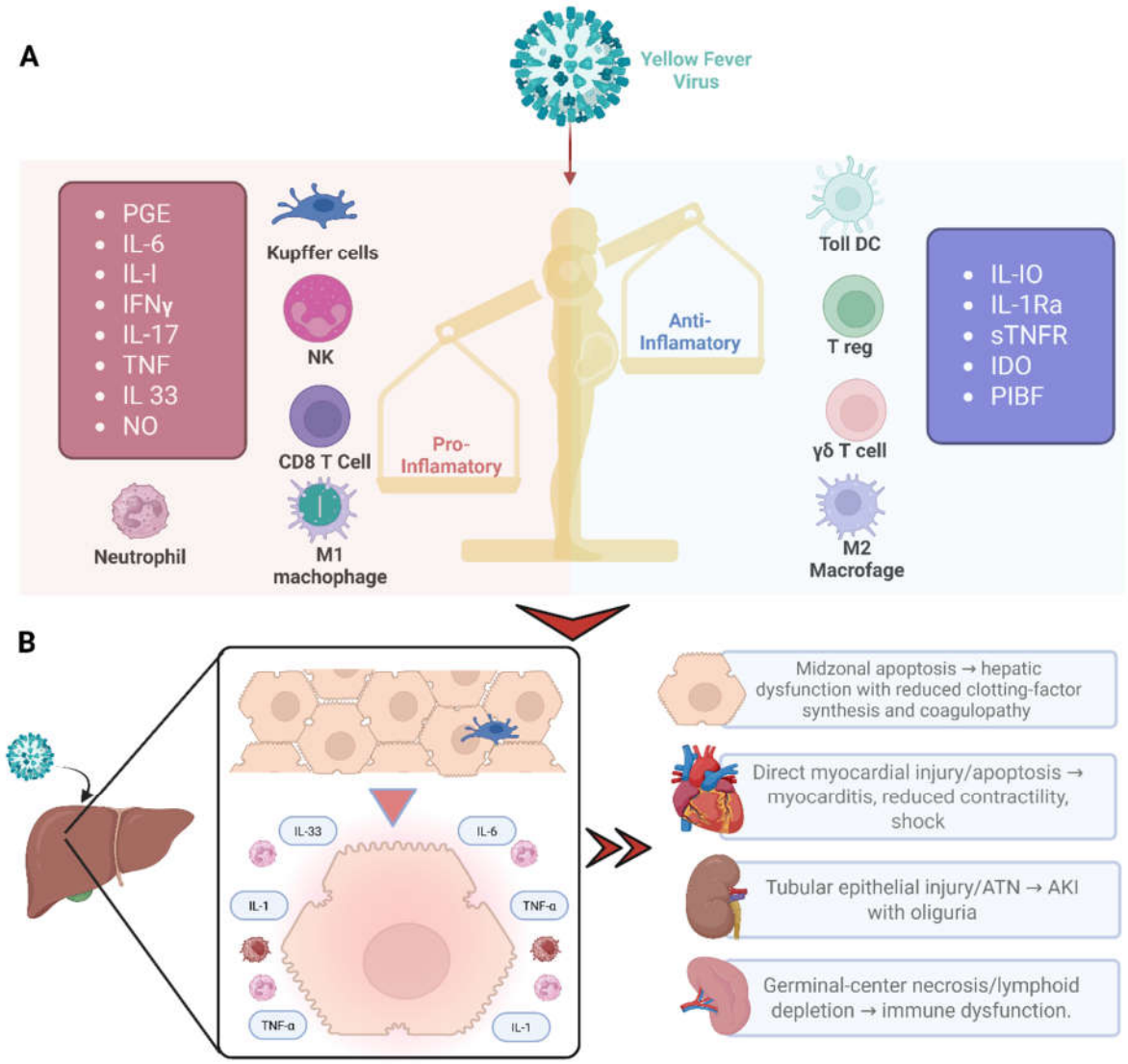

Figure 1. Immune balance during the tolerant phase of pregnancy and proposed multiorgan pathophysiology of severe yellow fever. (A) Conceptual model of the tolerant (anti-inflammatory–leaning) immune phase in pregnancy, highlighting regulatory cells and mediators on the anti-inflammatory side (tolerogenic DC, Treg, γδ T cells, M2 macrophages; IL-10, IL-1Ra, sTNFR, IDO, PIBF) versus pro-inflammatory effector cells and mediators (Kupffer cells, NK cells, CD8 T cells, M1 macrophages, neutrophils; PGE, IL-6, IL-1, IFN-γ, IL-17, TNF, IL-33, NO). The yellow fever virus is depicted as a disruptor that can shift this equilibrium toward inflammatory dominance. (B) Proposed sequence of severe yellow fever injury: intrahepatic infection and cytokine signaling (e.g., IL-1, IL-6, TNF-α, IL-33) contributing to hepatocellular dysfunction and systemic inflammation, followed by characteristic organ involvement—liver: midzonal hepatocyte apoptosis → hepatic dysfunction with reduced clotting-factor synthesis and coagulopathy; heart: direct myocardial injury/apoptosis → myocarditis, reduced contractility, shock; kidney: tubular epithelial injury/acute tubular necrosis (ATN) → acute kidney injury (AKI) with oliguria; spleen/lymphoid tissue: germinal-center necrosis/lymphoid depletion → immune dysfunction. Abbreviations: AKI, acute kidney injury; ATN, acute tubular necrosis; DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon gamma; IL-1Ra, interleukin-1 receptor antagonist; NK, natural killer; NO, nitric oxide; PGE, prostaglandin E; PIBF, progesterone-induced blocking

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factor; sTNFR, soluble TNF receptor; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cell. Created with help of BioRender (https://BioRender.com).

YF virus primarily targets hepatocytes, endothelial cells, and immune cells, leading to widespread hepatic injury, vascular dysfunction, and systemic inflammatory responses (Figure 1) [38]. In pregnant women, these effects may be amplified by pregnancy-related changes in hepatic metabolism, coagulation pathways, and cardiovascular physiology [38–41]. The combination of viral-induced liver failure, thrombocytopenia, and coagulopathy increases the risk of hemorrhagic complications, obstetric bleeding, and multi-organ dysfunction, posing significant threats to maternal survival [42,43].

The placenta represents a critical interface between maternal and fetal compartments and may serve as both a barrier and a potential target for viral infection. Although vertical transmission of YF appears to be rare, placental inflammation, endothelial injury, and altered perfusion may contribute to fetal hypoxia, growth restriction, and pregnancy loss. In addition, systemic maternal illness, fever, hemodynamic changes, and metabolic disturbances can indirectly compromise fetal well-being [44–46].

The pregnancy-associated shift toward a T helper 2–dominant immune profile, which is essential for fetal tolerance, may also attenuate virus-specific cytotoxic T-cell responses required for efficient clearance of flavivirus infections. This immunological modulation may contribute to suboptimal cellular immunity and accelerated waning of protective antibody titers following natural infection or vaccination. Consequently, some pregnant women may initially seroconvert but experience more rapid declines in antibody levels over time. This mechanism provides a plausible biological explanation for reduced long-term immunity observed during pregnancy and supports current recommendations for post-pregnancy booster vaccination in high-risk populations [47–50].

These pregnancy-specific pathophysiological mechanisms underscore the heightened vulnerability of pregnant women to severe YF and highlight the need for early recognition, close monitoring, and integrated maternal–fetal care in endemic and outbreak settings [13].

Importantly, no dedicated mechanistic studies have yet examined YF virus infection in human placental tissue, and current hypotheses are largely based on biological plausibility and indirect evidence.

Diagnosis in Pregnant Women

The diagnosis of YF in pregnant women is often challenging due to nonspecific early clinical manifestations and frequent overlap with other infectious and non-infectious conditions. Initial symptoms, including fever, headache, myalgia, nausea, and malaise, are indistinguishable from those of other arboviral infections, viral hepatitis (including hepatitis E and its well-known association with poor materno-fetal outcomes), malaria, leptospirosis, and obstetric complications such as preeclampsia with hepatic involvement, HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelet count), and acute fatty liver of pregnancy (AFLP) (Table 2) [51–54]. As a result, early high clinical suspicion is essential, particularly in women with recent exposure to endemic areas or ongoing outbreaks (e.g., Tolima in Colombia, 2024-2026) [55].

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Table 2. Differential Diagnosis of Acute Febrile Illness with Hepatic Involvement in Pregnancy in Endemic Areas.

Condition	Key Epidemiologic Clues	Typical Clinical Features	Laboratory Pattern	Pregnancy-Specific Considerations	Initial Tests to Prioritize	Immediate Management Priorities / Notes
Yellow fever	Travel/residence in endemic or outbreak area; forest/peri-forest exposure; unvaccinated or uncertain status	Acute fever, myalgia, headache; may progress to jaundice, hemorrhage, shock, encephalopathy	AST/ALT elevation (often marked), hyperbilirubinemia, thrombocytopenia, coagulopathy, possible renal dysfunction	Higher risk of hemorrhage and multi-organ failure; fetal compromise secondary to maternal instability	RT-PCR (early); IgM/serology (later) with careful interpretation; CBC, CMP, PT/INR, creatinine; urinalysis	Supportive care, ICU if severe; avoid hepatotoxic drugs; multidisciplinary obstetric + critical care
Dengue (including severe dengue)	Aedes exposure; urban/peri-urban transmission; recent local dengue activity; household clusters	Fever, retro-orbital pain, rash; warning signs: abdominal pain, bleeding, lethargy; plasma leakage in severe cases	Leukopenia, thrombocytopenia, hemoconcentration; mild–moderate transaminase rise; shock in severe disease	Risk of hemorrhage, preterm birth; fluid management must balance maternal perfusion and pulmonary edema risk	NS1 antigen/RT-PCR (early); IgM/IgG (later); CBC trends and hematocrit; ultrasound for plasma leakage	Careful fluids; avoid NSAIDs; manage bleeding; monitor fetal status in severe illness
Zika virus infection	Aedes exposure; sexual transmission possible; outbreak history; travel to endemic areas	Often mild: rash, conjunctivitis, arthralgia, low-grade fever	Usually mild lab abnormalities; occasional leukopenia or mild transaminase elevation	Primary concern is fetal neurodevelopment; timing of infection is critical; prolonged maternal viremia can occur	RT-PCR (serum/urine early); serology with cross-reactivity caveats; targeted fetal ultrasound if infected/exposed	Counseling; fetal surveillance per protocol; report and follow pregnancy closely
Chikungunya	Aedes exposure, community outbreaks, travel to affected areas	High fever, severe polyarthralgia,	Variable labs; mild transaminase rise possible;	Peripartum maternal infection can be associated with	RT-PCR early; serology later; CBC and CMP	Analgesia compatible with pregnancy; hydration; peripartum neonatal

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		rash; may be debilitating	thrombocytopenia less prominent than dengue	neonatal infection; severe maternal pain affects hydration and function		readiness if maternal illness near delivery
Acute viral hepatitis (A, B, C, D, E)	Food/water exposure (A/E); contact with known cases; endemicity; sanitation; outbreaks; blood/sexual exposure (B/C)	Jaundice, malaise, anorexia, nausea; RUQ pain; may be profound fatigue	Marked ALT/AST elevation; hyperbilirubinemia; variable INR; platelets often normal unless severe	Hepatitis E can be severe in pregnancy in some settings; the risk of fulminant hepatic failure	Hepatitis panel (HAV IgM, HBsAg, anti-HBc IgM, HCV Ab/RNA, HDV IgM, HDV Ag, HEV IgM/RNA, where available); PT/INR, CMP	Supportive care; assess for acute liver failure; infection control; specialist input; manage coagulopathy
Malaria (especially *Plasmodium falciparum*)	Travel/residence in malaria-endemic area; night-time mosquito exposure; lack of prophylaxis	Fever with chills, headache, anemia; severe disease: altered mental status, respiratory distress, hypoglycemia	Anemia, thrombocytopenia; hypoglycemia; acidosis; mild–moderate transaminase elevation; renal dysfunction in severe cases	Higher parasitemia and severe disease risk; fetal loss and low birthweight; treat promptly	Thick/thin smear or rapid diagnostic test; PCR; CBC; glucose; creatinine; lactate if severe, liver enzymes	Start pregnancy-appropriate antimalarial urgently; manage hypoglycemia and anemia; fetal monitoring in severe cases
Leptospirosis	Exposure to floodwater/rodents/animal urine; occupational risk; outbreaks after heavy rains	Fever, severe myalgias (calves), conjunctival suffusion; jaundice in severe cases (Weil disease)	Elevated bilirubin, creatinine; thrombocytopenia; mild–moderate transaminase elevation, leukocytosis, neutrophilia	Can mimic viral hepatitis/YF; may cause fetal loss; antibiotics reduce severity	*Leptospira* PCR (early) or serology; CMP, CBC, urinalysis; consider CXR if pulmonary symptoms	Start appropriate antibiotics promptly; supportive care; assess renal/pulmonary involvement
Acute cholangitis / biliary disease	History of gallstones; biliary colic; prior episodes;	RUQ pain, fever, jaundice;	Cholestatic pattern (ALP, GGT, bilirubin);	Pregnancy increases gallstone disease;	RUQ ultrasound; CBC; CMP; ALP,	Early antibiotics and source control; surgical/ERCP

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	pregnancy-related cholestasis risk	nausea/vomiting; may have hypotension if severe	variable AST/ALT; leukocytosis	imaging choice matters	GTP, AST, ALT, Bilirrubins; blood cultures if septic	consult; maternal stabilization
HELLP syndrome / severe preeclampsia with hepatic involvement	Hypertension/proteinuria or symptoms after 20 weeks; prior preeclampsia; multiple gestation	RUQ/epigastric pain, headache, visual symptoms; nausea/vomiting; may have edema	Hemolysis, elevated liver enzymes, low platelets; proteinuria; possible AKI	Obstetric emergency; can resemble viral hepatitis/YF; timing and BP clues are key	BP measurement; urine protein; CBC with smear; AST/ALT; LDH; creatinine; coagulation profile	Stabilize mother; magnesium sulfate as indicated; antihypertensives; plan delivery based on severity/GA
Acute fatty liver of pregnancy (AFLP)	Typically 3rd trimester; risk with multiple gestation; prior AFLP; may overlap with preeclampsia	Nausea/vomiting, abdominal pain, jaundice; encephalopathy possible	Moderate transaminase elevation, hypoglycemia, elevated ammonia, coagulopathy, renal dysfunction	Rapidly progressive; maternal–fetal mortality without urgent care	Glucose; CMP; PT/INR; ammonia if available; CBC; consider Swansea criteria	ICU-level supportive care; correct hypoglycemia/coagulopathy; expedite delivery once stabilized
Herpes simplex virus hepatitis	Primary HSV infection; mucocutaneous lesions may be absent; third trimester	Fever, abdominal pain, encephalopathy; often anicteric	Marked AST/ALT elevation, thrombocytopenia, leukopenia, and coagulopathy	High mortality if untreated; often misdiagnosed	HSV PCR (blood/lesions); liver enzymes; CBC	Immediate empiric acyclovir; ICU support
Sepsis from other causes (e.g., pyelonephritis, pneumonia)	Urinary symptoms; respiratory symptoms; risk factors for infection; recent procedures	Fever, tachycardia, hypotension; organ dysfunction; may have focal symptoms	Leukocytosis or leukopenia; lactate elevation; LFTs may rise in shock liver	Pregnancy alters vitals and labs; fetal distress can be an early sign of maternal sepsis	Blood/urine cultures; lactate; CBC; CMP; imaging guided by symptoms	Early antibiotics, fluids, source control; fetal monitoring in viable pregnancy; ICU if needed

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Laboratory confirmation relies primarily on molecular and serological methods [55]. In clinical practice, during the viremic phase, reverse transcription polymerase chain reaction allows direct detection of viral RNA and provides high diagnostic specificity. After the acute phase, serological testing for virus-specific antibodies becomes the main diagnostic tool. However, serological interpretation, even for IgM antibodies, may be complicated by cross-reactivity with other flaviviruses, prior vaccination, and pre-existing immunity, which are common in endemic regions [56].

In areas with recent vaccination campaigns, detection of YF–specific IgM may reflect recent immunization rather than acute infection, and confirmatory testing with plaque-reduction neutralization assays may be required in selected cases [57].

Pregnancy-related physiological changes, including hemodilution, altered immune responses, and modifications in liver enzyme levels, may further obscure diagnostic interpretation. In addition, limited access to advanced laboratory facilities in resource-constrained settings often delays confirmation. Consequently, clinical, epidemiological, and laboratory information must be integrated to support timely diagnosis. Early identification and accurate diagnosis of YF is critical to guide appropriate supportive management, fetal monitoring, and public health interventions aimed at reducing transmission and preventing adverse maternal and neonatal outcomes [58,59].

Clinical Management and Supportive Care

There is no specific antiviral therapy for YF, and clinical management in pregnant women is primarily based on early recognition and comprehensive supportive care. Given the potential for rapid clinical deterioration, suspected or confirmed cases should be managed in healthcare facilities with capacity for close monitoring and advanced supportive interventions. Initial management focuses on stabilizing vital signs, maintaining adequate hydration, correcting electrolyte imbalances, and maintaining hemodynamic stability [56,60].

Maternal hyperthermia itself may increase uterine contractility and has been associated with adverse obstetric and neurodevelopmental outcomes [56,61]. Substantial evidence suggests that fever during pregnancy, irrespective of the underlying pathogen, may represent a risk factor for neurodevelopmental disorders, autism spectrum disorders, and congenital cardiovascular malformations [56,61]. Nevertheless, results remain heterogeneous, and not all studies have demonstrated a significant increase in risk. These findings highlight the importance of investigating the causes of fever and implementing timely antipyretic and supportive measures in pregnant women with suspected or confirmed YF [56,61].

Acute liver failure, renal impairment, metabolic disturbances, and coagulopathy frequently complicate severe disease [62]. Regular monitoring of liver enzymes, renal function, coagulation parameters, and platelet counts is essential for early detection of organ dysfunction [63]. Blood products, vitamin K, and careful transfusion support may be required in the presence of significant bleeding or severe thrombocytopenia. Nephrotoxic and hepatotoxic medications should be avoided whenever possible [56,64].

In severe cases, reactive hemophagocytic lymphohistiocytosis has also been reported as a complication of YF, reflecting profound immune dysregulation and systemic inflammation. This condition should be suspected in patients with persistent fever, cytopenias, hyperferritinemia, and progressive organ dysfunction. In selected critically ill patients with refractory disease, adjunctive therapies such as intravenous immunoglobulin and intensive therapeutic plasma exchange have been proposed as rescue interventions in addition to standard supportive care, with emerging evidence suggesting potential benefit in severe forms of YF [56,65].

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Obstetric management should be individualized and coordinated within a multidisciplinary team involving infectious disease specialists, obstetricians, intensivists, and neonatologists. Continuous fetal monitoring is recommended in viable pregnancies, particularly in critically ill patients. Decisions regarding timing and mode of delivery must balance maternal clinical status, gestational age, and fetal well-being. In cases of maternal instability, priority should be given to optimizing maternal condition, as this remains the most effective strategy for improving fetal outcomes [11,13,15,17–20,45,59]. Any pregnant woman in an endemic zone with active YF virus circulation, presenting with fever, jaundice, and other warning signs, should bypass primary care and go straight to a center with dialysis and transplant capability. Time-to-transfer is the only variable that saves lives in fulminant hepatic failure [66], especially now in countries with ongoing outbreaks in South America (2024-2026).

Postpartum follow-up is important for monitoring maternal recovery, assessing neonatal health, and providing appropriate counseling on future pregnancies and preventive measures [11,13,15,17–20,45,59].

In addition to maternal supportive care, careful consideration of fetal and neonatal risks is essential in the management of YF during pregnancy. YF during pregnancy represents a significant clinical challenge due to the risk of vertical and perinatal transmission and potentially severe fetal and neonatal complications. Although available evidence is limited and consists mainly of isolated case reports, although rare, vertical transmission has been documented, particularly when maternal infection occurs late in pregnancy or around delivery and may result in fulminant neonatal disease. Published data describe a wide spectrum of outcomes ranging from asymptomatic congenital infection to fulminant neonatal disease and death. The best-documented perinatal case, reported in Brazil in 2009, described probable vertical transmission leading to neonatal hemorrhagic hepatitis, multi-organ failure, disseminated intravascular coagulation, seizures, and death within the first two weeks of life, underscoring the potential severity of congenital infection [12,67]. Experimental animal studies have also demonstrated fetal growth restriction and reduced viability following early gestational exposure, suggesting increased vulnerability during the first trimester [68].

Cohort studies of inadvertent exposure to the 17D vaccine during pregnancy have not shown a consistent increase in major congenital malformations, although minor dysmorphisms have occasionally been reported, and rare cases of congenital infection following maternal vaccination have been documented [16,69–71]. In addition, the possibility of peripartum and lactational transmission, including through breast milk, further complicates risk assessment and clinical management [12,45].

Despite these concerns, there are currently no standardized fetal surveillance protocols specifically designed for pregnant women with confirmed or suspected YF. Existing guidelines do not define optimal monitoring intervals, diagnostic modalities, or evidence-based intervention thresholds [72]. Consequently, clinical management relies on general obstetric principles, including confirmation of maternal infection, close assessment of maternal stability, and individualized fetal surveillance using serial ultrasound for growth assessment, fetal wellbeing testing, and Doppler studies when clinically indicated [72]. In endemic settings, prevention remains central and focuses on preconception vaccination, individualized risk–benefit assessment during pregnancy, intensified surveillance of febrile pregnant women, and appropriate breastfeeding guidance following vaccination [45]. Prospective studies and pregnancy registries are urgently needed to determine true vertical transmission rates, characterize prenatal imaging findings, and establish evidence-based fetal and neonatal follow-up strategies to improve perinatal outcomes [12,67].

Prevention Strategies in Pregnancy

Prevention of YF and other arboviral diseases in pregnant women relies on an integrated approach combining vector control, personal protective measures, risk assessment, and targeted public health

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interventions [73], including attention to the immune status of pregnant women and people of childbearing potential. In endemic and high-risk areas, reducing exposure to infected mosquitoes remains a fundamental strategy [73,74]. Environmental management to eliminate breeding sites, regular insecticide application, and community-based vector control programs play a central role in limiting transmission [75]. At the individual level, pregnant women should be encouraged to use repellents approved for use during pregnancy, wear protective clothing, install window screens, and use bed nets, particularly in areas with intense vector activity [1,4,7,32]. At the individual level, women at risk of transmission may be advised to avoid pregnancy during periods of high transmission and outbreaks.

Risk reduction is especially important for women living in rural, peri-urban, and forest-adjacent settings, as well as those engaged in agricultural or outdoor occupations. Travel to endemic regions during pregnancy should be carefully evaluated, and non-essential travel should be postponed when feasible, particularly during outbreaks [76]. When travel is unavoidable, personalized counseling is essential to minimize exposure and ensure access to appropriate preventive measures [77].

Surveillance systems and early warning mechanisms based on epizootic monitoring, climatic indicators, and human case detection contribute to timely outbreak response and targeted prevention efforts. Integrating YF prevention into routine antenatal care provides an opportunity to identify at-risk women, reinforce protective behaviors, and facilitate access to vaccination when appropriate. Strengthening community engagement, health education, and intersectoral collaboration is essential to sustain preventive strategies and reduce the burden of YF among pregnant populations [78,79]. In low-resource settings, maintaining adequate vaccine storage conditions and cold chain integrity represents an additional critical challenge, as failures in temperature control may compromise vaccine potency and undermine prevention efforts, particularly in remote and underserved communities [80–83].

Community perceptions of febrile illness and its management, as well as local patterns of human–animal interactions, play a central role in shaping the risk of YF transmission among pregnant women. Underestimation of symptoms and delayed care-seeking remain common in many settings. Addressing these factors through culturally appropriate health education can improve risk awareness, promote timely healthcare utilization, and empower pregnant women with practical strategies to prevent infection and recognize early warning signs [84].

YF Vaccination in Before and During Pregnancy

Because protective immunity to YF after infection or vaccination lasts for decades in most people [85], there is a broad window of opportunity for immunological interventions prior to pregnancy. Vaccination, remains the most effective and reliable strategy for preventing YF and reducing disease-related morbidity and mortality in endemic and outbreak settings (Table 3) [1]. Beyond active immunization, passive immunization strategies, including the use of monoclonal antibodies for prophylactic and therapeutic purposes, have emerged as promising complementary tools, particularly for pregnant or immunocompromised individuals in outbreak settings, and may represent a feasible future approach to outbreak mitigation through targeted stockpiling and rapid deployment [86]. Vaccination against YF, including among pregnant women in high-exposure areas is critical in a condition with a case fatality rate higher than 40% [7]. The currently available live-attenuated vaccine has demonstrated high effectiveness and an adequate safety profile over several decades of use worldwide (Table 4) [2]. It induces robust and long-lasting immunity in most recipients and has been instrumental in controlling transmission and preventing large-scale epidemics [87]. Accumulated evidence indicates that this vaccine is safe for use in the general population and represents a cornerstone of global YF prevention [1,38].

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Table 3. Risk–Benefit Framework for Yellow Fever Vaccination in Pregnant Women.

Scenario	Transmission Risk at Destination/ Residence	Maternal Exposure Profile	Gestational Age	Vaccination Recommendation	Rationale	Suggested Follow-Up / Additional Measures
Active outbreak in the area of residence	High	Resident in outbreak-affected municipality; routine daily exposure	Any trimester	Vaccinate after risk–benefit counseling	Risk of severe yellow fever and maternal mortality likely outweighs theoretical vaccine risk	Enhanced mosquito avoidance; close maternal–fetal monitoring; report to pregnancy registry if available
Active outbreak; unavoidable travel (work/humanitarian/ essential)	High	Unavoidable travel to outbreak zone; prolonged stay or rural/peri-forest exposure	Any trimester	Vaccinate (preferably before travel)	Substantial exposure risk; postponement not feasible	Pre-travel counseling; mosquito precautions; plan for access to care; consider post-vaccination serology if policy supports
Endemic area without current outbreak; sustained sylvatic circulation	Moderate	Resident or frequent travel to forest fringe/riverine/rural areas	2nd–3rd trimester	Consider vaccination if exposure is ongoing and significant	Ongoing exposure increases cumulative risk; later gestation may simplify obstetric monitoring	Strengthen vector protection; routine antenatal follow-up; document shared decision-making
Endemic area without current outbreak; low exposure	Low–Moderate	Urban residence, limited outdoor exposure, good vector control	Any trimester	Defer vaccination; emphasize vector precautions	Lower short-term exposure risk; avoid live vaccine when not clearly needed	Reassess if epidemiology changes; reinforce repellents, screens, bed nets
Non-endemic area; traveler considering discretionary travel to an endemic region	Moderate	Elective tourism or flexible itinerary	2nd–3rd trimester	Avoid travel or postpone; if travel cannot be postponed, individualize vaccination decision	Best prevention is avoiding exposure; the vaccine is live-attenuated	If travel proceeds: strict mosquito precautions; select lower-risk routes/locations; ensure travel insurance and care access

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First trimester in a moderate-risk setting	Moderate	Planned travel or intermittent exposure; ability to postpone or modify exposure	1st trimester	Prefer deferral and exposure avoidance when feasible	Theoretical concerns are greatest early in gestation; many exposures can be mitigated by postponement	Reassess in the 2nd trimester if risk persists; prioritize non-pharmacologic protection
Late pregnancy with high exposure and limited access to care	High	Rural residence; limited healthcare access; intense vector exposure	3rd trimester	Vaccinate; prioritize maternal protection	Severe maternal disease near term can be catastrophic; protecting the mother is central to fetal survival	Plan delivery site with higher-level care; continuous fetal surveillance if clinically indicated
Inadvertent vaccination before pregnancy is recognized	N/A	Vaccinated peri-conception or early pregnancy (unintentional)	Any	No intervention required solely for vaccination; provide reassurance	Most evidence does not show consistent severe adverse outcomes from inadvertent vaccination	Routine obstetric care; offer targeted ultrasound per local practice; report to pharmacovigilance
Previously vaccinated (documented or credible history)	Depends	Prior YF vaccination before conception; no contraindications	Any	No revaccination in pregnancy in most cases	Prior vaccination likely provides durable protection; avoid unnecessary live vaccine exposure	Verify documentation if possible; counsel on mosquito protection; consider booster only if policy requires and risk is extreme
Uncertain vaccination history; high-risk exposure	High	No records; high-risk residence/travel; limited time for verification	Any trimester	Treat as unvaccinated and consider vaccination if exposure is substantial	Delay may increase infection risk; decision must be pragmatic in emergencies	Document uncertainty; consider serology if available and timely; reinforce mosquito precautions
Postpartum—breastfeeding mother needs vaccination due to outbreak/travel	High	Breastfeeding with imminent exposure risk	Postpartum	Vaccinate; counsel on rare risk of vaccine virus transmission via breast milk. Temporary interruption of breastfeeding for at least 10 days should be recommended for infants younger than 6 months.	Maternal protection is important; breastfeeding transmission appears rare but possible	Shared decision; consider temporary interruption of breastfeeding for a defined period if local guidance recommends; monitor the infant

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Mass vaccination campaign during the outbreak	High	Pregnant woman in campaign area; varying exposure levels	Any trime ster	Individual risk assessment within campaign framework; vaccinate when exposure is high	Population-level control vs individual considerations; avoid blanket exclusion if outbreak risk is significant	Clear consent processes; pregnancy registry; strengthened adverse event surveillance; tailored counseling

Table 4. Safety of Yellow Fever Vaccine in Pregnancy by Trimester [48,88,89,91–94,108].

Trimester of pregnancy	Safety considerations	Available evidence	General recommendation
First trimester (0–12 weeks)	Increased caution. Possible theoretical risk of teratogenicity and miscarriage (as it is a live attenuated virus vaccine). Animal studies have shown placental transmission, although evidence in humans is limited.	Retrospective studies have shown no significant increase in congenital malformations; however, the number of cases is limited.	Avoid if possible. Only manage if the risk of exposure is high and unavoidable. Perform detailed prenatal follow-up.
Second trimester (13–26 weeks)	Lower theoretical risk compared to the first trimester. A similar rate of adverse events has been reported in the vaccinated general population.	Most studies with positive data include women vaccinated in this trimester. There has been no evidence of an increase in miscarriage or fetal adverse effects.	It may be considered if the risk of exposure is high. Accompany with adequate obstetric monitoring.
Third trimester (27 weeks–delivery)	Low risk of teratogenic effects, but considered a risk of vertical transmission with the appearance of antibodies in the newborn.	IgM antibodies have been documented in neonates of vaccinated mothers, with no evidence of clinical disease.	It may be given if there is a clear indication. Low risk, but it is recommended to observe the newborn after birth.

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In the context of pregnancy, early theoretical concerns regarding fetal exposure to a replicating virus led to cautious recommendations and classification of the vaccine as one to be used with precaution (Table 4) [88]. However, growing observational evidence has consistently shown that YF vaccination during pregnancy is not associated with significant adverse maternal, fetal, or neonatal outcomes [21,89]. Although some studies have reported mild symptoms like headache, fever, and myalgias, in up to 19.6% of pregnant women who were inadvertently vaccinated early (at a mean of 5.7 weeks of gestation) in gestation [21] and fetal adverse events, mostly malformations (3.3%), with no differences in several types of major malformations except for Down's syndrome (3 cases in 304 babies exposed, p=0.003) [71] and spontaneous abortion (< 2%) in patients exposed before their last menstrual period or during the first trimester of pregnancy [90,91].

Multiple studies, including large cohort analyses and post-marketing surveillance data, have failed to demonstrate increased risks of miscarriage, congenital anomalies, stillbirth, preterm birth, or neonatal complications attributable to vaccination [21,48,88,89,92,93]. Importantly, inadvertent vaccination during early pregnancy, including during the first trimester, has not been linked to clinically relevant safety concerns [21,48,88,89,92,93]. Thus, vaccination against YF, including among pregnant women, in high-risk settings likely offers greater benefit than risk. Yet, defining precise epidemiological indices to justify including susceptible populations, such as pregnant women, in vaccination campaigns could be challenging.

Regulatory agencies and public health authorities have progressively incorporated this evidence into their guidance [94]. The United States Food and Drug Administration and other regulatory bodies consider the YF vaccine to be safe when administered during pregnancy under appropriate clinical circumstances (https://www.fda.gov/media/76015/download) (Accessed 9 February 2026). Brazil's National Immunization Program, in a technical document, points out that regarding the use of the YF vaccine in pregnant women, "if it is impossible to postpone vaccination, such as in situations of epidemiological emergency, outbreaks or epidemics, the health service should assess the risk versus benefit of vaccination" (https://www.gov.br/saude/ptbr/vacinacao/publicacoes/instrucao-normativa-calendario-nacional-de-vacinacao-2024.pdf) (Accessed 9 February 2026). Consequently, updated clinical guidance and public health messaging could empower primary care and obstetrical providers to incorporate YF vaccination as a key consideration in prenatal care [40,69,95].

Risk–benefit assessment remains central to vaccination decision-making regarding YF immunization during pregnancy. Several countries have adopted pragmatic, evidence-based policies that incorporate local epidemiology, gestational age, and individual exposure profiles. Based on these principles, a risk-based operational framework is proposed to guide vaccination decisions in clinical and outbreak settings (Figure 2) [1]. In areas with active transmission, recurrent outbreaks, or sustained sylvatic circulation, the risk of severe maternal disease, hemorrhagic complications, and maternal mortality clearly outweighs any potential vaccine-related concerns (https://www.minsalud.gov.co/Normatividad_Nuevo/Circular%20Externa%20No%20029%20de%202025.pdf) (Accessed 9 February 2026). In such settings, vaccination represents the most effective means of protecting both maternal and fetal health. Ideally, women of reproductive age in endemic regions who have not been previously immunized against YF should be vaccinated prior to becoming pregnant. Conversely, in low-risk environments or when exposure can be avoided, deferring vaccination and postponing travel may be considered [1,2,7]. At the population level, strengthening routine pre-pregnancy vaccination in endemic and epidemic-prone areas is a highly effective preventive strategy, analogous to public health approaches used for other infections with major implications for maternal and fetal health, such as hepatitis B and human papillomavirus.

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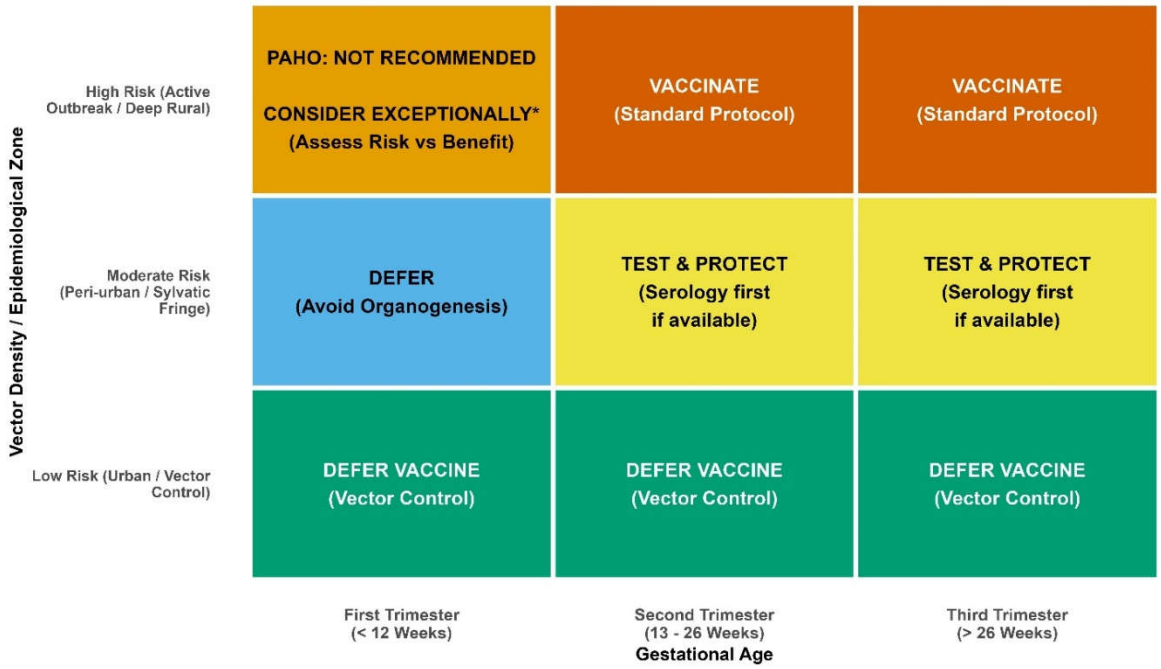

Figure 2. Proposed Operational Decision Matrix for Yellow Fever Vaccination in Pregnancy during the 2024–2026 Americas Outbreak. The matrix integrates gestational age and local transmission intensity to guide vaccination decisions in pregnant women. Recommendations reflect current evidence and regional public health guidance, emphasizing individualized risk–benefit assessment, particularly in high-risk outbreak settings. *<12 weeks: PAHO does not generally recommend vaccination during the first trimester due to theoretical risks. However, in high-risk zones, this protocol proposes its use as an exceptional measure based on Risk versus Benefit analysis (where the high probability of maternal mortality outweighs the theoretical risk to the fetus). In all scenarios, vector control and personal protection against vectors are recommended. Testing for immune status assessment is generally not readily available. Even if it were, limitations in serologic interpretation due to cross-reactions among flaviviruses could lead to false-positive results for yellow fever and prevent the vaccine from being recommended.

Multiple countries have adopted pragmatic, evidence-based policies reflecting this approach [96]. In the United States, the YF vaccine may be used as a precaution when balancing risks and benefits (https://www.cdc.gov/yellow-fever/hcp/vaccine/index.html) (Accessed 9 February 2026). Pregnant women should avoid or postpone travel to an area where there is a risk of YF. If travel cannot be avoided, discuss vaccination with your healthcare professional. In the United Kingdom, when travel is unavoidable, vaccination in pregnancy should be considered on a case-by-case basis. The possible fetal risks of vaccination should be weighed against the risk to mother and fetus from YF infection, which is associated with significant morbidity and mortality, particularly in immune-naïve individuals (https://uktis.org/monographs/yellow-fever-vaccination-in-pregnancy/) (Accessed 9 February 2026). Similarly, considerations and recommendations are in Canada (https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-4-immunization-pregnancy-breastfeeding.html) (Accessed 9 February 2026), Australia (https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/yellow-fever) (Accessed 9 February 2026), France (https://www.pasteur.fr/en/medical-center/vaccines-available-medical-center) (Accessed 9 February 2026), Germany (https://www.auswaertiges-amt.de/resource/blob/2279420/9f78874fa053f8a9cb15c505a5b03ef1/reise-impfempfehlungen-aa-data.pdf) (Accessed 9 February 2026), Spain (https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/programasDeVacunacion/e

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mbarazadas/mujeres/docs/Mujeres_edad_fertil_embarazadas_puerperio.pdf) (Accessed 9 February 2026) among other countries.

For example, following national safety assessments, Colombia recommends YF vaccination after 12 weeks of gestation for pregnant women residing in or traveling to high-risk areas (https://www.minsalud.gov.co/Normatividad_Nuevo/Circular%20Externa%20No%20029%20de%202025.pdf). Ecuador also recommends the use of YF for pregnant women in high-risk areas (https://www.salud.gob.ec/fiebre-amarilla). Similar risk-based strategies have been implemented in other endemic and non-endemic countries, integrating local epidemiology, individual exposure profiles, and gestational age into vaccination decisions. In Brazil, the vaccination may be recommended for pregnant women when there is a high risk of infection, and vaccination cannot be deferred. This applies to individuals who live in, or will travel to, areas with active transmission, provided that a health service has evaluated them. For travelers, the vaccine should be administered at least 10 days before departure (https://www.gov.br/saude/pt-br/vacinacao/calendario). When indicated after the first trimester, YF vaccination may be safely co-administered with inactivated vaccines, including seasonal influenza and COVID-19 vaccines, as available evidence indicates no clinically significant interference with immunogenicity or increase in adverse events [97].

In situations where YF vaccination is recommended, counseling should emphasize the vaccine's demonstrated safety and effectiveness, the high risk of natural infection, and the substantial benefit of maternal protection, especially during outbreaks. Shared decision-making, supported by clear and transparent information, enhances patient confidence and promotes adherence to preventive measures. Informed consent and appropriate documentation remain essential components of good clinical practice [11,17,45,48,92].

Post-vaccination follow-up should include routine obstetric monitoring and assessment of maternal well-being. Although most vaccinated pregnant women develop an adequate immune response, several studies have shown that seroconversion rates during pregnancy may be lower than in non-pregnant adults, and that long-term immunity may be less consistent [40,85,98,99]. In a cohort of 96 infants with available longitudinal follow-up, 51 were born to mothers who were seropositive for YF virus IgG. Among these infants, 36 (70.6%) were IgG-positive at birth, reflecting efficient transplacental transfer of protective maternal antibodies. Longitudinal analyses demonstrated a progressive decline in passively acquired IgG concentrations over time, with substantial interindividual variability in the rate of antibody waning. An additional area of uncertainty is whether high maternal antibody levels in highly endemic settings may transiently blunt infant immune responses to subsequent vaccination or natural exposure, potentially affecting long-term protection. These findings highlight the transient nature of maternally derived immunity and its limited contribution to sustained infant protection [100].

Studies have reported high short-term seroprotection rates following inadvertent YF vaccination during pregnancy, reaching up to 98% in early gestation (2-4 weeks) [21], although substantially lower seroconversion rates have been observed in some cohorts (38.6% at 6 weeks) [40]. Consequently, booster doses after pregnancy are recommended in several countries, including Canada (https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-25-yellow-fever-vaccine.html), USA (https://www.cdc.gov/yellow-fever/hcp/vaccine/index.html), Germany [99], Australia, and Colombia (https://www.minsalud.gov.co/Normatividad_Nuevo/Circular%20Externa%20No%20001%20de%202026.pdf), particularly for women who remain in or return to high-risk areas and were vaccinated during pregnancy [15,59,88,94].

Breastfeeding considerations should also be addressed. Few case reports have documented transmission of the YF vaccine virus through breast milk during the early neonatal period, leading to severe neurological complications in exposed infants. These observations provide a strong rationale for individualized risk assessment and support recommendations for temporarily interrupting breastfeeding when maternal vaccination is required, particularly during the first weeks of life [101,102]. Although transmission of vaccine-derived virus through breast milk is rare, individualized

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counseling is appropriate, especially in the early postpartum period. In most cases, the benefits of maternal immunization and continued breastfeeding outweigh potential risks [15,59,88,94]. In women who receive the YF vaccine during breastfeeding, a temporary interruption of breastfeeding for at least 10 days may be considered for infants younger than 6 months, given their increased vulnerability to vaccine-derived viral transmission. In contrast, continued breastfeeding is generally appropriate for infants older than 6 months, in whom the risk of adverse outcomes is substantially lower (Table 3) (https://www.minsalud.gov.co/Normatividad_Nuevo/Circular%20Externa%20No%20029%20de%202025.pdf).

From a public health perspective, strengthening preconception, adolescent, and routine adult immunization programs is essential to minimize the need for vaccination during pregnancy. Systematic assessment of vaccination history during antenatal care allows early identification of susceptible women and facilitates timely preventive interventions [18,19,93,95].

During mass vaccination campaigns, including those conducted in outbreak settings, pregnant women should not be systematically excluded. Instead, individualized medical assessment, clear operational guidance, and strengthened pharmacovigilance systems are required. The experience from recent outbreaks, including the 2024–2026 epidemic in Colombia, demonstrates that targeted vaccination after the first trimester can be safely implemented when transmission risk is high. It is also important to emphasize that, when vaccination is indicated during pregnancy, the standard full-dose YF vaccine should be administered rather than fractional doses. Although dose-sparing strategies have been implemented in outbreak settings, fractional dosing has not been adequately evaluated for safety or immunogenicity in pregnant women, and its effectiveness in this population remains uncertain [88]. In other populations, e.g., children, fractional doses do not sustain long-term appropriate antibody titers [103]. Even more, the WHO indicates that until data relevant to specific subgroups become available, children aged <2 years, individuals known to be HIV-infected, and pregnant women should preferentially be vaccinated using a standard dose [104]. Therefore, full-dose vaccination remains the preferred approach when maternal immunization is required [7].

In summary, extensive real-world experience and growing scientific evidence support the safety and effectiveness of YF vaccination in pregnancy. The vaccine is not contraindicated but should be used with precaution and informed clinical judgment. A risk-based approach that prioritizes maternal protection, supported by appropriate counseling and post-pregnancy booster strategies, represents the most rational and effective framework for preventing YF in pregnant women and their infants in endemic and re-emerging settings [48,105].

Limitations

This perspective has several important limitations that should be considered when interpreting its findings and recommendations. First, available evidence on YF in pregnancy remains limited and heterogeneous [15]. Much of the existing literature is derived from outbreak investigations, small case series, retrospective analyses, and isolated case reports. The scarcity of large, prospective, population-based studies restricts the ability to accurately estimate incidence, risk factors, and maternal and fetal outcomes.

Surveillance systems in many endemic regions do not routinely capture pregnancy status, gestational age, or detailed obstetric and neonatal outcomes. This contributes to underreporting, incomplete case characterization, and potential misclassification. Mild and asymptomatic infections are likely overlooked, leading to underestimation of the true burden of disease. Similarly, current knowledge on vertical and perinatal transmission is based on very few documented cases, limiting generalizability.

Most safety and immunogenicity data on YF vaccination during pregnancy originate from observational studies and post-marketing surveillance. These data sources are inherently subject to selection bias, incomplete follow-up, and residual confounding. In addition, immunogenicity studies

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are limited in size and geographic scope, which constrains conclusions regarding long-term protection and optimal booster strategies.

An additional limitation reflects the long-standing exclusion of pregnant women from vaccine and clinical research, a practice historically intended to minimize fetal risk but increasingly recognized as ethically problematic and scientifically counterproductive. This paternalistic approach has contributed to persistent evidence gaps, delayed access to effective interventions, and limited data to support informed decision-making. Failure to adequately include pregnant women in research may ultimately undermine autonomy and compromise maternal and fetal health outcomes. Addressing this structural barrier is essential to generate robust, pregnancy-specific evidence for YF prevention and management [106].

An additional limitation relates to global policy frameworks. The WHO Eliminate YF Epidemics (EYE) strategy, covering 2017–2026, does not explicitly address the specific needs of pregnant women [107]. Despite growing recognition of the impact of infectious diseases on maternal and fetal health, pregnancy-specific considerations remain largely absent from major YF control initiatives. As the EYE strategy nears completion, future updates from WHO and PAHO present an important opportunity to integrate targeted protection, surveillance, and research priorities for pregnant women into global YF prevention and response plans [107].

Finally, the recommendations presented in this article are influenced by evolving epidemiological patterns, national policies, and vaccine availability, all of which may change over time. Continued surveillance, standardized reporting, and well-designed prospective studies are essential to address these limitations and strengthen the evidence base for clinical and public health decision-making.

Conclusions

YF remains a major public health threat in endemic and re-emerging regions, and its impact on pregnant women represents an important yet underrecognized dimension of disease burden. Physiological, immunological, and social vulnerabilities during pregnancy may increase the risk of severe maternal illness and adverse fetal and neonatal outcomes, underscoring the need for targeted prevention, early diagnosis, and integrated clinical management. Despite limited and heterogeneous data, available evidence indicates that YF infection in pregnancy can be associated with significant maternal morbidity, pregnancy loss, preterm birth, and, in rare cases, perinatal transmission.

Vaccination remains the cornerstone of prevention. Accumulated real-world experience and observational studies consistently support the safety and effectiveness of the YF vaccine in pregnant women when used with appropriate clinical judgment. In high-risk settings, the benefits of maternal immunization clearly outweigh theoretical concerns, and risk-based strategies that prioritize maternal protection should be actively promoted. Strengthening preconception immunization, integrating vaccination assessment into antenatal care, and implementing postpartum booster strategies are essential components of comprehensive prevention programs.

Looking ahead, next-generation YF vaccines may further improve the safety profile of immunization in special populations. A Vero cell–derived vaccine based on selected 17D sub-strains with reduced neurotropism is currently in advanced stages of development and has demonstrated non-inferior immunogenicity compared with existing vaccines in clinical trials (https://clinicaltrials.gov/study/NCT04942210). This platform may potentially reduce the risk of serious adverse events and could be particularly relevant for pregnant women. However, pregnancy-specific safety data are unlikely to become available in the near future, underscoring the continued need for careful surveillance and dedicated research in this population [108].

From a clinical perspective, improved awareness among healthcare providers is critical to facilitate timely recognition, appropriate supportive care, and multidisciplinary management. Public health systems must enhance surveillance, incorporate pregnancy-specific indicators, and ensure equitable access to preventive and diagnostic services, particularly in vulnerable populations.

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Beyond currently available interventions, emerging and innovative approaches for YF prevention and management in pregnancy merit sustained attention and investment, particularly to strengthen preparedness and response in high-risk settings.

Future efforts should focus on establishing prospective pregnancy registries, strengthening pharmacovigilance, and expanding studies of vaccine safety, immunogenicity and effectiveness in pregnant populations. Such initiatives will help refine clinical guidelines and inform policy decisions. Addressing YF in pregnancy through coordinated clinical, epidemiological, and public health strategies is essential to protect maternal and neonatal health in endemic and re-emerging settings.

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