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Review Article

Prenatal exposure to viral infection and neuropsychiatric disorders in offspring: A review of the literature and recommendations for the COVID-19 pandemic

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ABSTRACT

The SARS-CoV-2 virus has emerged as a striking 21st century pandemic. Communities across the globe have experienced significant infection rates and widespread psychosocial stress and trauma, leading to calls for increased allocation of resources for mental health screening and treatment. In addition to the burden of psychosocial stress, there is increasing evidence of direct viral neuroinvasion of the central nervous system through physical contact with the nasal mucosa. In a parallel fashion, there is a significant body of ongoing research related to the risk of in utero viral transmission and the resulting neurodevelopmental impact in the fetus. Aberrant neurodevelopment secondary to viral transmission has previously been related to the later development of psychosis, schizophrenia, and schizophrenia spectrum disorders, generating the hypothesis that this population of individuals exposed to SARS-CoV-2 may see an increased incidence in future decades. We discuss the current understanding of the possible neurotropism and vertical transmission of SARS-CoV-2, and relate this to the history of viral pandemics to better understand the relationship of viral infection, aberrant immune response and neurodevelopment, and the risk for schizophrenia disorder.

1. Introduction

Originating as a cluster of unknown viral pneumonias reported in Wuhan, China, the SARS-CoV-2 pandemic now exceeds 17 million cases. At the time of writing this review, the United States has faced 4.6 million cases and the death toll stands above 150,000. All estimates suggest that these numbers will continue to increase. The psychological burden of the pandemic has been significant and will likely unfold for decades to come.

The widespread psychological trauma endured during this time may not be the only precipitant of long-term neuropsychiatric outcomes as a result of this pandemic. Infection of the central nervous system with the virus itself and the host immunologic response may play a critical role in the development of future neuropsychiatric sequelae. Although still disputed, it is proposed that the virus is able to incite immune changes resulting in high neurosusceptibility through its physical contact with

the nasal mucosa and upper respiratory tract (Li et al., 2020b). Given the question of direct neuroinvasion, there is increasing speculation of a wave of neuropsychiatric outcomes (Troyer et al., 2020).

Evidence from previous influenza epidemics reveal a pattern of increased incidence of psychiatric conditions such as anxiety, insomnia, depression, and psychosis (Honigsbaum, 2013b; Menninger, 1926). During the influenza pandemic of the early 20th century now known colloquially as the “Spanish Flu”, the incidence of an inflammatory central nervous system disease then known as encephalitis lethargica was observed to increase, characterized by catatonia, parkinsonism, and psychosis (Miller et al., 1932).

The literature on psychosis and pandemics was initially built upon early ecological studies, extended by birth cohort studies, and now is further supported by several preclinical models. Both epidemiologic and birth cohort studies have demonstrated an association between infections and a corresponding increased incidence of schizophrenia

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spectrum disorders. In particular, it has been demonstrated that in utero exposure to a variety of pathogens is likely a replicated risk factor for the neurodevelopmental insults that contribute to the later-onset schizophrenia spectrum disorders, among several other neuropsychiatric conditions.

Given the emerging association between prenatal infection and schizophrenia spectrum disorders, it is important that this risk is considered in the context of the unfolding pandemic. Here we review the existing literature on the link between epidemics, pandemics and the increased incidence of schizophrenia spectrum disorders. In line with the body of evidence reviewed, it is plausible that exposure to SARS-CoV-2 in utero may put children born during this pandemic at risk for specific neuropsychiatric outcomes, including schizophrenia. This presents a novel opportunity to study these offspring who may be considered to have an increased risk of neuropsychiatric symptoms later in life. Longitudinal monitoring of this population may be able to assist in the discovery of complex neurodevelopmental mechanisms that have long eluded the psychiatric field.

2. Influenza

Briefly, the influenza virus is an RNA virus that is grouped into three genera (types A, B, and C) and characterized by its envelope glycoproteins (hemagglutinin and neuraminidase) (Wright, 2018). Thus far, all influenza pandemics have been caused by type A influenza, but their glycoproteins vary (Wright, 2018). For example, the influenza pandemic of 1918, also referred to as the Spanish Flu, was caused by H1N1, whereas the Hong Kong Flu of 1968 was caused by H3N2. Each influenza pandemic and its relationship to psychosis in both infected patients and children of infected pregnant women will be briefly reviewed. Neuropsychiatric sequelae of infected patients are notable because for much of the history of influenza, the research focus has been on infected nonpregnant patients. Only as of the 1957 H2N2 pandemic did attention shift to infected pregnant women (Kepinska et al., 2020). For extensive reviews, the reader is referred to Kepinska (Kepinska et al., 2020) and Brown and Derkits (Brown and Derkits, 2010).

2.1. H2N8

The H2N8 pandemic of 1889–1892 (also known as the Russian Flu) saw reports of insomnia, depression, and occasional frank psychosis in those infected (Knapp, 1892). As it has been described (Honigsbaum, 2013a), influenza was noted at this time to have so many neurologic symptoms and sequelae that it was sometimes viewed as primarily a neurologic disease with secondary respiratory symptoms. Despite these descriptions of neurological and psychiatric symptoms amongst those exposed to the virus, it is unknown whether children born during the H2N8 pandemic had increased rates of neuropsychiatric disorders later in life.

2.2. H1N1 1918–1919

Nearly three decades later, the 1918–1919 H1N1 pandemic also had reports of psychiatric symptoms related to infection. In 1919, Menninger noted that many patients with presumed influenza had delirium, dementia praecox (a term coined by Kraepelin meaning early onset dementia or psychosis (Adityan et al., 1999)), or other psychoses. Von Economo first wrote of encephalitis lethargica, a condition that may be related to this pandemic and was characterized by psychosis and catatonia (Kepinska et al., 2020).

Some ecologic studies have attempted to elucidate a possible link between influenza infection in utero and later development of schizophrenia (Adams et al., 1993; Barr et al., 1990; Kendell and Kemp, 1989; Takei et al., 1996). First, Kendell and Kemp (1989) found that individuals in utero during the 1918–1919 pandemic were not at increased risk in developing schizophrenia. Another ecologic study

demonstrated no association between the incidence of schizophrenia and incidence of influenza infection (Adams et al., 1993). Lastly, an ecologic study that evaluated data in Denmark from 1911 to 1950 found that there was an association between the incidence of influenza and rate of schizophrenia development (Barr et al., 1990). In sum, these early ecologic studies demonstrated little consensus about the link between maternal influenza infection and later schizophrenia development in offspring. Importantly, none of these ecologic studies confirmed influenza infection in individual pregnant women, but rather assumed that all pregnant women during the 1918–1919 pandemic were infected with influenza. This assumption significantly weakens the findings in these studies and should be interpreted with caution (Manjunatha et al., 2011).

2.3. H2N2

As with the prior influenza pandemics, the H2N2 pandemic of 1957–1958 (also referred to as the Asian Flu) had cases of acute psychosis in those infected (Bental, 1958). Unlike other influenza pandemics though, the H2N2 pandemic saw a focus on infected pregnant individuals rather than just infected nonpregnant ones (Kepinska et al., 2020). Some studies have found an association between likely exposure to influenza in utero and later development of schizophrenia (Adams et al., 1993; Izumoto et al., 1999; Kunugi et al., 1995; Limosin et al., 2003; Mcgrath and Castle, 1995; Mednick et al., 1994, 1988; O'Callaghan et al., 1991), while other studies failed to replicate this association (Erlenmeyer-Kimling et al., 1994; Mino et al., 2000; Selten et al., 1998; Selten and Slaets, 1994; Susser et al., 1994).

In contrast to previous ecologic studies, the investigations during the 1957 H2N2 pandemic included confirmed influenza cases in pregnant women, rather than the assumption of infection in women pregnant during a given pandemic. This was an important extension of the literature. However, the studies varied in their methods of confirming infection. For example, Crow and Johnstone (1991) used interviews and chart review to identify 16,179 pregnant women infected with influenza during the 1957 H2N2 pandemic and found that these women were no more likely to give birth to a child who later developed schizophrenia than uninfected women. Importantly, it is unclear if interviews alone counted as a positive case of influenza, or if these interviews were used only in conjunction with confirmed cases of influenza. Similarly, a prospective study used self-reports to identify women infected with influenza during the 1957 pandemic and found that these women were not more likely to give birth to individuals who would later develop schizophrenia than uninfected women (Cannon et al., 1996).

To address the limitations of self-report data, Brown and colleagues (Brown et al., 2004) used maternal serum influenza assays to determine presence of infection in pregnant women during the 1957 pandemic. Using data from birth cohorts, they compared 64 individuals with schizophrenia and controls. The authors found that individuals exposed to influenza in utero during the first trimester were 7 times more likely to develop schizophrenia later in life than were those uninfected in utero during the same period. They also found that infection in early-to-mid pregnancy led to a 3-fold increased risk of developing schizophrenia later in life.

With the focus on maternal infection came the recognition that the seasonality of influenza could potentially explain the seasonality of births of children who later develop schizophrenia (O'Callaghan et al., 1991; Takei et al., 1992; Torrey et al., 1997). The suggestion that maternal infection may lead to psychiatric pathology in offspring was reinforced by the finding that children born in cities were more likely to develop schizophrenia than their non-urban counterparts; human density lends itself to infection and, quite possibly, neuropsychiatric sequelae (Takei et al., 1992).

2.4. H3N2

The 1968–1970 H3N2 pandemic led to approximately 1 million deaths worldwide, mostly affecting those over age 65 (1968 Pandemic (H3N2 Virus), 2019; Glezen, 1996). There are only a few human studies regarding H3N2 infection during pregnancy, including one (McGregor et al., 1984) that presented a patient who had evidence of transplacental influenza infection. Although there is a dearth of human studies for H3N2, there are two notable animal studies (Kwit et al., 2015; Short et al., 2010). First, a study in gilts (young female pigs) found no evidence of transmission of H3N2 to offspring, suggesting that if there are any effects on offspring of women infected with H3N2, the effects would be less likely due to direct infection and more likely due to maternal fever or increased inflammation (Kwit et al., 2015). Additionally, Short and colleagues (Short et al., 2010) modeled H3N2 infection with twelve infected rhesus monkeys and found no evidence of vertical transmission. However, they did note reduced cortical gray matter in the offspring of infected monkeys in late childhood, suggesting that H3N2 infection has implications for neurodevelopment and possible neuropsychiatric sequelae. This strengthens the argument that even in the absence of vertical transmission, prenatal infection can be a possible risk factor for neuropsychiatric pathologies. Nonetheless, there is no published literature regarding psychosis in nonpregnant or pregnant patients infected with H3N2.

2.5. H1N1 2009–2010

The first influenza pandemic of the 21st century, H1N1 (Swine Flu) of 2009–2010, had comparatively few reports of psychosis associated with infection. Only 9.7% of children (ages 0.5–12.6, median age 4.8, $n = 506$) in Australian hospitals with influenza had neurologic symptoms (Khandaker et al., 2012). Of note, 43% of affected patients in this study had preexisting neurologic conditions, and one-third of those with neurologic symptoms had a seizure (primarily febrile). There were 2 reported cases of psychosis (Chang et al., 2015) and 4 reported cases of other neurologic sequelae in children with influenza (“Neurologic Complications Associated with Novel Influenza A (H1N1) Virus Infection in Children - Dallas, Texas, May 2009,” 2009).

Children born to mothers infected with H1N1 from 2009 to 2010 are now about 10 years old. Given the breadth of evidence for the neuropsychiatric consequences for the offspring of infected pregnant women, it will be crucial to continue to monitor the mental health of these offspring as they approach adolescence and young adulthood.

3. Other epidemics and pandemics

3.1. Rubella

In addition to the literature on influenza, several other viral pandemics have been studied that add to the association between viral infection and risk for psychosis. The 1964 epidemic of rubella in the United States is one such example. As a pathogen, rubella is of particular significance as it is known to directly infect the fetal brain and cause aberrant neurodevelopment including neuronal death, gliosis, and a disruption of mitosis (Brown et al., 2000). Brown et al. (2000) conducted a seminal study on this epidemic, following up on a birth cohort in which individual participants were prospectively documented by both serological testing and clinical exam to have been exposed to rubella in utero between 1964 and 1965. The rubella-exposed birth cohort was compared to two unexposed samples, the members of which were born after 1967, when the rarity of rubella infection makes exposure unlikely. A significantly higher proportion of rubella-exposed individuals were found to have nonaffective psychosis (15.7%) compared to non-exposed participants (3.0%). In a further study by this research group, the Rubella Birth Defects Evaluation Projection, over 20% of subjects from the 1964 rubella epidemic whose mother’s serologically and clinically

tested positive for rubella infection during pregnancy were diagnosed with schizophrenia spectrum disorders, demonstrating a 10–15 fold increased risk. The rubella-exposed cases also demonstrated a decline in IQ between childhood and adolescence that was significantly greater than that seen among rubella-exposed controls, further highlighting a likely association. Another birth cohort study conducted by Buka and colleagues (2001) followed more than 55,000 pregnancies in the United States between 1959 and 1966, and measured levels of IgA and IgG antibodies to rubella; however, no significant difference regarding schizophrenia risk in adult offspring was found between case and control mothers (Buka et al., 2001).

3.2. Poliovirus

Epidemics across the globe of poliomyelitis offer another chance to assess the association between congenital infection and risk of psychosis. Polio was first implicated as a candidate risk factor in the development of schizophrenia when a decline in the incidence of the disorder was noted in several countries following the introduction of the polio vaccine (Eagles, 1992). In Finland, an ecological study found that exposure to poliovirus 5 months prior to birth increased the risk of developing schizophrenia later in life, which is in accordance with significant literature reporting on the risk of neurodevelopmental insult following infectious exposure in the second trimester (Suvisaari et al., 1999). This study did not use a direct measurement of poliovirus exposure. Using ecological data alone, the number of cases of paralytic polio from the three largest cities and all provinces in Finland was used as a surrogate marker of exposure status, however paralytic symptoms develop in less than 1% of those infected with poliovirus (Suvisaari et al., 1999). In Australia and New Zealand, a similar study attempted to replicate the findings of the previous Finnish study, with no group previously examining the link between poliomyelitis epidemics and rates of schizophrenia in the Southern Hemisphere (Cahill et al., 2002). Once again, the study utilized ecological data alone. Despite eight clearly defined poliomyelitis epidemics in Queensland during the period analyzed, no statistically significant association was found between exposure and risk of schizophrenia development later in life (Cahill et al., 2002).

3.3. Herpes simplex virus

Herpes simplex virus type-2 is a globally endemic infection, with over 491 million (13%) individuals age 15–49 infected worldwide (WHO). Neonatal herpes infection, although rare, is a very serious condition that can lead to lasting neurological deficit and possibly death. Buka et al. (2001) noted that elevated HSV type-2 antibodies were associated with increased risk of psychosis (Buka et al., 2001). Further epidemiological studies followed, and although not born out of an epidemic, this literature still offers important insights. A large birth cohort, collected between 1959 and 1966, demonstrated that offspring exposed to genital and reproductive infections during the periconceptional period were five times more likely to develop schizophrenia spectrum disorders than non-exposed offspring, with adjustments for maternal race, education, and history of mental illness (Babulas et al., 2006). The study also found a significant interaction between infection and family history of psychosis on risk of schizophrenia in the offspring (Babulas et al., 2006). However, there was not a clear definition of genital/reproductive infections, with inclusions spanning a breadth of clinical disease such as endometritis, cervicitis, pelvic inflammatory disease, vaginitis, syphilis, condylomas, “venereal disease”, and gonorrhea. While preclinical models have produced significant support for HSV as a candidate risk factor in the pathogenesis of schizophrenia spectrum disorders, significantly more prospective epidemiological work is needed.

3.4. Zika virus

The Zika virus (ZIKV) epidemic in South America in 2015 led to the discovery that in utero exposure to ZIKV can precipitate significant neurodevelopmental insult with a wide range in clinical phenotypes. Brasil et al. (2016) utilized a group of women with PCR-confirmed ZIKV infection during pregnancy and using ultrasonographic examination documented numerous neurological insults, including cerebellar atrophy, ventriculomegaly, diminished cerebral artery flow, anhydramnios, cerebral calcifications, and microcephaly (Brasil et al., 2016). Although the recency of the ZIKV epidemic precludes it from having produced data on the risk of schizophrenia spectrum disorders, the breadth of ongoing preclinical studies in this field will provide important insights. Preclinical studies using human brain organoid cultures have confirmed microcephaly as a significant neurological outcome of congenital ZIKV infection, demonstrating that the virus preferentially infects and causes apoptosis of neural progenitor cells (Malaspina et al., 2008; Oh et al., 2017; Wells et al., 2016; Wen et al., 2017). In non-human primate models, transplacental infection has been shown to occur with high efficiency, and yet microcephaly has not been demonstrated in this population (Nguyen et al., 2017). This is in accordance with human models, in which severe congenital malformation is a relatively less common phenotype. However, considering the high efficiency of transplacental infection demonstrated, the long-term consequences of in utero ZIKV infection are critical to understand, particularly when it comes to neuropsychiatric outcomes. Large epidemiological studies with recurrent neurocognitive testing can help define this phenotype, including elucidating the risk of schizophrenia and other psychoses.

3.5. HIV and Ebola

Although the HIV epidemic continues to be a major global public health crisis, claiming more than 32 million lives (WHO), birth cohorts and preclinical models have yet to elucidate the contribution of this virus to prenatal infection and subsequent neurodevelopmental insult. Possible reasons for this include several confounding neuropsychiatric outcomes such as cognitive deficits and mood disorders, thought to be the result of HIV-mediated damage to the central nervous system (Dubé et al., 2005). Similarly, the Ebola virus (EVD) outbreak of 2014–2016 has extremely limited data. Birth cohorts of pregnant patients with EVD saw an aggregate maternal mortality of 86% and EVD is considered to be almost universally fatal to the developing fetus (Bebell et al., 2017).

4. Coronaviruses

Coronaviruses are a family of viruses organized into six genera, three of which include viruses that can infect humans. One genus, alphacoronavirus, includes strain 229E. Betacoronaviruses include HKU1, MERS, NL63, OC43, SARS-CoV-1, and SARS-CoV-2 (Covid-19) (Riedel et al., 2019).

4.1. OC43 and 229E

Some coronaviruses have been shown to be neurotropic. Bonavia and colleagues (Bonavia et al., 1997) demonstrated that both fetal and adult neurons could be infected by coronaviruses OC43 and 229E. More specifically, they showed that OC43 was able to infect fetal and adult astrocytes as well as adult microglia. 229E was able to infect fetal astrocytes, adult microglia, and a mixture of adult oligodendrocytes and astrocytes (Bonavia et al., 1997). Interestingly, they found that only fetal astrocytes were able to release viruses and that the infection in adult neurons “appears abortive”. A few years later, Arbour and colleagues (Arbour et al., 2000) found evidence of coronavirus OC43 and 229E RNA in human post-mortem brains.

Beyond neurotropism, there is evidence in both human and animal models for the association between coronavirus infection and

neuropsychiatric symptoms (Jacomy et al., 2006; Severance et al., 2011). Jacomy and colleagues demonstrated that the human coronavirus strain OC43 could infect murine neural cells in culture. Importantly, the neurons did not show the ability to perpetuate infection but did undergo apoptosis between 10% and 20% of the time. Next, they infected BALB/c mice with coronavirus strain OC43 and observed an encephalitis-like syndrome as well as neural apoptosis and necrosis. They observed that one year after initial infection, these mice showed decreased hippocampal volume despite negative OC43 antigen, pointing toward possible continued neurodegeneration post-infection. The small sample size ($n = 21$) and the modeling of human coronavirus infection with mice both limit these findings. However, there is evidence that coronaviruses are neurotropic and are associated with neuropsychiatric symptoms (Arbour et al., 2000; Bonavia et al., 1997; Jacomy et al., 2006; Jacomy and Talbot, 2003).

Further supporting the association between coronaviruses and neuropsychiatric sequelae, Severance and colleagues (Severance et al., 2011) found an association between coronavirus infection and new onset psychosis. They first identified 106 individuals with recent onset psychosis, defined as within the past 2 years. Half were diagnosed with a mood disorder and half were diagnosed with schizophrenia or related psychotic disorder. The control group included 196 individuals without any psychiatric history, among other criteria. After testing each individual's blood for 4 coronavirus strains (229E, HKU1, NL63, and OC43), they found that recent onset psychosis was significantly associated with both coronavirus exposure and increased levels of IgG against coronavirus strains HKU1, NL63, and OC43. Strains HKU1 (OR = 1.3) and NL63 (OR = 2.4) remained significantly associated with new onset psychosis after multivariate analyses that included demographic variables. Limitations of this work included having a possibly disproportionately healthy control group, lack of control for other viral infections, single time point antibody collection, as well as diagnostic uncertainty. Even considering these limitations, they provide evidence that, at the very least, immunoreactivity and psychosis have a relationship worth exploring further.

4.2. Severe acute respiratory syndrome coronavirus (SARS-CoV-1)

The severe acute respiratory syndrome coronavirus (SARS-CoV-1) was first identified in 2003 (Graham et al., 2013). The novel SARS-CoV-1 outbreak of 2002–2003 (Ksiazek et al., 2003; Rota et al., 2003) infected about 8000 individuals with almost 800 subsequent deaths (Peiris et al., 2004; Summary of Probable SARS Cases with Onset of Illness from 1 November 2002 to 31 July 2003, 2003). Although most of the symptoms of SARS-CoV-1 were non-psychiatric (Zhao et al., 2003), there were some reports of SARS-CoV-1 neurotropism as well as neuropsychiatric sequelae.

Several lines of evidence support the neurotropism of SARS-CoV-1. First, there were two case reports of SARS-CoV-1 in the CSF (Hung et al., 2003; Lau et al., 2004). Additionally, Xu and colleagues (Xu et al., 2005) successfully isolated SARS-CoV-1 from brain tissue of a deceased patient who had severe SARS-CoV-1 with CNS symptoms. However, Tsai and colleagues (Tsai et al., 2004) reported that 2 patients infected with SARS-CoV-1 who had neuromuscular manifestations had CSF negative for SARS-CoV-1. As with all case reports, much caution needs to be taken when considering the implications of the positive and negative findings. Lastly, transgenic mice were used to show that SARS-CoV-1 enters the CNS through the olfactory bulb but does not seem to directly enter neurons (Netland et al., 2008). Taken together, we see there is some evidence for the neurotropism of SARS-CoV-1, albeit very limited.

There have also been reports of neuropsychiatric sequelae of SARS-CoV-1. Cheng and colleagues (Cheng et al., 2004) evaluated 10 patients in Hong Kong with psychiatric symptoms accompanying their SARS-CoV-1 infections. Four patients had “organic hallucinosis,” 3 of whom had worsening symptoms with decreased doses of corticosteroids during SARS treatment. Other patients had depressive symptoms,

adjustment disorder, or anxiety symptoms related to isolation, or concern for other patients or family members.

Thus far we have seen that SARS-CoV-1 has occasionally led to psychiatric symptoms and may be directly infecting the CNS. Regarding the implications for pregnant, infected women and their offspring, Lam and colleagues (Lam et al., 2004) conducted a case-control study that investigated differences in symptoms and outcomes in 10 infected, pregnant individuals compared to 40 infected, nonpregnant individuals. They found that while symptoms did not differ between pregnant and nonpregnant individuals, pregnant individuals were significantly more likely ($p = 0.012$) to be admitted to the ICU, have renal failure ($p = 0.006$), have DIC ($p = 0.006$), and to die ($p = 0.006$) (Lam et al., 2004). The question of the effect of SARS-CoV-1 and its complications on the offspring of these women has not been investigated.

While we have no data identifying the psychiatric complications of offspring born to infected mothers, we do have case reports of fetal complications due to maternal SARS-CoV-1 infection that may have implications for their future neuropsychiatric health. Wong and colleagues (Wong et al., 2004b) presented data from 12 cases of pregnant women with confirmed SARS-CoV-1 by RT-PCR and/or serology. Seven women were in the first trimester and 5 were in the late second or third trimesters. Of the 7 women in the first trimester, 4 had spontaneous miscarriages. Four of the 5 patients in the second or third trimesters had preterm deliveries. None of the 5 births resulted in positive SARS-CoV-1 RT-PCR or serologies (Wong et al., 2004b). Additionally, Yudin and colleagues (Yudin et al., 2005) reported a single case of SARS-CoV-1 in a pregnant woman who ultimately gave birth to a healthy child at full term. Zhang and colleagues (Zhang et al., 2003) similarly reported relatively uncomplicated births of 5 children to 5 women infected with SARS-CoV-1 (one twin passed away).

Taken together, we see that there is some, though limited, evidence of the neurotropism and pregnancy complications due to SARS-CoV-1 infection. Indeed, there are less than 30 documented cases of women with SARS-CoV-1 in pregnancy in the scientific literature (Di Mascio et al., 2020). Individuals who may have been exposed to SARS-CoV-1 in utero are now approaching the typical age of onset for schizophrenia. Follow-up studies of these individuals are warranted given the possibility that they may be at increased risk for psychosis.

4.3. Middle East respiratory syndrome (MERS)

Nearly ten years after the first noted SARS-CoV-1 infection, Middle East respiratory syndrome (MERS) was first identified in Saudi Arabia and has continued to exist predominantly in that region (Middle East Respiratory Syndrome, 2020; Ramadan and Shaib, 2019). As with SARS-CoV-1, MERS has some limited evidence of its neurotropism. MERS can infect human neural cell lines (Chan et al., 2013). There have also been reports of neurologic symptoms in infected patients. Arabi and colleagues (Arabi et al., 2015) reported 3 patients in Saudi Arabia who had severe neurologic symptoms including ataxia, motor deficits, and altered mental status from MERS infection. They tested CSF from two of the three patients, and both were negative for MERS by RT-PCR. Four patients with MERS were reported to have neurologic symptoms, including ICU-related weakness, sensory deficits, and Guillain-Barré syndrome, weeks after infection onset (Kim et al., 2017).

Though there is no current evidence supporting the vertical transmission of MERS (Schwartz and Graham, 2020), there is some limited evidence that MERS-CoV may lead to adverse maternal and fetal outcomes. There are currently only 12 known cases of MERS in pregnancy (Alfaraj et al., 2019). A case report of 5 infected pregnant patients in Saudi Arabia revealed substantial maternal and fetal morbidity and mortality, with death in 2/5 pregnant women and in 4/5 infants (Assiri et al., 2016), though the MERS case fatality rate for infected pregnant women is roughly the same as the case fatality rate for the general population (Alfaraj et al., 2019).

As with SARS-CoV-1, it is too soon to study whether MERS infection

in pregnancy confers an increased risk for psychosis in the offspring, though follow up is also warranted. Table 1

5. Limitations

A summary of the findings from the previous section as well as limitations of the literature are summarized in Table 1. The current literature reviewing the link between pandemic-associated viral illnesses and neuropsychiatric outcomes, specifically schizophrenia, presents intriguing questions, though also several limitations. These limitations stem from the nature of the type of data collected in previous studies (i.e., ecological vs serological), models used to study the effect of these viruses on human nervous and immunological systems, and even current knowledge of the developing brain and immune system interactions. Additionally, as is the case with many human studies, it is difficult to address potential comorbidities or disabilities – for example, the high rates of neurodevelopmental abnormalities seen in the individuals born to mothers with rubella exposure (Brown et al., 2000). Another important limitation is the issue of the large sample sizes required to achieve adequate statistical power in these studies (Cahill et al., 2002). It is not only important to consider these limitations when studying maternal immune activation in humans, but it is also important to consider these limitations when designing future studies that address the role of viral exposure and subsequent risk of psychiatric illness.

Many of the studies reviewed herein, particularly earlier studies, focused on retrospective data, which limits the availability of clinical data and/or serological confirmation or measurement of viral titers (Babulas et al., 2006; Cahill et al., 2002; Suvisaari et al., 1999). Importantly, these retrospective studies do not prove a causal relationship or a specific inflammatory mechanism. There is additionally no published data on developmental trajectories, confounding or moderating factors, or biomarkers (i.e., blood based, neuroimaging) that might provide mechanistic evidence for the relationship between viral exposure in utero and later diagnosis of a psychotic disorder. Moreover, the field is still limited in its understanding of timing of maternal exposure and whether there may be differences in risk by trimester (Brown et al., 2000).

Many of these limitations have the potential to be addressed during the current COVID-19 pandemic. There is a compelling need for long-term prospective studies with large sample sizes and increased power to investigate the impact of infection during pregnancy (i.e. the pathogen, extent of immune and inflammatory response, timing of infection), as well as other factors seen in postnatal exposure, that may lead to increased risk of psychoneurological disorders in offspring. The current coronavirus pandemic is an opportunity to link known exposure to psychosis risk thanks to increasing rates of testing of pregnant women. Data could be collected prospectively, and patients involved could be followed with imaging, serological, neurocognitive, and biomarker studies, so that many of the previous limitations would be addressed. Moreover, there are opportunities to understand protective mechanisms that keep individuals from developing psychosis later in life. Prospectively designed studies would also allow for the control of potential confounding variables, such as stress, family history of psychiatric disorders, gut microbiome, socioeconomic status, and medical comorbidities.

6. Maternal Immune Activation (MIA) models

A review of psychosis risk in individuals born to mothers with known viral exposures would be incomplete if the rich literature on maternal immune activation models was not introduced. Though a thorough discussion is beyond the scope of this largely clinical review, we point the reader to a number of excellent reviews on the topic (Brown and Meyer, 2018; Estes and McAllister, 2016; Kentner et al., 2019). Briefly, due to ethical limitations of experimentally infecting pregnant women with immune-altering agents, models using laboratory animals have

Table 1
Findings and limitations of evidence for psychiatric outcomes with prenatal infection.

| Virus | Subtype | Primary Positive Findings | Negative Findings and Limitations |
|----------------------|------------------|---|---|
| Influenza | H2N8 | Psychosis, insomnia, depression, and other neurological symptoms. (Knapp, 1892; Honigsbaum, 2013a) | No studies conducted regarding neuropsychiatric sequelae in children born during pandemic. |
| | H1N1 (1918–1919) | Delirium and dementia praecox (Adityanjee et al., 1999) Ecologic studies of the association between in utero influenza infection and subsequent schizophrenia (Adams et al., 1993; Barr et al., 1990; Kendell and Kemp, 1989; Takei et al., 1996) | Some early ecologic studies had conflicting results about the association between maternal influenza and schizophrenia in offspring (infection was assumed and not confirmed by serology) |
| | H2N2 | Acute psychosis (Bental, 1958) Some studies found an association between in utero influenza infection and subsequent schizophrenia (Adams et al., 1993; Izumoto et al., 1999; Kunugi et al., 1995; Limosin et al., 2003; Mcgrath and Castle, 1995; Mednick et al., 1994, 1988; O'Callaghan et al., 1991) One study used maternal serum influenza assays, and found that first trimester in utero influenza exposure was associated with subsequent schizophrenia risk. (Brown et al., 2004) | Some studies failed to find an association between likely exposure to in utero influenza and later development of schizophrenia (Erlenmeyer-Kimling et al., 1994; Mino et al., 2000; Selten et al., 1998; Selten and Slaets, 1994; Susser et al., 1994) Variable methods in confirmation of infection during pregnancy |
| | H3N2 | Study in rhesus monkeys found reduced cortical gray matter in the offspring of infected monkeys in late childhood (Short et al., 2010) | Limited human studies regarding infection during pregnancy Study in gilts found no evidence of transmission of H3N2 to offspring (Kwit et al., 2015) Study in rhesus monkeys found no evidence of vertical transmission of (Short et al., 2010) |
| | H1N1 (2009–2010) | 2 reported cases of psychosis in children (Chang et al., 2015) 4 reported cases of neurologic sequelae in children with influenza (Dallas, Texas, May 2009, 2009). | Few reports of psychosis associated with infection Low percentage of children infected displayed neurologic symptoms (Khandaker et al., 2012) |
| Rubella | | Directly infects the fetal brain and causes aberrant neurodevelopment including neuronal death, gliosis, and a disruption of mitosis (Brown et al., 2000) A significantly higher proportion of nonaffective psychosis in rubella exposed versus unexposed (15.7% vs 3.0%) (Brown et al., 2000) >20% of subjects from the 1964 rubella epidemic whose mother's serologically and clinically tested positive for rubella infection during pregnancy were diagnosed with schizophrenia spectrum disorders (10–15-fold increased risk, Brown et al., 2000). | No significant difference regarding schizophrenia risk in adult offspring was found between infected and non-infected mothers (Buka et al., 2001). |
| Poliovirus | | Decline in the incidence of schizophrenia was noted in several countries following the introduction of the polio vaccine (Eagles, 1992). An ecological study found that exposure to poliovirus 5 months prior to birth increased the risk of developing schizophrenia (Suvisaari et al., 1999) | Some studies did not use a direct measurement of poliovirus exposure and instead relied on ecological data. No statistically significant association was found between exposure and risk of schizophrenia in Australia and New Zealand (Cahill et al., 2002) |
| Herpes Simplex Virus | | Neonatal herpes infection can lead to lasting neurological deficits and possibly death. Elevated HSV-2 antibodies were associated with increased risk of psychosis (Buka et al., 2001) Offspring exposed to genital/reproductive infections during the periconceptual period were five times more likely to develop schizophrenia spectrum disorders (Babulas et al., 2006) Significant interaction between infection and family history of psychosis on risk of schizophrenia in the offspring (Babulas et al., 2006) | No clear definition of genital/reproductive infections (Babulas et al., 2006) |
| Zika Virus | | PCR-confirmed ZIKV infection during pregnancy associated with neurological insults in offspring, including cerebellar atrophy, ventriculomegaly, diminished cerebral artery flow, ahydramnios, cerebral calcifications, and microcephaly (Brasil et al., 2016) Preclinical studies using human brain organoid cultures have confirmed microcephaly as a significant neurological outcome of infection (Malaspina et al., 2008; Oh et al., 2017; Wells et al., 2016; Wen et al., 2017) | Recency of the virus epidemic precludes it from having produced data on the risk of schizophrenia spectrum disorders |
| HIV and Ebola | | HIV causes several neuropsychiatric outcomes such as cognitive deficits, psychotic disorders? and mood disorders possibly due to CNS damage (Dubé et al., 2005) | Birth cohorts and preclinical models on HIV have yet to elucidate the contribution of this virus to prenatal infection and subsequent neurodevelopmental insults. Extremely limited data due to recency of Ebola epidemic and high mortality (Bebell et al., 2017) |
| Coronavirus | OC43 and 229E | OC43 can infect fetal and adult astrocytes (Bonavia et al., 1997). 229E can infect fetal astrocytes, adult microglia, and a mixture of adult oligodendrocytes and astrocytes (Bonavia et al., 1997). Human and animal models show association between coronavirus infection and neuropsychiatric symptoms (Jacomy et al., 2006; Severance et al., 2011), including new onset psychosis (Severance et al., 2011) | Small sample size and the modeling of human coronavirus infection with mice both limit the findings (Jacomy et al., 2006) Disproportionate healthy control groups, lack of control for other viral infections, single time point antibody collection, and diagnostic uncertainty (Severance et al., 2011). |
| | SARS-CoV-1 | 2 case reports of SARS-CoV-1 in the CSF (Hung et al., 2003; Lau et al., 2004) SARS-CoV-1 isolated from brain tissue of a deceased patient with CNS symptoms (Xu et al., 2005) | 2 infected patients with neuromuscular manifestations had negative CSF for SARS-CoV-1 (Tsai et al., 2004) Transgenic mice showed that SARS-CoV-1 enters the CNS but does not directly enter neurons (Netland et al., 2008) |

(continued on next page)

Table 1 (continued)

| Virus | Subtype | Primary Positive Findings | Negative Findings and Limitations |
|-------|---|--|--|
| | | 4 patients had “organic hallucinosis,” 3 of whom had worsening symptoms with decreased doses of corticosteroids during SARS treatment. Depressive symptoms, adjustment disorder, or anxiety symptoms related to isolation, or concern for other patients or family members also reported (Cheng et al., 2004). Case reports of fetal complications due to maternal SARS-CoV-1 infection that may have implications for future neuropsychiatric health | A case-control did not find neurological differences in pregnant vs non-pregnant women (Lam et al., 2004) Absence of data on psychiatric complications of offspring born to infected mothers Cases of SARS-CoV-1 infected pregnant women who gave relatively uncomplicated births to healthy children (Yudin et al., 2005; Zhang et al., 2003) |
| | Middle East respiratory syndrome (MERS) | MERS can infect human neural cell lines (Chan et al., 2013) Ataxia, motor deficits, and altered mental status in infected patients (Arabi et al., 2015). 4 patients were with neurologic symptoms, including ICU-related weakness, sensory deficits, and Guillain-Barré syndrome, weeks after infection onset (Kim et al., 2017) | No current evidence supporting the vertical transmission of virus (Schwartz and Graham, 2020) Only 12 known cases of MERS in pregnancy (Alfaraj et al., 2019) |

proven to be effective for studying causal mechanisms of immune activation and risk for neuropsychiatric sequelae in the offspring. Various agents have been used, including polyinosinic:polycytidylic (poly(I:C)) to mimic viral infection, lipopolysaccharide (LPS) to mimic bacterial infection, as well as exposure to cytokines themselves. Type of exposure, as well as dose and timing can be experimentally manipulated to test various hypotheses regarding exposure and risk. Regarding risk for schizophrenia, animals born to exposed moms have shown many homologous findings to patients with schizophrenia, including structural abnormalities in brain morphology (Knuesel et al., 2014), changes in dopaminergic tone (Meyer, 2014), increased circulating markers of inflammation (Arsenault et al., 2014), reduced dendritic spine densities (Coiro et al., 2015), and behavioral deficits such as deficits in sensorimotor gating and impairments in attention and working memory, and sensitivity to psychotomimetic drugs (Meyer, 2014). Moreover, some of these findings have been shown to be reversed with antipsychotic medications (Reisinger et al., 2015). Together with the epidemiologic literature, these models have been useful tools to understand the causal mechanisms underlying viral exposures and risk for neuropsychiatric outcomes later in life.

7. Current understanding of SARS-CoV-2

As of October 10, 2020 the United States alone has over 7.6 million cases of SARS-CoV-2, with over 36.9 million cases globally (COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University, 2020). Even if only a fraction of these individuals become infected during pregnancy, the public health crisis of the delayed neuropsychiatric sequelae amongst those infected in utero will be significant and costly. One clear implication of this research is that if prenatal infection is a true candidate risk factor in the development of schizophrenia spectrum disorders, then public health interventions may be capable of reducing the incidence of schizophrenia, reinforcing the myriad of interventions the world has taken to implement social distancing in the time of SARS-CoV-2.

This section will review the possible neurotropism of SARS-CoV-2 as well as the effects of SARS-CoV-2 on the intrapartum, peripartum, and postpartum periods, knowing it is quite likely that by the time this review is published much more will be known about SARS-CoV-2 and pregnancy. Importantly, this discussion is not comprehensive – we do not aim to provide a systematic, scoping review of the literature, but rather to highlight what is currently known about pregnancy and perinatal outcomes in the setting of SARS-CoV-2 infection, given the understanding that infectious etiologies play a substantial role in the pathophysiology of schizophrenia (Brown and Derkits, 2010). We focus mainly on fetal and infant outcomes, not maternal outcomes, given our concern that SARS-CoV-2 has the potential to be a risk factor for schizophrenia development in infants born to infected pregnant women.

7.1. Possible neurotropism of SARS-CoV-2

There is emerging evidence that SARS-CoV-2 can infect the CNS. A retrospective, observational case series of 214 patients with SARS-CoV-2 found that 36.4% had neurologic manifestations of infection, though all of the reports were subjective patient histories (Mao et al., 2020). Other self-reported neurologic symptoms of SARS-CoV-2 infection include headache (8% of $n = 41$ (Huang et al., 2020); 6% of $n = 52$ (Yang et al., 2020b); 6.5% of $n = 138$ (Wang et al., 2020a); 8% of $n = 99$ (Chen et al., 2020b); 11% of $n = 274$ (Chen et al., 2020d)), dizziness (9.4% of $n = 138$ (Wang et al., 2020); 8% of $n = 274$ (Chen et al., 2020d)), confusion (9% of $n = 99$ (Chen et al., 2020b)), altered mental status (31% of $n = 125$ (Varatharaj et al., 2020)) and olfactory dysfunction (92% of $n = 50$ (Freni et al., 2020)). Helms and colleagues (2020) reported that of their 84% of 58 SARS-CoV-2 positive patients had neurologic symptoms including confusion, corticospinal tract signs, and agitation.

There are several case reports that bolster the evidence for the possible neurotropism of SARS-CoV-2. There have been two reports of SARS-CoV-2 encephalitis, both with positive nasopharyngeal swabs and negative CSF results (Pilotto et al., 2020; Ye et al., 2020). Four cases of meningoencephalitis have also been reported (Bernard-Valnet et al., 2020; Espíndola et al., 2020; Moriguchi et al., 2020), with one CSF sample positive for SARS-CoV-2 (Moriguchi et al., 2020). Brun and colleagues (2020) reported evidence of acute demyelination secondary to SARS-CoV-2 in a 54-year-old patient. One 6-week-old infant had neurologic symptoms in the context of SARS-CoV-2 and rhinovirus coinfection (Dugue et al., 2020). Finally, there has been a report of elevated cytokines in the CSF of a SARS-CoV-2 positive patient, though there was no evidence of neuroinvasion (Farhadian et al., 2020).

In addition to reports on the neurologic symptoms of SARS-CoV-2, there is increasing evidence for direct CNS invasion of the virus, although this work continues to be explored and is often still conflicting (Paniz-Mondolfi et al., 2020; Pougá, 2020; Solomon et al., 2020). The infection of human induced pluripotent stem cell (hiPSC)-derived monolayer brain cells and region-specific brain organoids revealed little direct infection of neurons and astrocytes, however choroid plexus epithelial cells underwent robust infection, which was associated with increased cell death and transcriptional dysregulation (Jacob et al., 2020). However, use of iPSC-derived BrainSphere models revealed infection of a fraction of neural cells within 6 h of incubation with SARS-CoV-2 and replication of the virus within the cells at 72 h. The infected cells were confirmed to shed the virus into the supernatant, however it remains unclear if the infection is sustained by infecting other cells (Bullen et al., 2020). Further confirming the hypothesis that there is a direct inflammatory process within the CNS are two case reports of persistent hypometabolism of the olfactory gyrus and other brain regions characterized by 18F-FDG PET in patients with confirmed diagnosis of SARS-CoV-2 (Guedj et al., 2020).

Several proposed mechanisms for SARS-CoV-2 neuroinvasion include direct infection of neural tissue, hematogenous spread through

the blood brain barrier secondary to cytokine-induced increased permeability, hypoxia-induced cerebral edema, ACE-2 (angiotensin converting enzyme 2) neuronal expression – the receptor critical for viral entry into the lungs – and possible blood brain barrier compromise as a result of binding, cerebral hemorrhage, or cerebrovascular accident, among other possible mechanisms (Baig et al., 2020; Baig and Sanders, 2020; Li et al., 2020b; Toljan, 2020; Wu et al., 2020). In particular, there is increasing evidence for the entry of SARS-CoV-2 into host cells through the binding of ACE-2, and new studies suggest that a similar mechanism occurs at the olfactory epithelium through the use of neuropilin-1 receptors (NRP1), a receptor which has also been demonstrated to be expressed in the CNS at the olfactory gyrus and parolfactory gyri (Davies et al., 2020). The reader is referred to other reviews for a detailed discussions of these mechanisms (Wu et al., 2020; Li et al., 2020b).

SARS-CoV-2 has been implicated in cerebrovascular abnormalities, including acute ischemic stroke and frontotemporal hypoperfusion (Helms et al., 2020; Merkler et al., 2020; Oxley et al., 2020). While the cerebrovascular complications of SARS-CoV-2 present concerns for subsequent neuropsychiatric pathology in these patients, the evidence for acute ischemic stroke does not, to the best of our knowledge, provide support for the possible neurotropism of SARS-CoV-2 and thus we will not address the cerebrovascular complications here. For a thorough review of neurotropism of SARS-CoV-2, the reader is referred to Aghagoli et al. (2020).

7.2. SARS-CoV-2 intrapartum, peripartum, and postpartum

One remaining question, among many, is how maternal SARS-CoV-2 infection affects fetal brain development, if at all. First, how many pregnant women have been infected with SARS-CoV-2 to date? As of October 8, 2020 there have been 25,351 confirmed cases of SARS-CoV-2 in pregnant women in the United States (Data on COVID-19 during Pregnancy, 2020), though this is likely an underestimate given the shortage of testing, prevalence of asymptomatic patients, and absence of reported data (Arons et al., 2020; Bai et al., 2020; COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University, 2020; Emanuel et al., 2020; Gandhi et al., 2020). Here, we will explore the effect of SARS-CoV-2 on the intrapartum, peripartum, and postpartum periods. The reader is referred to Allotey et al. 2020 and Wastnedge et al. 2020 for complete reviews.

Fortunately, pregnant mothers have had few intrapartum complications due to SARS-CoV-2, especially when compared to SARS-CoV-1 and MERS (Dashraath et al., 2020; Khalil et al., 2020; Liu et al., 2020d; Schwartz, 2020). There have also been very few reports of fetal intrapartum complications due to SARS-CoV-2, though of 55 pregnant, infected patients, 9% had intrauterine growth restriction (Dashraath et al., 2020). Understanding fetal intrapartum complications has been complicated by difficulty determining timing of maternal exposure during pregnancy and will benefit from more robust collection of fetal and maternal data, sorted by trimester of exposure (Allotey et al., 2020).

Testing of amniotic fluid and other tissue samples during the intrapartum period has resulted in conflicting evidence. Two SARS-CoV-2 positive patients in their second trimester tested negative for viral particles in the amniotic fluid (Yu et al., 2020). However, Vivanti et al. report a case of a SARS-CoV-2 positive patient with positive amniotic fluid prior to the rupture of membranes, followed by viral detection in placental tissues and fetal nasopharyngeal and rectal swabs (Vivanti et al., 2020).

One prominent and consistent intrapartum change that should not be ignored is the overall increase in incidence of anxiety and depression in pregnant women during the pandemic relative to pre-pandemic levels (Berthelot et al., 2020). As we know, these maternal neuropsychiatric symptoms have been repeatedly shown to influence fetal development leading to delayed-onset neuropsychiatric sequelae (Glover, 2011; Wu et al., 2020).

Dashraath and colleagues (Dashraath et al., 2020) suggest that differences in immunologic phenotypes could explain why maternal SARS-CoV-2 infection seems to be less severe than SARS-CoV-1 and MERS. First, during SARS-CoV-1 infection, there was a shift in maternal immunity toward the inflammatory Th1 cell phenotype (Wong et al., 2004a). Second, SARS-CoV-2 has (at least thus far) led to balanced inflammatory Th1 and anti-inflammatory Th2 cell phenotypes (Huang et al., 2020). This difference in immune phenotype could possibly explain the mild symptoms and few complications reported in women infected with SARS-CoV-2 relative to those with SARS-CoV-1 or MERS (Al-Tawfiq, 2020; Dashraath et al., 2020).

How have deliveries been affected by maternal SARS-CoV-2 infection? Among 55 patients, 43% had preterm births in the setting of maternal SARS-CoV-2 infection compared to 25% and 27% in SARS-CoV-1 and MERS, respectively (Dashraath et al., 2020). By contrast, Z. Yang and colleagues (Yang et al., 2020c) reported a preterm birth rate of 21.3% in a sample size of 114 pregnant patients. An extensive review of reports amounting to 385 pregnant women positive for SARS-CoV-2 found that of the 252 (65.5%) who gave birth, 15.5% had preterm deliveries and 69.4% had cesarean sections (Elshafeey et al., 2020). A larger, more recent review found that the odds of a preterm birth for a woman with SARS-CoV-2 was 3 times higher than the odds of an uninfected pregnant woman ($n = 339$, 2 studies, 95% CI 1.16–7.85) (Allotey et al., 2020). Importantly, some of these pregnant mothers had comorbidities that likely contributed to the preterm births (Chen et al., 2020) and some studies have recently found no increased incidence of preterm birth in pregnant women with SARS-CoV-2 (Ahlberg et al., 2020). Even so, we must not ignore the effects that SARS-CoV-2 may have on preterm births, especially since it is associated with risk of developing psychiatric disorders later in life (Johnson and Marlow, 2011; Nosarti et al., 2012). Presently, data are available only for patients infected in the third trimester. Therefore, maternal SARS-CoV-2 infection may be an independent predictor of preterm births, but additional data on patients infected in the first and second trimesters are needed (Mehan et al., 2020). Conflicting evidence exists as to whether pregnancy and delivery seem to worsen SARS-CoV-2 symptoms and computerized tomography imaging (CT) findings in pregnant women (Liu et al., 2020a; Yang et al., 2020c). While numerous studies demonstrated no change, meta-analysis revealed that pregnant patients infected with SARS-CoV-2 reported fewer symptoms of fever and myalgia relative to non-pregnant women. However, despite reporting fewer symptoms, positive pregnant women were more likely to require admission to an intensive care unit or invasive ventilation (Allotey et al., 2020; Dashraath et al., 2020). Placental vasculature abnormalities and inflammation have been noted in SARS-CoV-2 patients (Baergen and Heller, 2020; Hosier et al., 2020; Shanes et al., 2020). Two groups have reported positive placental swabs in a SARS-CoV-2 patient without any indication of vertical transmission (Ferraiolo et al., 2020; Hosier et al., 2020) while one group has reported a case of positive placental swab accompanied by positive nasopharyngeal and rectal swabs in the neonate (Vivanti et al., 2020). There have been 2 cases of SARS-CoV-2 present in human breastmilk, but there is currently no evidence that the virus can be transmitted via human breastmilk (Groß et al., 2020).

There are few case reports of possible vertical transmission of SARS-CoV-2 (Table 2) (Allotey et al., 2020; Dashraath et al., 2020; Knight et al., 2020). Notably, there was a case of a newborn in Wuhan, China with IgM antibodies against SARS-CoV-2 born to an infected woman (Dong et al., 2020). The pregnant mother was found to have a positive nasopharyngeal swab per RT-PCR as well as elevated IgM and IgG antibodies, though her vaginal secretions were negative for SARS-CoV-2 per RT-PCR. At 2 h of age, the baby had elevated IgM, IgG, Interleukin (IL)-6, and IL-10. All 5 nasopharyngeal swabs between 2 h and 16 days of life were negative. Zeng and colleagues (2020a) also reported cases of elevated IgM and IgG antibodies in neonates. Importantly, the presence of IgM antibodies is evidence of infection in utero, as IgM antibodies do not pass through the placenta (Burrell et al., 2017). These groups do not

Table 2
Select reports of fetal outcomes in pregnant women with SARS-CoV-2.

| Study | Sample size (N) | Cesarean section (n, %) | Preterm (n, %) | Neonatal + swab (n) | Neonatal IgM+ (n) | Neonatal IgG+ (n) |
|---------------------------|-----------------|-------------------------|----------------|---------------------|-------------------|-------------------|
| Alzamora et al. (2020) | 1 | 1 (100) | 1 (100) | 1 | 0 | 0 |
| Chen H 2020 | 9 | 9 (100) | 4 (44) | 0 | NA | NA |
| Chen S 2020 | 5 | 2 (40) | 0 (0) | 0 | NA | NA |
| Chen Y 2020 | 4 | 3 (75) | 0 (0) | 0 | NA | NA |
| Dong 2020 | 1 | 1 (100) | 1 (100) | 0 | 1 | 0 |
| Ferrazzi et al. (2020) | 42 | 18 (42.8) | 7 (16.6) | 3** | NA | NA |
| Hu 2020 | 7 | 6 (85.7) | 0 (0) | 1*** | NA | NA |
| Khan 2020 | 3 | 0 (0) | 1 (33) | 0 | NA | NA |
| Kirtsman et al. (2020) | 1 | 1 (100) | 0 (0) | 1 | NA | NA |
| Li 2020 | 16 | 14 (87.5) | 3 (18.8) | 0 | NA | NA |
| Liu 2020 | 13 | 10/10 (100) | 6/10 (60) | 0/10 | NA | NA |
| Lu 2020 | 1 | 1 (100) | 0 (0) | 0 | NA | NA |
| Qiancheng 2020 | 23 | 17 (60.7) | 1 (4.3) | 0 | NA | NA |
| Vivanti 2020 [†] | 1 | 0 (0) | 1 (100) | 1 | NA | NA |
| Wang 2020 | 1 | 1 (100) | 0 (0) | 1 [^] | NA | NA |
| Xiong et al. (2020) | 1 | 1 (100) | 0 (0) | 1 | NA | NA |
| Yan 2020* | 50 | 44 (88) | 16 (32) | 0 | NA | NA |
| Yu 2020 | 7 | 7 (100) | 0 (0) | 1 [^] | NA | NA |
| Zeng H 2020 | 6 | 6 (100) | – | 0 | 2 | 5 |
| Zeng L 2020 | 33 | 26 (78.8) | 4 (12.1) | 3 ^{^^} | NA | NA |
| Zhu 2020 | 10 | 7 (70) | 6 (60) | 0 | NA | NA |

[†] Also found positive amniotic fluid prior to rupture of membranes.

* 50 laboratory-confirmed SARS-CoV-2 cases in pregnant women who delivered; the group also “clinically diagnosed” 49 pregnant women with SARS-CoV-2, but those women were excluded from this table.

** Two had contact, including breastfeeding, with SARS-CoV-2 positive patients without masks.

*** Neonate tested at 36 h of life and was isolated after birth.

[^] Neonate tested at 36 h of life.

^{^^} Not tested until the second day of life.

– Not listed, though all infants were delivered in the third trimester.

have an explanation for the negative swabs in the neonates, though they acknowledge that the nasopharyngeal swab RT-PCR test does not have 100% sensitivity.

Zeng and colleagues (2020b) report 3 cases of possible vertical transmission. This study, among others (Wang et al., 2020b; Yu et al., 2020a, 2020b), did not obtain nasopharyngeal swab tests of the neonates until day two of life, providing opportunities for non-maternal sources of infection, or a postpartum maternal source. This study highlights the inconsistencies among case reports and cohort studies; some studies test neonates immediately after birth while others wait hours or even days.

Fortunately, there have also been many reports of uninfected babies born to infected mothers (Chen et al., 2020a, 2020c, 2020e; Cooke et al., 2020; Khan et al., 2020; Li et al., 2020a; Liu et al., 2020b, 2020c; Lu et al., 2020; Marín Gabriel et al., 2020; Peng et al., 2020; Pereira et al., 2020; Qiancheng et al., 2020; Yan et al., 2020; Yang et al., 2020a; Zhu et al., 2020; Elshafeey et al., 2020). However, there is concern about the incidence of cesarean section and preterm births for those infected with SARS-CoV-2 (Table 1) (Della Gatta et al., 2020), so, while few newborns have had positive RT-PCR findings (1.6% in Elshafeey et al. and 5% in Knight et al.), researchers still need to consider the possible neuropsychiatric outcomes of unnecessary cesarean sections and increased rates of preterm births (Allotey et al., 2020; Elshafeey et al., 2020; Knight et al., 2020; Zhang et al., 2019). It is also critical to note that to date there is no literature regarding the specificity and sensitivity of a neonatal nasopharyngeal swab for SARS-CoV-2 RT-PCR.

8. Implications for SARS-CoV-2

Viral epidemics and pandemics offer a compelling opportunity to capitalize on uniquely large sample sizes to investigate associations between prenatal infection and schizophrenia spectrum disorders. Early ecological studies suggested such an association, and yet key study limitations hindered the generalizability of this work. Birth cohort studies navigated around many of those weaknesses and provided even

more compelling evidence for the association of prenatal infection with schizophrenia spectrum disorders; however, the absence of serologic and clinical confirmation of infection in many studies may have further diluted a (likely) small effect size. Parallel to this work, preclinical models have shown that maternal immune activation leads to aberrant neurodevelopment and behavior profiles analogous to phenotypes observed in schizophrenia (Fig. 1).

Given this compelling evidence in the face of an ongoing global viral pandemic, there exists an obligation by the scientific community to better assess the risk of prenatal infection in the development of schizophrenia through the use of rigorous study design and opportunity. This body of work has been underdeveloped in prior global health crises, and rarely does such a unique and reliable at risk population present itself for use in longitudinal analysis. Multiple strategies are needed, in particular high-quality sentinel surveillance and seroprevalence surveys of mothers to critically enhance our understanding of this phenotype. This would ideally include both qualitative and quantitative measures of serology, pyrexia profiles, inflammatory cytokine panels, placental samples, vaginal swabs, and importantly – a timeline of the changing levels of infectious biomarkers and inflammatory response biomarkers over the course of neurodevelopment in utero. Children born to mothers should also undergo qualitative and quantitative measures of serology and clinical infection, as well as recurrent neurocognitive testing, imaging, and on-going biometrics to better understand the cognitive and behavioral phenotypes emerging from the post-viral pandemic (Buekens et al., 2020). Culminative analyses comparing those who develop schizophrenia with those who do not could be utilized for furthering our understanding of this illness.

While many potential confounding factors must be considered, such as history of other infections, family history, obstetric complications, socioeconomic status, race and ethnicity, and access to prenatal care, furthering our understanding of the implications of stress during pregnancy will be important to understanding the true effect of this pandemic. In a letter to the editor, Barišić et al. (2020) reminded the public that stress in pregnancy is “conceptualized as a teratogen” and

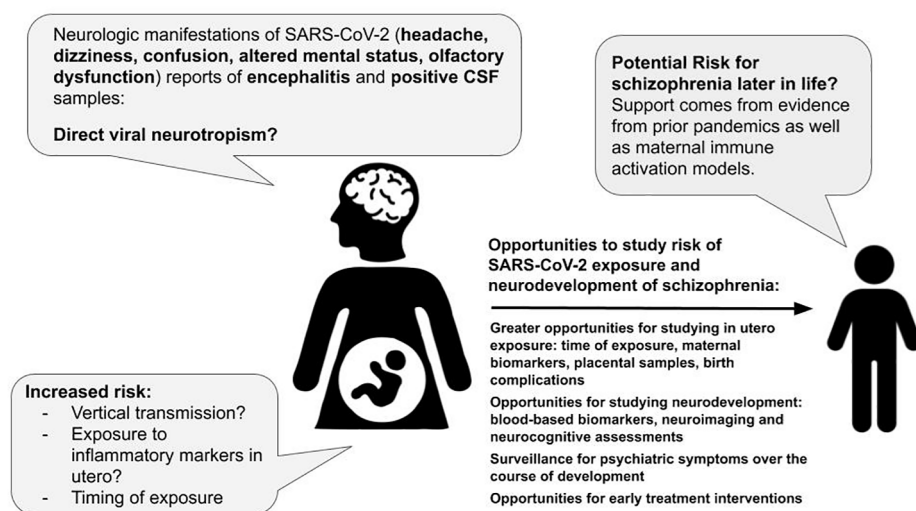


Fig. 1. There is growing evidence to support neurotropism and possible vertical transmission of SARS-CoV-2. Pandemic-associated epidemiological data and maternal immune activation models demonstrate that exposure to viral pathogens and inflammation in utero yields increased risk for neuropsychiatric disorders later in life, such as schizophrenia. Thus, the current pandemic offers a novel opportunity to study the neurodevelopment of schizophrenia, with increased opportunity to study exposure variables, brain morphology, and utilize increased surveillance of symptoms over the course of development.

that it is critical that we evaluate pregnant women for stress and encourage stress prevention, as well as follow the neurodevelopment of children born to women who endure significant stress over the course of their pregnancy (Barišić, 2020). Interestingly, both war and famine have been associated with an increased incidence of schizophrenia (St Clair et al., 2005; Susser and Lin, 1992). There is no doubt that the on-going pandemic has caused considerable national and global stress with unprecedented rates of unemployment and social isolation, and these stressors will need to be carefully considered and controlled for in the pursuit of this work.

Further unique barriers related to the SARS-CoV-2 pandemic include the implication of asymptomatic, serologically positive women, a likely risk given the high rates of asymptomatic infections (Gao et al., 2020). This underlines the importance of universal testing, particularly in this vulnerable population. Large numbers of asymptomatic carriers will also necessitate careful recruiting of control groups. This could include births from mothers with known negative testing, however this system could introduce significant error given the on-going hurdles surrounding testing in the United States. The current gold standard for diagnosis is real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) based assays performed on respiratory specimens. Although serological assays are emerging, the CDC and FDA both warn of their ongoing inconsistencies. Alternatively, control data could be extrapolated from previously collected cohort data however there are significant benefits to prospectively collecting control data for the purpose of elucidating the maternal phenotype.

With increasingly complex preclinical models such as the promising research emerging from brain organoid (organ-like) cultures, parallel and confirmatory studies will enable a translational approach capable of simultaneously uncovering the biochemical neural insults contributing to the schizophrenia phenotype. Brain organoid models are three-dimensional cultures derived from human pluripotent stem cells and have created immense opportunity for in depth research modeling psychoneurological disorders and therapeutic treatments. (Wang, 2018). Although the use of previous models like rodents and non-human primates continue to help make great strides in our understanding of the schizophrenia phenotype, the unique complexity of the human brain makes prior models appear, in comparison, far less accurate of an approximation. The human brain organoid models have recently been used to confirm several theories of aberrant neurodevelopment underlying neuropsychiatric disease mechanisms including signaling molecule cascades and factors, binding protein complexes, and cell-line populations that appear to be linked to bipolar disorder, autism, schizophrenia, and depression (Wang, 2018). Preclinical studies using the brain organoid model like those done with Zika virus were able to

identify microcephaly as a significant neurological outcome of congenital ZIKV infection (Wells et al., 2016), and could be applied in the future not just to further research regarding COVID-19 maternal infection, but understanding other maternal viral infections effect on the brain as well. Maternal inflammation and immune response could be separated from pathogenic viral insult to the brain and the models compared to advance contemporary understanding of immune and pathogen interplay on brain development. The timing of viral pathogen or immune activation insult during brain development could be measured with greater accuracy and studied more extensively than ever before.

9. Conclusion

The SARS-CoV-2 pandemic has had a significant global impact and resulted in rates of viral infection previously unheard of in the 21st century. While explorations have been made previously into defining the relationship between viral pandemics and the resulting risk of schizophrenia spectrum disorders, this work has been limited primarily to epidemiologic and birth cohort studies, with the only recent arrival of several preclinical models including brain organoid models. The current rate of viral infection begets the unique opportunity to capitalize on a significant sample size to create a better understanding of causality and the mechanisms underlying viral immune activation and aberrant neurodevelopment in the risk of schizophrenia disorder and psychosis. With increased vigilance there exists the opportunity to forward our understanding of this psychiatric phenomenon, but it also affords the opportunity to reduce the impact of these diseases among future generations.

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