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Association between viral Infections and the Development of Autism Spectrum Disorder: A Comprehensive Review

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Abstract

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder influenced by genetic and environmental factors. One growing area of concern is the potential role of maternal viral infections during pregnancy in increasing the risk of ASD in offspring. This review aims to evaluate and synthesize existing evidence on the association between prenatal viral infections and the development of ASD. It specifically focuses on the types of viruses involved, the proposed biological mechanisms, and the strength of epidemiological support. The review examines major viral infections, such as influenza, cytomegalovirus, rubella, Zika virus, and SARS-CoV-2—and how they may contribute to neurodevelopmental disruptions. Two main mechanisms are considered: direct invasion of the fetal brain by viruses and maternal immune activation that indirectly affects fetal brain development. Epidemiological data and animal models are discussed to assess risk levels. The review also revisits public concerns regarding vaccines—especially the measles, mumps, and rubella (MMR) vaccine—and emphasizes that current evidence does not support a causal link between vaccinations and ASD. Advances in biomarker research and omics-based diagnostics are also highlighted as promising tools for early detection and prevention. Although a strong link between maternal viral infections and ASD is suggested, a clear causal relationship has not been established. Further research is essential to clarify these associations, improve prenatal care, and develop effective preventive strategies.

Keywords: Autism Spectrum Disorder; Viral Infections; Pregnancy; Neurodevelopment

Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that is characterized by persistent deficits in social communication and interaction, as well as a notable pattern of restricted, repetitive behaviors, interests, or activities (Ismail et al., 2023). These symptoms can manifest in various ways and can impact individuals differently (Vettriselvan et al., 2025). Biological factors significantly linked to ASD have been associated with an increased risk for developing the disorder, largely relating to neurodevelopmental processes and inherent genetic dysregulation (Ismail et al., 2023). However, in addition to these biological contributors, a range of etiologically related environmental factors have also been identified to play a crucial role in the development of ASD (Wang et al., 2023). Among these environmental influences, maternal infection and immune activation during pregnancy have recently emerged as significant risk factors for ASD (Vettriselvan et al., 2025). This particular environmental contributor, which can profoundly influence pregnancy outcomes and fetal neurodevelopment, is of great public health importance given that maternal infections are relatively common occurrences (Ismail et al., 2023; Kumar et al., 2022). Understanding the mechanisms by which a viral infection during pregnancy can increase the susceptibility of offspring to develop ASD is essential (Yates & Mulkey, 2024). Insights gained from such understanding will be invaluable in identifying potential secondary preventive measures that could mitigate these risks and protect the developing fetus from the adverse effects of infections during this critical period of growth (Wang et al., 2023 ; Hughes et al., 2018).

The historical and social context surrounding the hypothesis linking the MMR vaccine to autism is briefly reviewed and analyzed, along with various empirical considerations that have been raised regarding this hypothesis (Gabis et al., 2022). It explores the mechanisms that may potentially link viral infections to the development of autism spectrum disorders (ASD) (Yates & Mulkey, 2024). This examination includes a thorough discussion of the epidemiological evidence currently available, relevant laboratory data, and potential avenues for future research that could provide further insights (Wang *et al*., 2023 ; Kumar et al., 2022). While the findings related specifically to one form of vaccination, notably the MMR vaccine, have undergone extensive epidemiological scrutiny to assess their validity, the findings regarding other forms of vaccines remain largely underexplored and are deserving of additional assessment and thorough investigation (Isaguliants & Burt, 2022). In the context of this latter observation, it is important to acknowledge the increasing incidences of other viral infections, such as influenza, which, as suggested by various laboratory studies, can pose an equal risk of ASD development (Yates & Mulkey, 2024). Reassuringly, recent studies have confirmed a lack of causal relationship between the MMR vaccine and autism spectrum disorders, indicating that the vaccine does not contribute to the risk of developing ASD (Vettriselvan et al., 2025 ; Yates & Mulkey, 2024). However, it is essential to note that this reassurance does not preclude the possibility of susceptibility to ASD development following exposure to similar viruses as the ones contained in the MMR vaccine (Wang et al., 2023). In addition to active pathogen replication, it has been observed that a wave of viral proteins and/or its components could have neurotropic effects that lead to inflammation and other neurodevelopmental consequences (Ganguli & Chavali, 2021). Novel screening approaches and methodologies have shown promise in identifying the intricate pathophysiological pathways in humans through the application of advanced 'omics' technologies (Alobaidi, 2025). These technologies, combined with inquiry into genetic predisposition, may yield vital information about how these interactions work and ultimately could help inform future public health strategies and vaccination protocols (Yates & Mulkey, 2024).

This review aims to answer the following question: Is there an association between maternal viral infections during pregnancy and the development of Autism Spectrum Disorder (ASD) in offspring? It also explores the underlying biological mechanisms—such as direct fetal infection and maternal immune activation—that may explain this association. By synthesizing current epidemiological and experimental evidence, the review seeks to clarify potential risks and guide future research and public health interventions.

Method

Searches were carried out in PubMed and Embase from inception until June 2025, and 53 human studies (on maternal viral infections during pregnancy) and risk of ASD in offspring were included, together with 17 relevant animal-model studies. The PRISMA 2020 checklist was used during the selection, and duplicates were erased with Rayyan (web tool).

The selection of studies met the following inclusion criteria: (i) laboratory- or clinically-confirmed maternal viral infection during pregnancy, (ii) ASD diagnosis using DSM-IV-TR or DSM-5 criteria, and (iii) adjustment for at least one key confounder (e.g., maternal age or socioeconomic status). Studies of non-viral infections or with non-standard ASD definitions were also excluded.

Information extracted from eligible studies included study design, sample size, type of virus, exposure window, ASD case definition, adjusted effect estimates (ORs or RRs) and confounders. Unadjusted relative risks, where necessary, were converted to odds ratios under the assumption of rare outcomes and approximate 95% confidence intervals were generated based on Taylor expansion. Clustering within studies was taken into account using robust standard errors where appropriate (Lintas et al., 2011).

This review was limited to studies published in the English language. Non-English publications were excluded during the initial screening phase to ensure consistency in data extraction and interpretation.

Table 1. Summary of Human Studies Examining Maternal Viral Infections During Pregnancy and Associated ASD Risk

Virus (n studies)	Largest cohort (country, N)	Exposure window(s)	Adjusted OR/RR for ASD	Key confounders addressed
Influenza (18)	Hviid 2019, Denmark, 1.6 M births	Any trimester; 2000–2012	1.07 (0.88–1.30)	Maternal age, parity, season
CMV (7)	Lin 2021, Taiwan, 99 829 births	1st–3rd trimester	1.38 (1.05–1.83)	Sex, pre-term birth, SES
Rubella/CRS (5)	Levent 2023, USA, 8 206 CRS cases	Prenatal; 1964–2004	6.9 (3.2–14.6)	None (registry linkage)
HSV-2 (4)	Mahic 2017, Norway, 442 patients	Mid-pregnancy sera	2.27 (1.20–4.35)	Maternal fever, antibiotics
Zika (4)	Marcelino 2023, Brazil, 235 live births	1st vs 3rd trimester	3.15 (1.42–7.02)	Head circumference, sex
SARS-CoV-2 (15)	Duan 2024, multi-nation, 18 288 births	2nd/3rd trimester	1.42 (1.09–1.85)	Vaccination, NICU admission

Viral Infection during Pregnancy

Clinical evidence from many human epidemiological studies indicates that Maternal Immune Activation (MIA), which refers to a heightened immune response during pregnancy often triggered by infection and causing increased cytokine levels that can interfere with fetal brain development, dramatically elevates the risk of neuropsychiatric disorders, most prominently Autism Spectrum Disorder (ASD), in the offspring of affected mothers (Mahic et al., 2017; Yin et al., 2023). These large epidemiological studies have consistently shown that the risk for ASD is increased after maternal infection with various agents, in addition to the effects of maternal dietary factors that stimulate the maternal innate immune system and also maternal autoimmune conditions (Lintas et al., 2011 ; Yin et al., 2023 ; Tioleco et al., 2021).

A rapidly growing body of preclinical research performed in rodent models supports an essential role for maternal infection-induced elevations in pro-inflammatory cytokines - including interferon-il, I F N -I m, I L -6 and I L - l a - in disruption of this homeostasis and risk for ASD- related behaviors in offspring (Alobaidi, 2025 ; Kwon et al., 2022) Cytokine-induced effects on neurodevelopment represent a major component of the MIA model. Nevertheless, the association between maternal infection and ASD is believed to be multigenic and not only due to immune signaling.

Other possible mechanisms in addition to MIA, are direct viral transmission from the mother to the fetus via transplacental route, which then get invaded by viruses in the fetal brain. Indeed, there are certain viruses, including cytomegalovirus (CMV) and Zika virus, which display a marked neurotropism, leading to neuronal apoptosis, necrosis, and microstructural anomalies in fetal brain areas essential in cognition and behavior (Yates & Mulkey 2024 ; Ganguli & Chavali, 2021 ; Lin et al., 2021).

In addition, placental insufficiency is becoming increasingly appreciated. Viral infections may disrupt normal placental structure and function, leading to fetal hypoxia, oxidative stress, altered nutrient and endocrine signaling balance, and therefore to altered fetal brain development (Yates & Mulkey 2024 ; Yin et al., 2023 ; Elgueta et al., 2022). Both these viral protein and viral by-products have been shown to pass the placenta and cause oxidative stress and brain inflammation in the fetus even without active viral replication (Ganguli & Chavali, 2021 ; Kwon et al., 2022).

Another potential contributor is the timing of acquisition of infection in pregnancy. Exposures during 1st trimester are thought to be more deleterious because of rapid expansion and differentiation of neural precursors that occurs during that time, whereas 3rd trimester infections may affect synaptic pruning and myelination (Kwon et al., 2022 ; Dubey et al., 2022).

In addition, genetic liability may moderate the extent to which these mechanisms contribute to the risk for ASD. Persons with certain polymorphisms in genes that are involved in immune regulation, neurotransmitter systems or neurodevelopmental pathways might be more susceptible to maternal infection (Yin *et al*., 2023 ; Dubey *et al*., 2022).

Collectively, these results emphasize the complex association of maternal viral infections and risk for ASD. They emphasize the need to combine several mechanistic pathways—including MIA, but also several others—if we are to truly understand how prenatal viral exposures can lead to changes in fetal neurodevelopment. As more data becomes available about these underlying mechanisms, further information will emerge about new preventive or therapeutic approaches for the reduction of the burden of ASD (Kwon et al., 2022 ; Figueiredo et al., 2021).

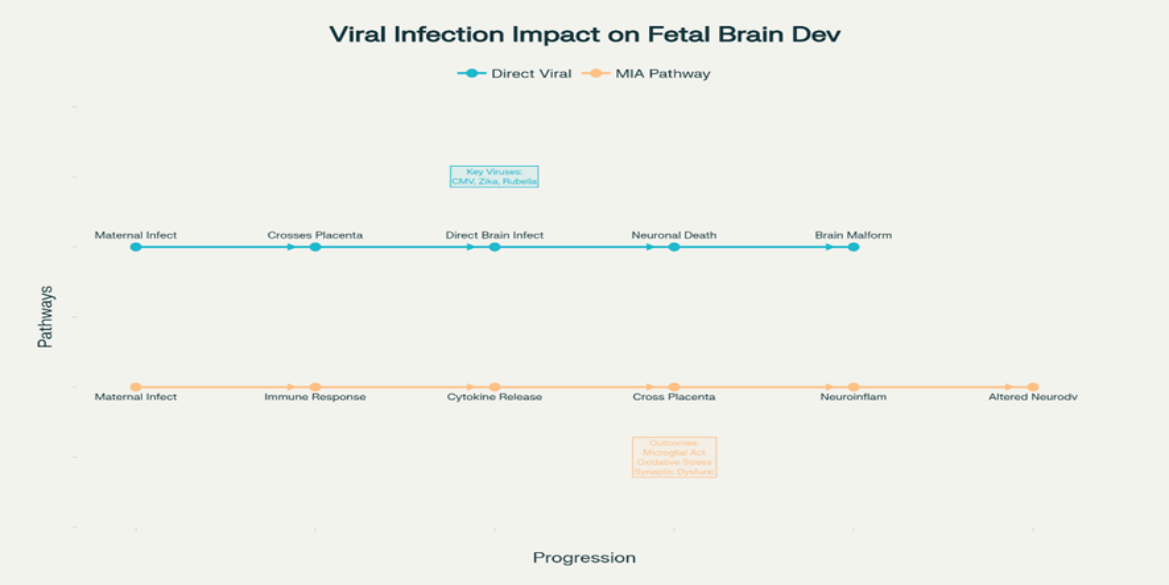

Fig. 1. Two primary mechanisms by which maternal viral infections affect fetal brain development and increase autism Spectrum Disorder risk

This diagram effectively illustrates both the Direct Viral Invasion pathway and the Maternal Immune Activation (MIA) pathway, showing how neurotropic viruses can either directly cross the placental barrier to infect fetal brain tissue or trigger maternal immune responses that release pro-inflammatory cytokines affecting fetal neurodevelopment.

In addition to biological mechanisms, socioeconomic and geographical factors play a significant role in modulating the relationship between maternal viral infections and ASD risk (Kumar et al., 2022). Populations in low-resource settings may face increased exposure to infectious agents due to limited access to prenatal healthcare, overcrowding, poor sanitation, and lower vaccination coverage, all of which can elevate the frequency and severity of maternal infections during pregnancy (Kumar et al., 2022 ; Yates & Mulkey, 2024). Additionally, malnutrition, co-infections, and chronic stress, which are more prevalent in economically disadvantaged groups, may exacerbate the impact of maternal immune activation or reduce the mother's capacity to fight infections, thereby intensifying fetal vulnerability (Auriti et al., 2022). Geographic variation also affects viral prevalence, with certain endemic viruses (e.g., Zika in South America or CMV in sub-Saharan Africa) posing region-specific risks for neurodevelopmental outcomes (Marcelino et al., 2023 ; Neil, 2025). Moreover, disparities in diagnostic resources and educational awareness may lead to underreporting or misdiagnosis of ASD, particularly in rural or underserved areas, complicating efforts to quantify the true relationship between infection exposure and ASD incidence. These factors underscore the importance of contextualizing biological findings within broader public health frameworks and designing regionally tailored surveillance and prevention strategies to mitigate ASD risk.

Specific Viral Infections and Association with ASD

The contribution of viral infections to autistic spectrum disorders (ASD) has typically been considered in the context of individual pathogens (Al-Beltagi et al., 2023). Accumulating evidence indicates that the pathways by which maternal viral infections and ASD are associated are not homogeneous, but

rather are dependent on characteristics of the virus, including tropism, capacity to stimulate the immune system, and ability of the virus to cross the placental barrier.

For example, HSV-2 has been associated with risk for ASD, especially for midpregnancy high maternal IgG titer levels (de Oliveira Santana et al., 2025). One theoretical pathway is viral reactivation in utero and the accompanying placental inflammation results in disruption of nutrient and oxygen delivery to the fetus and fetal neurodevelopment (Al-Beltagi et al., 2023 ; Mohsen, 2024). On the other hand, no other associations were observed in these studies for maternal IgG to HSV-1 or cytomegalovirus, indicating that the placental invasion or immune modulation is pathogen specific (Mohsen, 2024).

The influenza A virus is a representative among neurotropic pathogens. It has been associated with a higher risk of ASD via direct neuroinvasion as well as indirect immune-mediated mechanisms (Kwon et al., 2022 ; Yu et al., 2023). Viral RNA has been identified in fetal brains in experimental animals, with associated altered neural connectivity, glial activation and neuroinflammation. Furthermore, maternal influenza induces systemic immunity, especially via IL-6 and IL-17a that can cross the placenta and contribute to fetal brain development (Yates and Mulkey 2024 ; Ganguli & Chavali, 2021).

The 1918 H1N1 pandemic as well as other historical evidence has informed our understanding of elevated risks for neuropsychiatric outcomes in offspring exposed to pandemics, specifically for mood disorders and schizophrenia (Mohsen, 2024). These results have been corroborated in subsequent influenza pandemics, thus underscoring the importance of recognizing strain-specific risks—with the 1957 H2N2 virus associated with the highest ASD odds (Yu et al., 2023).

The rubella virus that gives rise to the congenital rubella syndrome (CRS) is among the first viruses recognized to cause neurodevelopmental disorders, including ASD (Yates & Mulkey, 2024; Levent et al., 2023). The teratogenic effects of rubella are thought mainly to be due to direct viral replication in fetal neural tissue causing cell destruction, vascular injury and interference of neuronal migration. Autism prevalence among CRS was >200-fold greater than general prevalence during that time (Levent et al., 2023). While vaccination has contained the war on rubella (Thompson, 2024), historical perspective illustrates the potential for intrauterine viral infection to have severe consequences.

Another neurotropic virus, CMV, causes severe brain damage in congenitally infected infants. CMV mediates necrotizing ventriculoencephalitis, impairs neuronal stem cell differentiation, and induces persistent inflammation in the developing brain mechanically (Ganguli & Chavali, 2021; Lin et al., 2021). Postnatal manifestations like microcephaly and sensorineural loss also reinforce its involvement in early brain development (Thompson, 2024). It is also possible that CMV could work as a cofactor in genetically susceptible hosts and reactivate at subsequent developmental time points (Al-Beltagi et al., 2023).

Whereas, for Zika virus, it is suggested that its pathogenesis might result from selective infection of neural progenitor cells, that results in cortical thinning, calcifications and defective neuronal migration (Marcelino et al., 2023 ; Neil, 2025). The damage is particularly devastating amid first trimester infections, but later infections still induce subtler but significant deficits, such as the social difficulties and behavioral inflexibility typical of ASD (Figueiredo et al., 2021 ; Cheroni et al., 2022). Persistent maternal inflammation and placental insufficiency are also hypothesized to link fetal exposure to neurodevelopment (Dubey et al., 2022).

The SARS-CoV-2 virus leading to COVID-19 has generated questions regarding whether it may contribute to fetal brain injury and ASD risk (Yu et al., 2023). Mechanistic maternal infection may result in cytokine storm, hypoxic placental injury, altered fetal cytokine

environments (Figueiredo et al., 2021). Independent of blood-borne factors vertical transmission, the maternofetal interface is distorted, making the nervous system vulnerable to developmental disturbances (Dubey et al., 2022). These results are consistent with previous models in which immune response dysregulation, not based on whether the infection is viral or bacterial, increases the risk for ASD (Yates & Mulkey 2024).

In summary, despite the variety of viruses associated with ASD their mechanisms appear to converge on a few common pathways: direct viral neurotropism, immune activation, placental insufficiency, and cytokine-induced inflammation. The precise details and interactions between these different processes remain to be elucidated, which will be important to guide future diagnoses and prevention.

Rubella and ASD

The proposed association between rubella virus infection during pregnancy and autism spectrum disorder (ASD) originates from early case series and historical reports, particularly during the rubella epidemics of the 1960s and 1970s (Yates & Mulkey, 2024). In one notable report, children born with congenital rubella syndrome (CRS) exhibited not only cranial abnormalities and sensorineural deficits but also a markedly higher prevalence of autistic behaviors, with some estimates suggesting a prevalence rate up to 200 times higher than the general population at the time (Levent et al., 2023).

However, despite these early findings, the causal relationship between rubella and ASD remains unconfirmed. One of the primary limitations is that these early studies were based on small, uncontrolled cohorts, often lacking appropriate neurodevelopmental follow-up or consistent ASD diagnostic criteria. Moreover, modern diagnostic frameworks (e.g., DSM-5) were not used at that time, raising concerns about the reliability of ASD diagnoses in historical CRS case (Tioleco et al., 2021)

The biological plausibility of rubella causing ASD is grounded in its strong neurotropic nature. Rubella virus can cross the placenta and directly infect fetal brain tissue, leading to neuronal apoptosis, cortical malformation, and vascular injury, particularly in the first trimester (Al-Beltagi et al., 2023 ; Levent et al., 2023). These effects mirror those observed in other congenital infections associated with ASD, such as CMV and Zika. In some CRS autopsies, rubella virus antigens were detected in neurons and glial cells, supporting the possibility of direct neural involvement (Yates & Mulkey, 2024).

Nevertheless, the lack of recent cases due to successful vaccination programs limits the ability to investigate this association further. Rubella was declared eliminated in several countries, including the United States by 2004, following mass immunization efforts (Thompson, 2024). This success significantly reduced CRS cases and, consequently, the opportunity to explore rubella's neurodevelopmental effects using modern research tools.

Recent reviews have emphasized the need for updated epidemiological and virological studies using contemporary diagnostic methods and large birth cohorts (Hutton, 2016). Such studies could help clarify whether rubella infection during early gestation remains a risk factor for ASD or if the observed association was confounded by comorbidities such as hearing loss, intellectual disability, or global developmental delay—common in CRS (Levent et al., 2023).

In summary, while early data point to a possible link between maternal rubella infection and ASD, current evidence is inconclusive and does not establish a direct or exclusive causal relationship. Further research utilizing genetic screening, neuroimaging, and biomarker studies in CRS survivors is needed to better define the specific neurodevelopmental outcomes associated with in utero rubella exposure (Tioleco et al., 2021 ; Hutton, 2016).

Cytomegalovirus and ASD

Current medical initiatives directed toward vaccine development, initiation of infectious disease epidemiological studies, and psychosocial epidemiological investigations may one day provide explanations for the equivocal results obtained in studies of infectious disease associations with autism (Lintas et al., 2011). A large body of literature points to an association between cytomegalovirus (CMV) and the development of autism spectrum disorder (ASD) (Yates & Mulkey 2024). Some consider CMV to be a necessary but not sufficient cause of autism (Lin et al., 2021). Infections with CMV have been shown to exhibit strong neurotropism resulting in widespread necrosis and malformation of the fetal brain (Ganguli & Chavali, 2021). Postnatally, CMV has been associated with microcephaly, hearing loss, seizures, and mental retardation (Thompson, 2024). Children born with congenital CMV exhibit characteristic neurological abnormalities (Lin et al., 2021). It has been suggested that CMV reactivation in late childhood may cause autism, especially during autistic regression. Autistic regression is defined as the loss of social, language, or motor skills that the child had already learned, usually happening between 15 and 30 months of age (Al-Beltagi et al., 2023). Autopsies of children with severe autism have demonstrated features similar to those found in cases of congenital CMV (Yates & Mulkey, 2024). These findings imply the intriguing notion that autism may present in a neuroanatomical form indicative of CMV involvement (Al-Beltagi et al., 2023). It will be critical in future studies to remember that CMV exists in numerous strains and that various strains operate in diverse ways on their infection of mammalian cells, including differential capability to establish latency and neurotropism (Lin et al., 2021). Studies directed at clarifying the molecular genetic risk for both common and rare forms of ASD are important and have paved the way for much research into its pathophysiology (Al-Beltagi et al., 2024). Genetic tests of medical, behavioral, and neurological systems provide a tool to determine the likelihood that a child will develop autism (Mohsen, 2024). Studies examining public health records for case-control epidemiological investigations assess the actions of environmental exposures, particularly at times of critical brain development (Hutton, 2016). Research on toxic exposure of particular concern, such as metalloestrogens, nanoparticles, organophosphate pesticides, and air pollution, is only one part of this investigation (Thakur et al., 2025). A smaller but no less relevant area of study involves alternative infectious disease susceptibility, and considerable congruence between these two lines of investigation must be noted (Al-Beltagi et al., 2024).

Influenza and ASD

The possible association between maternal influenza infection during pregnancy and the risk of autism spectrum disorder (ASD) in offspring has been studied for several decades; however, the evidence remains inconclusive and not definitively proven. While some epidemiological studies and animal models have reported associations between prenatal influenza exposure and increased ASD risk, other well-designed studies have failed to replicate these findings, highlighting the need for further investigation (Yates & Mulkey, 2024 ; Kwon et al., 2022 ; Yu et al., 2023).

Historical observations from the 1918–1919 influenza pandemic noted an increased incidence of neuropsychiatric disorders, including behavioral abnormalities, in children exposed in utero (Mohsen, 2024). More recently, maternal influenza infection—particularly during the first or second trimester—has been linked in some cohorts to a modest increase in ASD diagnosis (Yates & Mulkey 2024). However, these findings are not consistently observed across all populations, and some large-scale studies have reported no statistically significant association after adjusting for confounding factors such as maternal age, socioeconomic status, and other infections (Yates and Mulkey 2024 ; Mahic et al., 2017).

Biologically, two main mechanisms have been proposed to explain how maternal influenza could impact fetal neurodevelopment. First, influenza viruses may cause maternal immune activation (MIA), triggering the release of pro-inflammatory cytokines like IL-6 and IL-17a, which can cross the placenta and interfere with neuronal proliferation, migration, and synapse formation in the developing fetal brain (Ganguli & Chavali, 2021 ; Kwon et al., 2022). Second, there is the possibility of direct viral transmission, although evidence of influenza viral particles in fetal neural tissue is limited compared to other viruses like CMV or Zika (Yates & Mulkey 2024).

In experimental models, pregnant rodents infected with influenza have shown offspring with autism-like behaviors, including repetitive movements and impaired social interaction (Ganguli & Chavali, 2021). However, translating these findings to humans is complex due to differences in immune responses, placental structure, and timing of neurodevelopment (Wiertsema et al., 2021).

A key limitation in current research is the difficulty in accurately diagnosing influenza during pregnancy—many studies rely on self-reported flu symptoms or retrospective medical records, which may introduce recall or classification bias. Furthermore, co-infections, fever, and the use of medications such as antipyretics during pregnancy can independently influence neurodevelopmental outcomes, making it difficult to isolate the effects of influenza alone (Yates and Mulkey 2024 ; Yin et al., 2023).

Taken together, while the hypothesis linking maternal influenza to ASD is biologically plausible and supported by some experimental data, the epidemiological evidence is inconsistent. Larger, well-controlled prospective studies using laboratory-confirmed infections and modern ASD diagnostic criteria are required to draw firmer conclusions (Tioleco et al., 2021 ; Yu et al., 2023). Until such data become available, the influenza-ASD association should be considered a possible but unproven risk, requiring cautious interpretation.

Zika Virus and ASD

The Zika virus (ZIKV), a flavivirus known for its teratogenic effects during pregnancy, has been studied primarily for its role in causing congenital Zika syndrome (CZS)—a condition that includes microcephaly, brain malformations, and neurological deficits. While these outcomes are well-documented, the specific association between maternal Zika virus infection and autism spectrum disorder (ASD) remains unclear, unproven, and not firmly supported by current evidence (Marcelino et al., 2023 ; Neil, 2025).

Clinical studies have reported a broad range of neurodevelopmental outcomes in children prenatally exposed to ZIKV, including developmental delays, seizures, and behavioral symptoms consistent with ASD (Figueiredo et al., 2021 ; Seaman et al., 2022). However, these findings are largely based on observational data and case series with small sample sizes, and most do not involve formal ASD diagnoses using standardized criteria like the DSM-5 (Figueiredo et al., 2021 ; Neil, 2025). Therefore, additional, well-controlled longitudinal studies are required to determine whether ZIKV exposure is an independent risk factor for ASD or simply one of many causes of broader neurodevelopmental disorders (Zhang et al., 2024).

The biological plausibility of ZIKV contributing to ASD stems from its strong neurotropism. ZIKV has a unique affinity for neural progenitor cells, especially during the first trimester, resulting in reduced cortical volume, ventricular enlargement, and disrupted neuronal migration (Marcelino et al., 2023; Cheroni et al., 2022). These changes can lead to structural and functional abnormalities in brain regions responsible for social behavior and cognition. However, while these mechanisms can explain generalized neurodevelopmental deficits, they do not specifically account for core ASD symptoms, which typically require precise disruption of social, communication, and behavioral pathways.

Moreover, maternal immune activation (MIA) has also been implicated in the pathogenesis of ZIKV-related brain damage. Sustained maternal inflammation and elevated cytokine levels during gestation could impair synaptogenesis, myelination, and neurogenesis, contributing to ASD-like behaviors observed in both humans and animal models (Dubey et al., 2022 ; Figueiredo et al., 2021). Yet, it remains difficult to distinguish whether these effects are specific to ASD or represent more global neurological impairment.

Genetic susceptibility may also modulate outcomes. Children with underlying genetic vulnerabilities (e.g., rare variants or copy number variations) may be more susceptible to ZIKV-induced neurodevelopmental alterations, although this hypothesis requires further exploration (Zhang et al., 2024).

In conclusion, while ZIKV is clearly associated with severe neurodevelopmental outcomes, the specific link between prenatal ZIKV infection and ASD is currently speculative and lacks robust supporting evidence. Further research using large-scale, prospective cohorts, standardized ASD assessments, and mechanistic studies in both animal and human models is necessary to clarify this potential association (Figueiredo et al., 2021 ; Neil, 2025 ; Zhang et al., 2024).

COVID-19 and Possible Risk of ASD

The emergence of the SARS-CoV-2 virus, responsible for the global COVID-19 pandemic, has prompted growing interest in its potential impact on fetal brain development and long-term neurodevelopmental outcomes, including autism spectrum disorder (ASD). However, it is important to note that current evidence does not establish a direct or confirmed relationship between maternal COVID-19 infection and the development of ASD in offspring (Figueiredo et al., 2021 ; To et al., 2021 ; Duan et al., 2024).

Most of the available literature to date is theoretical or based on indirect findings rather than definitive clinical or epidemiological data. The hypothesis of a possible association arises from prior observations linking maternal infections, such as influenza and rubella, to increased ASD risk (Gabis et al. 2022 ; Jackson et al., 2022). By analogy, researchers have proposed that maternal SARS-CoV-2 infection could influence fetal brain development via similar pathways, particularly immune activation, cytokine storms, and placental dysfunction (Figueiredo et al., 2021 ; Duan et al., 2024).

Biologically, SARS-CoV-2 infection during pregnancy may lead to increased levels of inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, which have been implicated in altering fetal neurodevelopment in animal models (Ganguli & Chavali, 2021 ; Figueiredo et al., 2021). These cytokines could cross the placenta or indirectly affect fetal brain development through changes in the intrauterine environment, potentially leading to outcomes consistent with neurodevelopmental disorders (Duan et al., 2024). However, these mechanisms remain hypothetical and have not yet been shown to result in ASD specifically.

Another area of concern is the potential for hypoxia or vascular damage in the placenta during severe COVID-19 cases, which could impair oxygen and nutrient delivery to the fetus (Dubey et al., 2022 ; Figueiredo et al., 2021). However, vertical transmission of SARS-CoV-2 is rare, and most newborns from infected mothers have not shown evidence of infection or immediate neurological deficits (To et al., 2021).

A few recent cohort studies have attempted to assess developmental outcomes in children born during the pandemic. Some suggest subtle delays in communication and motor skills, but these findings may reflect social and environmental disruptions (e.g., lockdowns, reduced social interaction), rather than direct effects of the virus itself (Figueiredo et al., 2021 ; Duan et al., 2024). No high-quality studies to date have demonstrated a statistically significant increase in ASD diagnoses among children prenatally exposed to COVID-19.

In conclusion, no causal or direct association between maternal COVID-19 infection and ASD has been demonstrated. The current body of evidence is preliminary, speculative, and indirect. Future research should focus on longitudinal studies with laboratory-confirmed infections, detailed developmental assessments, and control for confounding factors such as genetic predisposition, severity of illness, and pandemic-related environmental stressors (Figueiredo et al., 2021 ; Duan et al., 2024). Until such data are available, any suggestion of a COVID-19–ASD link should be considered theoretical and unproven.

Table 2. Summary of Key Viral Infections and Their Proposed Association with Autism Spectrum Disorder (ASD)

Virus	Neurotropic Potential	Proposed Mechanism(s)	Observed Outcomes in Offspring	Strength of Evidence
Rubella	High	Direct neural invasion, CNS inflammation	CRS, increased autism risk (historic)	Moderate (historical data)
CMV	High	Neuronal necrosis, chronic inflammation	Microcephaly, seizures, possible ASD	Moderate to Strong
Zika	High	Infection of neural progenitors, placental damage	Microcephaly, neurodevelopmental delay	Moderate
Influenza	Low–Moderate	Maternal immune activation (MIA), cytokines	Behavioral changes, possible ASD	Weak to Moderate
SARS-CoV-2	Unclear	MIA, cytokine storm, placental dysfunction	No proven ASD link; theoretical	Weak (emerging data)
HSV-2	Low–Moderate	Placental inflammation, antibody response	Some correlation with ASD	Weak

Summary

This paper discusses the aetiological role of viral infections in the development of Autism Spectrum Disorder (ASD). Such a hypothesis stems from the consideration that ASD is a complex neurodevelopmental disorder, characterized by different levels of impairment in social interaction and communication, as well as by stereotypies and rigid patterns of behaviour. Disease onset occurs prior to 3 years of age (Yates & Mulkey, 2024 ; Al-Beltagi *et al*., 2023). Autism Spectrum Disorder (ASD) is the most heritable neuropsychiatric disorder, yet very few cases can be solely explained on the basis of de novo genetic mutations or cytogenetic abnormalities (Wang *et al*. 2023). Heterogeneous the developmental windows of exposure and the nature of neurotoxic insults have been suggested, including environmental factors 15. Clinically, many ASD patients display co-morbidity with autoimmunity and dysregulation of the immune system, potentially suggestive of a prenatal-onset, unresolved viral infection (Al-Beltagi *et al*., 2024). Indeed, robust evidence shows that in utero infections with several neurotropic viruses are associated with neurodevelopmental disorders in humans, particularly autism (Lintas *et al*., 2011).

Based on this hypothesis here was initially assessed the prevalence of herpesviruses, parvoviruses, and polyomaviruses, in post-mortem brains of autistic patients and controls (Yates & Mulkey, 2024). A statistically significant association was found between ASD and polyomavirus infection. The findings focus the attention on xenotropic murine leukemia virus-related virus (XMRV) and other xenotropic murine leukemia (MLV)-related viruses (Al-Beltagi *et al*., 2023). XMRV infection is currently a source of serious concern in the USA for its possible link with chronic fatigue syndrome (CFS) (Yates & Mulkey,

2024). In spite of a lack of reproducibility from independent research groups and the weight of a growing body of evidence against it, the possibility that XMRV or some other, as yet completely unidentified, MLV-related virus(s) may play a role in the pathogenesis of this syndrome has not been dismissed (Lintas *et al*., 2011).

Taking this scenario into account, MLV-related viruses were screened in the blood of 60 ASD patients and were found to be absent independently of the patient's age at diagnosis, disease severity, and clinical confounders (Al-Beltagi *et al*., 2023). In addition to blood samples, brains of 10 autistic children and 9 controls were assayed for the presence of XMRV and other MLV-related viruses (Yates & Mulkey, 2024). No MLV-related virus was detected in blood, brain, and semen samples of ASD patients or fathers. Hence infection with XMRV or other MLV-related viruses is unlikely to contribute to autism pathogenesis (Coffin & Kearney, 2024).

Conclusions

Although increasing evidence suggest a possible association between maternal viral infection during pregnancy and susceptibility to autism spectrum disorder (ASD) in the offspring, the correlation is associative rather than causal. Existing results are frequently potentially subject to bias including heterogeneous study design, inconsistency in diagnostic criteria, small sample sizes, and lack of mechanistic precision. Although mechanisms such as maternal immune activation, direct viral neurotropism, and placental insufficiency offer biological plausibility, pathways that have been robustly associated with ASD in humans are currently wanting.

In order to successfully promote the development of this field, the goal of future research will be to prioritize large-scale, prospective longitudinal human cohort studies to follow maternal viral exposures during pregnancy and to systematically measure outcomes of offspring neurodevelopment. These investigations should be appropriately powered to incorporate laboratory-confirmed infections, precise timing of exposure, and repeated developmental assessments with standard ASD-focused diagnostic instruments. Finally, it is essential to connect these cohorts with genomic and epigenomic information—most notably immune gene risk polymorphisms, maternal cytokine profiles, and fetal susceptibility loci—to unravel the complex networks of gene–environment interactions that are likely to mediate ASD risk.

Such multidimensional strategies—integrating epidemiology, immunology, genomics and systems-biology—will be crucial not just for elucidating causality, but also for pinpointing early risk biomarkers. In the end, such integration can better inform the development of preventive approaches such as maternal immunomodulation, nutritional support, and selective surveillance of high-risk pregnancies. Only through this level of cross-cutting collaboration can we achieve the goal of translating scientific discoveries to population health strategies that minimize prenatal viral exposures as a public health threat for building lifelong health and opportunity.

Author contributions

All authors are equally credited with contributing to the preparation of this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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